Introduction

Page 3. *As sixteenth-century Swiss physician.* Philippus Theophrastus Aureolus Bombastus von Hohenheim (1493-1541), later known as Paracelsus, was a founder of the field of toxicology. The maxim "the dose makes the poison" paraphrases what Paracelsus wrote in German: "*Alle Dinge sind Gift, und nichts ist ohne Gift; allein die dosis machts, daß ein Ding kein Gift sei*." This is translated into English as: "All things are poison and nothing is without poison; only the dose makes it so that a thing is not a poison."

1. Paracelus, Theophrastus. "Die dritte Defension wegen des Schreibens der neuen Rezepte." In *Septem Defensiones 1538*. Werke Bd. 2, Darmstadt 1965, S. 510. Accessed June 19, 2023: http://www.zeno.org/nid/20009261362.

Page 3. *At the wrong dose.* Atmospheric oxygen can become toxic at partial pressures higher than those at sea level. Excess reactive oxygen species like superoxide radicals may overwhelm antioxidant buffering mechanisms and damage biomolecules prone to oxidation, such as lipids.

2. Fridovich, I. (1998). "Oxygen Toxicity: A Radical Explanation." *Journal of Experimental Biology*, *201*(8), 1203–1209. https://doi.org/10.1242/jeb.201.8.1203

Page 4. *The chemicals that I call toxins.* The "war of nature" quote is from page 490 of the first British edition of the book that became known as The Origin of Species by Charles Darwin, who wrote: "Thus, from the war of nature, from famine and death, the most exalted object which we are capable of conceiving, namely, the production of the higher animals, directly follows." *Darwin mused about how.* The "entangled bank" quote is from page 489.

3. Darwin, C. (1859). *On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life*. London: Murray (1st edition). Accessed June 19, 2023: http://darwin-online.org.uk/Variorum/1859/1859-490-c-1860.html.

Page 7. *It often hosts more great gray owls*. The Sax-Zim Bog supports many great gray owl (*Strix nebulosa*) individuals during irruption years when microtine rodent populations wane in more northerly regions.

4. Svingen, P.H. and Lind, J.W. (2005). "The 2004–2005 influx of northern owls part II: Great gray owl." *The Loon* 77: 194–208. Accessed June 19, 2023: https://www.moumn.org/loon/pdf/2005.pdf#page=194.

Page 8. *The local school*. The Toivola-Meadowlands School was initially closed by Independent School District #710 in 1992 owing to decreasing enrollment and then briefly operated as a charter school before permanently closing in 1998. Noah Whiteman received his high school diploma from the charter school in 1994.

5. Whiteman, N. 2023. Personal observation.

Chapter 1. Deadly Daisies

Page 9. *Within the infant rind.* This quote is from Act 2, Scene 3 from William Shakespeare's *Romeo and Juliet*. Friar Laurence carries a basket containing medicinal herbs that hold both the power to cure and the power to harm.

6. Shakespeare, W. (1594). *The Tragedy of Romeo and Juliet*. Open Source Shakespeare. George Mason University. Accessed June 20, 2023: https://www.opensourceshakespeare.org.

Page 9. *Even in its "infant rind," the mum*. Matricin, also known as matricine, is a sesquiterpene lactone chemical produced by Asteraceae. In the acidic environment of the human stomach, matricin is converted into chamazulene carboxylic acid, which decarboxylates into chamazulene. Chamazulene carboxylic acid and chamazulene are hypothesized to have anti-inflammatory effects with modes of action similar to synthetic non-steroidal anti-inflammatory drugs (NSAID) ibuprofen and naproxen. This is likely due to the structural similarities between chamazulene carboxylic acid, chamazulene and NSAIDs, which inhibit proinflammatory enzymes. Chamazulene was the most abundant terpenoid released by the mountain yarrow *Achillea collina* after aphid infestation, implicating its role as an anti-herbivore defense.

7. Ramadan, M., Goeters, S., Watzer, B., Krause, E., Lohmann, K., Bauer, R., Hempel, B., & Imming, P. (2006). "Chamazulene Carboxylic Acid and Matricin: A Natural Profen and Its Natural Prodrug, Identified through Similarity to Synthetic Drug Substances." *Journal of Natural Products*, *69*(7), 1041–1045. https://doi.org/10.1021/np0601556

8. Safayhi, H., Sabieraj, J., Sailer, E. -R., and H. P. T. Ammon. (1994). "Chamazulene: An antioxidant-type inhibitor of leukotriene B_4 formation." *Planta Medica 60*: 410–413. https://doi.org/10.1055/s-2006-959520.

9. Giorgi, A., Panseri, S., Nanayakkarawasam, N., N. M. C., Chiesa, L. M. (2012). "HS-SPME-GC/MS analysis of the volatile compounds of *Achillea collina*: Evaluation of the emissions fingerprint induced by *Myzus persicae* infestation." *Journal of Plant Biology 55*: 251–260. https://doi.org/10.1007/s12374-011-0356-0.

Page 9. *The eastern white pine held its own piperidine alkaloids*. Piperidine is a heterocyclic amine (see Appendix) naturally produced by plants like those in the genus *Piper*. Piperidine was discovered in the 19th century when piperine was treated with nitric acid in the laboratory. Piperine and an isomer of piperine called chavicine are the predominant molecules that drive the peppery taste of black pepper (*Piper nigrum*). The piperidine ring is also used as the foundation for synthetic drugs, including fentanyl. Piperidine alkaloids are found in many species of spruce, fir, and pine, including the eastern white pine (*Pinus strobus*), which produces pinidine. These chemicals are also made by distantly related plants, such as poison hemlock (*Conium maculatum*), which produces the highly toxic piperidine alkaloid coiinne, and by pitcher plants (*Sarracenia* spp.), which ostensibly paralyzes the insects that fall into the pitcher. Coiinine and related alkaloids in poison hemlock may have killed Socrates. Insects also synthesize piperidine alkaloids, including fire ants (*Solenopsis* spp.), which produce solenopsins that are venom components, and coccinellid beetles, which produce other piperidines that are secreted in defensive glands or during reflex bleeding. Piperidine alkaloids thus play a defensive role against natural enemies of both the plants and insects that synthesize these chemicals.

10. Ørsted, Hans Christian (1820). "Über das piperin, ein neues pflanzenalkaloid." *Schweiggers Journal für Chemie und Physik 29*: 80–82. Accessed June 22, 2023: https://books.google.com/books?id=k-M4AAAAMAAJ&pg=PA80#v=onepage&q&f=false

11. Veličkovic', D., Liao, H.-L., Vilgalys, R., Chu, R. K., and Anderton, C. R. (2019). "Spatiotemporal transformation in the alkaloid profile of *Pinus* roots in response to mycorrhization." *Journal of Natural Products 82*: 1382–1386. Accessed June 22, 2023: https://pubs.acs.org/doi/full/10.1021/acs.jnatprod.8b01050.

12. Warnhoff, Edgar W. (1998). "When piperidine was a structural problem." *Bull. Hist. Chem* 22: 29-34. Accessed June 20, 2023: http://acshist.scs.illinois.edu/bulletin_open_access/num22/num22%20p29-34.pdf.

13. MacConnell, J. G., Blum, M. S., & Fales, H. M. (1971). The chemistry of fire ant venom. *Tetrahedron*, *27*(6), 1129–1139. https://doi.org/10.1016/S0040-4020(01)90860-9

14. Tawara, J. N., A. Blokhin, T. A. Foderaro, and F. R. Sermitz. (1993). "Toxic piperidine alkaloids from pine (*Pinus*) and spruce (*Picea*) trees. New structures and a biosynthetic hypothesis." *Journal of Organic Chemistry 58*: 4813–4818. Accessed June 22, 2023: https://pubs.acs.org/doi/abs/10.1021/jo00070a014

15. Mody, V., Henson, R., Hedin, P. A., Kokpol, U., and D. H. Miles. (1976). "Isolation of the insect paralyzing agent coniine from *Sarracenia flava*." *Experientia 32*: 829–830. Accessed June 22, 2023: https://link.springer.com/article/10.1007/BF02003710

16. Shtykova, L., Masuda, M., Eriksson, C., Sjödin, K., Marling, E., Schlyter, F., & Nydén, M. (2008). Latex coatings containing antifeedants: Formulation, characterization, and application for protection of conifer seedlings against pine weevil feeding. *Progress in Organic Coatings*, *63*(2), 160–166. https://doi.org/10.1016/j.porgcoat.2008.05.006

Page 9. *St. John's wort contains the phenolic compound hypericin*. St. John's Wort produces the anthraquinone derivative hypericin, which has a large chromophore structure (see Appendix) that absorbs visible light in the 590 nm range. Upon digestion, hypericin moves through the blood to the skin and can be toxic owing to the production of singlet oxygen, which is highly reactive with biomolecules. Hypericin is a toxin to herbivorous insects as well as livestock and other domestic animals that feed on this plant can be injured owing to photosensitivity. The plant is also widely used medicinally.

17. Volmer, J.J. and Rosenson J. (2004). "Chemistry of St. John's Wort: Hypericin and Hyperforin." *Journal of Chemical Education 81*: 1450–1465. Accessed June 22, 2023: https://pubs.acs.org/doi/pdf/10.1021/ed081p1450

18. Giese, A. C. (1980). "Hypericism." *Photochemical and Photobiological Reviews 5*:229–255. Accessed June 22, 2023: https://link.springer.com/chapter/10.1007/978-1-4684-3641-9_6

19. Pace, N. (1942). "The etiology of hypericism, a photosensitivity produced by St. John's Wort." *American Journal of Physiology 136*: 650–656. Accessed June 22, 2023: https://journals.physiology.org/doi/pdf/10.1152/ajplegacy.1942.136.4.650

20. Samuels, R., Knox, P. (1989). "Insecticidal activity of hypericin towards *Manduca sexta* larvae." *Journal of Chemical Ecology 15*: 855–862. Accessed June 22, 2023: https://link.springer.com/article/10.1007/BF01015181

Page 9. *and sea holly, the aldehyde eryngial*. The sea holly (*Eryngium maritimum*), a member of the dill family (Apiaceae) produces the aldehyde eryngial, also called *trans*-2-dodecenal (see Appendix). Other members of the dill family such as cilantro (coriander; *Coriandrum sativum*), ginger (*Zingiber officionale*), citrus (orange peel; *Citrus* x *sinensis*) also produce this compound, as do some *Rhinocricus* millipedes. Sea holly has been used as a medicinal for a variety of ailments.

21. Forbes, W. M., Gallimore, W. A., Mansingh, A., Reese, P. B., & Robinson, R. D. (2014). Eryngial (*trans* -2-dodecenal), a bioactive compound from *Eryngium foetidum* : its identification, chemical isolation, characterization and comparison with ivermectin *in vitro*. *Parasitology*, *141*(2), 269–278. https://doi.org/10.1017/S003118201300156X

22. Manville, R. W., & Abbott, G. W. (2019). Cilantro leaf harbors a potent potassium channel–activating anticonvulsant. *The FASEB Journal*, *33*(10), 11349–11363. https://doi.org/10.1096/fj.201900485R

23. Wheeler, J. W., Meinwald, J., Hurst, J. J., & Eisner, T. (1964). *trans* -2-Dodecenal and 2-Methyl-1,4-Quinone Produced by a Millipede. *Science*, *144*(3618), 540–541. https://doi.org/10.1126/science.144.3618.540

Page 10. *The needles of eastern white pine have long been used*. This species (*Pinus strobus*) and many others in the genus *Pinus* have been used by Indigenous peoples of North America as medicinals to treat a variety of conditions, from dermatological to respiratory. An example is given below, but also see

24. Rousseau, J., (1947). "Ethnobotanique Abenakise." *Archives de Folklore 11*: 145–182. Accessed June 22, 2023. Found by searching "*Pinus strobus* via http://naeb.brit.org/uses/species/2977.

25. Kimmerer, R. W. (2021). "Hearing the language of Trees." *Yes Magazine.* Excerpt from *The Mind of Plants: Narratives of Vegetal Intelligence,* eds. by J. C. Ryan, P. Viera, and M. Galiano, published by Synergetic Press (2021). Accessed June 23, 2023: https://www.yesmagazine.org/environment/2021/10/29/hearing-the-language-of-trees.

26. Flood, M., & Myhal, N. (2022). White Pine in Time and Place. *History of Pharmacy and Pharmaceuticals*, *63*(2), 302–327. https://doi.org/10.3368/hopp.63.2.302.

Page 10. *Hypericin in St. John's wort is widely used.*

27. Linde, K., Ramirez, G., Mulrow, C. D., Pauls, A., Weidenhammer, W., & Melchart, D. (1996). St John's wort for depression--an overview and meta-analysis of randomised clinical trials. *BMJ*, *313*(7052), 253–258. https://doi.org/10.1136/bmj.313.7052.253

28. Nahrstedt, A., & Butterweck, V. (2010). Lessons Learned from Herbal Medicinal Products: The Example of St. John's Wort. *Journal of Natural Products*, *73*(5), 1015–1021. https://doi.org/10.1021/np1000329

Page 10. *Finally, Jamaican scientists.*

29. Forbes, W. M., Gallimore, W. A., Mansingh, A., Reese, P. B., & Robinson, R. D. (2014). Eryngial (*trans* -2-dodecenal), a bioactive compound from *Eryngium foetidum* : its identification, chemical isolation, characterization and comparison with ivermectin *in vitro*. *Parasitology*, *141*(2), 269–278. https://doi.org/10.1017/S003118201300156X

Page 10. *One big hint came.*

30. Manville, R. W., & Abbott, G. W. (2019). Cilantro leaf harbors a potent potassium channel–activating anticonvulsant. *The FASEB Journal*, *33*(10), 11349–11363. https://doi.org/10.1096/fj.201900485R

Page 12. *We scattered his ashes.* The quote "shining Big-Sea-Water" of Lake Superior" is from Henry Wadsworth Longfellow's 1855 poem *The Song of Hiawatha III. Hiawatha's Childhood.* Accessessed June 23, 2023: https://www.hwlongfellow.org/poems_poem.php?pid=277. The relevant excerpt is here:

By the shores of Gitche Gumee,
By the shining Big-Sea-Water,
Stood the wigwam of Nokomis,
Daughter of the Moon, Nokomis.
Dark behind it rose the forest,
Rose the black and gloomy pine-trees,
Rose the firs with cones upon them;
Bright before it beat the water,
Beat the clear and sunny water,
Beat the shining Big-Sea-Water.

Page 13. *The two outermost pieces are of black walnut*. Juglone (5-hydroxy-1,4-naphthoquinone) is produced by walnut trees and when it leaches into the soil, can inhibit the growth of other plants. Juglone is an isomer of lawson (2-hydroxy-1,4-naphthoquinone), which is the red-staining dye in henna.

31. Cook, M.T. (1921). "Wilting caused by walnut trees." *Phytopathology 11*: 346. Not available online.

32. Willis, R. J. (2000). "*Juglans* spp., juglone and allelopathy." *Allelopathy Journal 7*: 1–55. Accessed June 23, 2023: https://www.allelopathyjournal.com/Journal_Articles/AJ%207%20(1)%20January,%202000%20(1-55).pdf.

Page 14. *In the Achilleid, first-century*. The origins of the imperfect vulnerability motif involving Thetis and her son Achilles from

33. Harrauer, C. (2010). "Why Styx? Some remarks on Satius's Achilleid." *Wiener Studien 123*: 167–175. Accessed June 23, 2023: https://www.jstor.org/stable/24752330.

Page 14. *As our own lineage*.

34. Bramble, D. M., & Lieberman, D. E. (2004). Endurance running and the evolution of Homo. *Nature*, *432*(7015), 345–352. https://doi.org/10.1038/nature03052

35. Gibbons, A. (2013). "Human evolution: Gain came with pain blame your bad back and sprained ankle on an imperfect reworking of the ape body plan." *Science*. doi: 10.1126/article.26387. Accessed June 24, 2023: https://www.science.org/content/article/human-evolution-gain-came-pain

Page 16. *Pyrethrum powder was first*. The first reference below has been translated into English online (if the website is visited the journal gives one the option of German or English). The second reference is an excellent history and detailed account of the use of pyrethrum powder over time.

36. Roth, K., & Vaupel, E. (2017). Von Insekten, Chrysanthemen und Menschen. *Chemie in Unserer Zeit*, *51*(3), 162–184. https://doi.org/10.1002/ciuz.201700786

37. McDonnell, C. C., Roark, R. C., & Keenan G. L. (1920). [revised 1926]. *Insect Powder. Bulletin No. 824.* U.S. Department of Agriculture. Accessed June 24, 2023: https://www.google.com/books/edition/Insect_Powder/XFZCAQAAMAAJ?hl=en&gbpv=0.

Page 17. *Chrysanthemums have been*. The role of Japanese scientists in particular is surveyed in the reference below.

38. Matsuo, N. (2019). "Discovery and development of pyrethroid insecticides. Proceedings of the Japan Academy." *Series B, Physical and Biological Sciences. 95*: 378–400. Accessed June 24, 2023: https://doi.org/10.2183/pjab.95.027.

Page 18. *This physiological reaction sounds bad*. A few examples of the off-target effects of natural and synthetic pyrethrins.

39. Antwi, F. B., & Reddy, G. V. P. (2015). Toxicological effects of pyrethroids on non-target aquatic insects. *Environmental Toxicology and Pharmacology*, *40*(3), 915–923. https://doi.org/10.1016/j.etap.2015.09.023

40. Haya, K. (1989). Toxicity of pyrethroid insecticides to fish. *Environmental Toxicology and Chemistry*, *8*(5), 381–391. https://doi.org/10.1002/etc.5620080504

Page 18. *Dose for dose*.

41. Roth, K., & Vaupel, E. (2017). Von Insekten, Chrysanthemen und Menschen. *Chemie in Unserer Zeit*, *51*(3), 162–184. https://doi.org/10.1002/ciuz.201700786

Page 18. *For example, a single*. Although this article focused on the rat, the authors changed one amino acid in one of the rat's voltage gated sodium channels to mimic the insect version and found that that one amino acid change can explain the high susceptibility of arthropods, including insects, to pyrethrins.

42. Vais, H., Atkinson, S., Eldursi, N., Devonshire, A. L., Williamson, M. S., & Usherwood, P. N. R. (2000). A single amino acid change makes a rat neuronal sodium channel highly sensitive to pyrethroid insecticides. *FEBS Letters*, *470*(2), 135–138. https://doi.org/10.1016/S0014-5793(00)01305-3

Page 18. *By contrast, cats*. Cats are missing an enzyme necessary for the detoxification of pyrethrins.

43. Boland, L. A., & Angles, J. M. (2010). Feline permethrin toxicity: Retrospective study of 42 cases. *Journal of Feline Medicine and Surgery*, *12*(2), 61–71. https://doi.org/10.1016/j.jfms.2009.09.018

Page 18. *Consider the sad story.* Although there are apocryphal stories of newts poisoning people in a variety of contexts, the below is a true story involving a dare gone wrong.

44. Bradley, S. G., & Klika, L. J. (1981). A Fatal Poisoning From the Oregon Rough-Skinned Newt (Taricha granulosa). *JAMA: The Journal of the American Medical Association*, *246*(3), 247. https://doi.org/10.1001/jama.1981.03320030039026

Page 18. *Although pyrethrins are made by plants, tetrodotoxin*.

45. Tani, T. (1945). Nihonsan Fugu no Chudokugakuteki Kenkyu (Toxicological Studies on Japanese Puffer). *Tokyo, Teikokutosho*, *1945*, 15-27.

46. Yokoo, A. (1950). Study on chemical purification of tetrodotoxin (3)-purification of spheroidine. *Journal of the Chemical Society of Japan*, *71*(11), 590-592.

47. Mosher, H. S., Fuhrman, F. A., Buchwald, H. D., & Fischer, H. G. (1964). Tarichatoxin—Tetrodotoxin: A Potent Neurotoxin. *Science*, *144*(3622), 1100–1110. https://doi.org/10.1126/science.144.3622.1100

48. Sheumack, D. D., Howden, M. E. H., Spence, I., & Quinn, R. J. (1978). Maculotoxin: A Neurotoxin from the Venom Glands of the Octopus *Hapalochlaena maculosa* Identified as Tetrodotoxin. *Science*, *199*(4325), 188–189. https://doi.org/10.1126/science.619451

49. Chau, R., Kalaitzis, J. A., & Neilan, B. A. (2011). On the origins and biosynthesis of tetrodotoxin. *Aquatic Toxicology*, *104*(1–2), 61–72. https://doi.org/10.1016/j.aquatox.2011.04.001

Page 18. *There is nothing inherently healthy about natural products.*

50. Meier, B. P., Dillard, A. J., & Lappas, C. M. (2019). Naturally better? A review of the natural-is-better bias. *Social and Personality Psychology Compass*, *13*(8). https://doi.org/10.1111/spc3.12494

Page 19. *Darwin remarked that the birds.* Quote "a gun here is almost superfluous; for with the muzzle of one I pushed a hawk off the branch of a tree"from reference below, also known as The Voyage of the Beagle.

51. Darwin, C. 1890. *Journal of researches into the natural history and geology of the various countries visited by H.M.S. Beagle etc.* (First Murray illustrated ed.), London: John Murray.

Page 20. *One of the largest in the world.*

52. Clark, D. B. (1979). A Centipede Preying on a Nestling Rice Rat (Oryzomys bauri). *Journal of Mammalogy*, *60*(3), 654–654. https://doi.org/10.2307/1380119

53. Ortiz-Catedral, L., Christian, E., Chimborazo, W., Sevilla, C., & Rueda, D. (2021). A Galapagos centipede *Scolopendra galapagoensis* preys on a Floreana Racer *Pseudalsophis biserialis*. *Galapagos Research*, *70*, 2-4.

54. Menezes, J. C. T., & Marini, M. Â. (2017). Predators of bird nests in the Neotropics: a review. *Journal of Field Ornithology*, *88*(2), 99–114. https://doi.org/10.1111/jofo.12203

Page 20. *Before working in the Galápagos.*

55. Clay, T. (1958). Revisions of Mallophaga genera. *Degeeriella* from the Falconiformes. *Bulletin of the British Museum of Natural History, Entomology 7*: 121–

207. Accessed June 26 2023: https://www.biodiversitylibrary.org/page/2279225#page/137/mode/1up

56. Price, R. D., & Beer, J. R. (1963). Species of *Colpocephalum* (Mallophaga: Menoponidae) Parasitic upon the Falconiformes. *The Canadian Entomologist*, *95*(7), 731–763. https://doi.org/10.4039/Ent95731-7

Page 20. *I wanted to use mutations.*

57. Whiteman, N. K., & Parker, P. G. (2005). Using parasites to infer host population history: a new rationale for parasite conservation. *Animal Conservation*, *8*(2), 175–181. https://doi.org/10.1017/S1367943005001915

Page 20. *It was likely that each hawk.*

58. Koop, J. A. H., DeMatteo, K. E., Parker, P. G., & Whiteman, N. K. (2014). Birds are islands for parasites. *Biology Letters*, *10*(8), 20140255. https://doi.org/10.1098/rsbl.2014.0255

Page 21. *The first hawk that I "dust ruffled."*

59. Clayton, D. H. and Drown D. M. (2001). Critical evaluation of five methods for quantifying chewing lice (Insecta: Phthiraptera). *Journal of Parasitology 87*: 1291–1300. Accessed June 26, 2023: https://doi.org/10.1645/0022-3395(2001)087[1291:CEOFMF]2.0.CO;2.

Page 21. *Through our research.*

60. Whiteman, N. K., Kimball, R. T., & Parker, P. G. (2007). Co-phylogeography and comparative population genetics of the threatened Galápagos hawk and three ectoparasite species: ecology shapes population histories within parasite communities. *Molecular Ecology*, *16*(22), 4759–4773. https://doi.org/10.1111/j.1365-294X.2007.03512.x

Page 21. *The mangrove finch.*

61. Fessl, B., Young, G. H., Young, R. P., Rodríguez-Matamoros, J., Dvorak, M., Tebbich, S., & Fa, J. E. (2010). How to save the rarest Darwin's finch from extinction: the mangrove finch on Isabela Island. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *365*(1543), 1019–1030. https://doi.org/10.1098/rstb.2009.0288

Page 21. *It is being ravaged.*

62. O'Connor, J. A., Sulloway, F. J., Robertson, J., & Kleindorfer, S. (2010). *Philornis downsi* parasitism is the primary cause of nestling mortality in the critically endangered Darwin's medium tree finch (*Camarhynchus pauper*). *Biodiversity and Conservation*, *19*(3), 853–866. https://doi.org/10.1007/s10531-009-9740-1

Page 21. *To control these awful flies.*

63. Causton, C. E. & Lincango, M. P. (2014). Review of chemical control methods for use against *Philornis downsi* in nests of threatened Galapagos birds, with an in-depth nontarget risk assessment of permethrin. Technical report No 1-2014. *Charles Darwin Foundation for the Galapagos Islands*. ISSN: 1390-6526.

64. Tebbich, S., Cimadon, A., Cunninghame, F., Anchundia, D., Causton, C., and Fessl, B. (2019). Protocolo para la aplicación de insecticidas en la base de nidos de aves terrestres amenazadas en Galápagos. Informe Tecnico No. 03 2019. *Charles Darwin Foundation, Galapagos, Ecuador*. Not available online.

Page 21. *Cleverly, ecologist Sarah Knutie.*

65. Knutie, S. A., McNew, S. M., Bartlow, A. W., Vargas, D. A., & Clayton, D. H. (2014). Darwin's finches combat introduced nest parasites with fumigated cotton. *Current Biology*, *24*(9), R355–R356. https://doi.org/10.1016/j.cub.2014.03.058

Page 22. *Russet sparrows in China gather the leaves of wormwood.*

66. Yang, C., Ye, P., Huo, J., Møller, A. P., Liang, W., & Feeney, W. E. (2020). Sparrows use a medicinal herb to defend against parasites and increase offspring condition. *Current Biology*, *30*(23), R1411–R1412. https://doi.org/10.1016/j.cub.2020.10.021

Page 23. *In fact, those first used by Indigenous healers have yielded nearly 50% of all modern drugs*. This is primarily based on the World Health Organization's estimate of 40% (Ref. 67). However, it is not clear how that 40% figure was calculated. I found that it is possible to arrive at a figure near this independently, considering two elements. The first element is the proportion of modern drugs in the strict sense (e.g., those prepared by the pharmaceutical industry and/or clinical settings) that are from natural products or inspired from them (e.g., mimics, use a natural product as a core, etc.), and the second is the proportion of these drugs that are derived from Indigenous knowledge/traditional healing practices in the broadest sense (e.,g., traditional medicine henceforth). I provide information on each element below, which gives me confidence that the *nearly 50% of all modern drugs* claim is reasonable.

Percent of modern drugs from nature or inspired by it: This quote, by authors of a quantitative review of the literature speaks for itself (Ref. 68): "By 1990, about 80% of drugs were either natural products or analogs inspired by them. Antibiotics (e.g., penicillin, tetracycline, erythromycin), antiparasitics (e.g., avermectin), antimalarials (e.g., quinine, artemisinin), lipid control agents (e.g., lovastatin and analogs), immunosuppressants for organ transplants (e.g., cyclosporine, rapamycins) and anticancer drugs (e.g., taxol, doxorubicin) revolutionized medicine." A slightly lower figure for natural product-derived drugs as a percentage of the total is given for 1993, when over 50% of all drugs used in clinical settings were still derived from natural products or inspired by them (Ref. 69). Similar estimates were arrived at by others (e.g,. Ref. 70). This figure of ~50% remained the same (Ref. 71) for *new* drugs as well: of 1881 total drugs approved by the Food and Drug Administration (FDA) and similar entities (from 1981-

2019) at least 921 (49.44%) were derived from natural products or inspired by them--the "at least" is because this figure does not include "biological macromolecules" that were also approved, which would include proteins or peptides derived originally from natural sources (e.g., components of cone snail venom, snake venom, leech saliva, etc.). Just for cancer drugs alone since 1981, of 185 new small molecules approved for cancer treatment, 120, or 64.9% were derived from natural products or inspired by them (Ref. 71).

In summary, for new drugs (from 1981-2019), the estimate of those coming from nature or inspired by those molecules is likely *at least* 50%, assuming some of the "biological macromolecules" are of natural origin but created through recombinant technology. Coupled with older estimates (e.g,. Ref. 69 as an example), the 50% figure for modern drugs being of natural product origin or inspired by them, seems quite reasonable and conservative.

Percent of drugs from natural products or those inspired by them that emerged from traditional medicine *sensu lato*: In Ref. 72, Fabricant and Farnsworth (2001) cleverly sought (there are many other similar studies as well) to determine what proportion of drugs used in modern medicine were *also* found in medicinal plants (which doesn't include fungi, animals, bacteria, etc.) that were deployed in traditional medicine:

> "We were requested by the WHO Traditional Medicine Programme (TRM) several years ago to provide evidence that ethnomedical information did indeed lead to useful drug discovery. We sent letters to the WHO–TRM centers throughout the world asking for their assistance in identifying all plant-derived pure compounds used as drugs in their respective countries. In addition, we surveyed pharmacopoeias of developed and developing countries to identify all such useful drugs. Next we surveyed the scientific literature to find the original papers reporting isolation of these compounds from their respective plants. This was done to determine whether the chemical efforts were stimulated by ethnomedical claims and to correlate current uses for the compounds with such ethnomedical claims (2)."

In other words, the question was whether plant-derived modern drugs were already found in the pharmacopeias of traditional knowledge-holders. The idea is that this is a highly non-random association between a plant used in traditional medicine and the fact that a modern drug exists derived from that plant or inspired by a molecule in it, likely owing to the use of that plant by the traditional healers in the first instance. The answer was that of 122 plant-derived pure compounds identified by Fabricant and Farnsworth used as drugs by physicians around the world, 80% were found in plants used by traditional healers. Flowing from this, we can deduce that if ~50% of modern drugs are from natural products or inspired by them, and that this has remained true for decades, the vast majority of medicines were derived from plants and other organisms used by traditional healers. The critical assumption is that the reason these plants and other organisms were the focus of study by modern medicine was due to the knowledge from traditional healers that was transmitted to practitioners of science in the modern sense, and then folded into the industrialized pharmacopeia. This isn't to say there is necessarily a great fit between what ailments the traditional healers targeted with a particular plant (or other organism or concoction, etc.) and the ultimate drug and target developed by the pharmaceutical industry. Still, if we accept that ~50% of modern drugs from natural sources or inspired by them is conservative, and that the vast majority of those drugs are likely to be found in traditional medicines already, it is reasonable for WHO to claim that over 40% of modern drugs are derived from traditional medicines. Thus, the statement that "nearly 50% of all modern drugs" having been brought to light through the wisdom of Indigenous knowledge is reasonable.

67. Quote from WHO Global Centre for Traditional Medicine: "Over 40% of pharmaceutical formulations are based on natural products and landmark drugs, including aspirin and artemisinin, originated from traditional medicine." Accessed June 27, 2023: https://www.who.int/initiatives/who-global-centre-for-traditional-medicine

68. Li, J. W.-H., & Vederas, J. C. (2009). Drug Discovery and Natural Products: End of an Era or an Endless Frontier? *Science*, *325*(5937), 161–165. https://doi.org/10.1126/science.1168243

69. Balandrin, M. F., Kinghorn, A. D., & Farnsworth, N. R. (1993). Plant-Derived Natural Products in Drug Discovery and Development. In *Human Medicinal Agents from Plants* (Vol. 534, pp. 2–12). American Chemical Society. https://doi.org/doi:10.1021/bk-1993-0534.ch001

70. "In addition, 61% of all new chemical entities introduced worldwide as drugs during the same period could be traced to or were inspired by natural products." From: Newman, D. J., Cragg, G. M., & Snader, K. M. (2003). Natural Products as Sources of New Drugs over the Period 1981−2002. *Journal of Natural Products*, *66*(7), 1022–1037. https://doi.org/10.1021/np030096l

71. Newman, D. J., & Cragg, G. M. (2020). Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019. *Journal of Natural Products*, *83*(3), 770–803. https://doi.org/10.1021/acs.jnatprod.9b01285

72. Fabricant, D. S., & Farnsworth, N. R. (2001). The value of plants used in traditional medicine for drug discovery. *Environmental Health Perspectives*, *109*(suppl 1), 69–75. https://doi.org/10.1289/ehp.01109s169

Page 23. *Self-medication in the animal world, or zoopharmacogosy*.

73. Rodriguez, E., & Wrangham, R. (1993). Zoopharmacognosy: The Use of Medicinal Plants by Animals. In *Phytochemical Potential of Tropical Plants* (pp. 89–105). Springer US. https://doi.org/10.1007/978-1-4899-1783-6_4

Page 23. *In real life, the ancient Romans.*

74. https://herbaria.plants.ox.ac.uk/bol/plants400/Profiles/ab/Achillea.

75. Jaeger, E. C. (1944). *A Source-book of Biological Names and Terms (2nd ed.).* Charles C. Thomas, Springfield, IL.

76. Applequist, W. L., & Moerman, D. E. (2011). Yarrow (Achillea millefolium L.): A Neglected Panacea? A Review of Ethnobotany, Bioactivity, and Biomedical Research1. *Economic Botany*, *65*(2), 209–225. https://doi.org/10.1007/s12231-011-9154-3

77. Dioscorides P. Osbaldeston T. A. & Wood R. P. A. (2000). *De materia medica : A new indexed version in modern English.* Pp. 927. Ibidis Press, Johannesburg. ISBN 0-62023435.

Page 23. *In addition to expounding.*

78. Culpeper, N. (1995). *Culpeper's Complete Herbal: A Book of Natural Remedies of Ancient Ills* (The Wordsworth Collection Reference Library). NTC/Contemporary Publishing Company. ISBN 1-85326-345-1.

79. Quote "expels wind…" from: https://www.gutenberg.org/files/49513/49513-h/49513-h.htm.

Page 23. *Yarrow, chamomile and other daisies like wormwood.*

80. Culpeper, N. (1995). *Culpeper's Complete Herbal: A Book of Natural Remedies of Ancient Ills* (The Wordsworth Collection Reference Library). NTC/Contemporary Publishing Company. ISBN 1-85326-345-1.

81. Tu, Y. (2011). The discovery of artemisinin (qinghaosu) and gifts from Chinese medicine. *Nature Medicine*, *17*(10), 1217–1220. https://doi.org/10.1038/nm.2471

Page 24. *Amazingly, Neanderthals live on in*.

82. Green, R. E., Krause, J., Briggs, A. W., Maricic, T., Stenzel, U., Kircher, M., Patterson, N., Li, H., Zhai, W., Fritz, M. H.-Y., Hansen, N. F., Durand, E. Y., Malaspinas, A.-S., Jensen, J. D., Marques-Bonet, T., Alkan, C., Prüfer, K., Meyer, M., Burbano, H. A., … Pääbo, S. (2010). A Draft Sequence of the Neandertal Genome. *Science*, *328*(5979), 710–722. https://doi.org/10.1126/science.1188021

Page 25. *The more ancient*.

83. Green, R. E., Krause, J., Briggs, A. W., Maricic, T., Stenzel, U., Kircher, M., Patterson, N., Li, H., Zhai, W., Fritz, M. H.-Y., Hansen, N. F., Durand, E. Y., Malaspinas, A.-S., Jensen, J. D., Marques-Bonet, T., Alkan, C., Prüfer, K., Meyer, M., Burbano, H. A., … Pääbo, S. (2010). A Draft Sequence of the Neandertal Genome. *Science*, *328*(5979), 710–722. https://doi.org/10.1126/science.1188021

Page 25. *In addition to their DNA.*

84. Hoffmann, D. L., Standish, C. D., García-Diez, M., Pettitt, P. B., Milton, J. A., Zilhão, J., Alcolea-González, J. J., Cantalejo-Duarte, P., Collado, H., de Balbín, R., Lorblanchet, M., Ramos-Muñoz, J., Weniger, G.-Ch., & Pike, A. W. G. (2018). U-

Th dating of carbonate crusts reveals Neandertal origin of Iberian cave art. *Science*, *359*(6378), 912–915. https://doi.org/10.1126/science.aap7778

Page 25. *Based on their cranial sizes.*

85. Holloway, R. L. (1981). Volumetric and asymmetry determinations on recent hominid endocasts: Spy I and II, Djebel Ihroud I, and the salè *Homo erectus* specimens, with some notes on neandertal brain size. *American Journal of Physical Anthropology*, *55*(3), 385–393. https://doi.org/10.1002/ajpa.1330550312

Page 25. *Neanderthals also probably share our ability.*

86. Lalueza-Fox, C., Gigli, E., de la Rasilla, M., Fortea, J., & Rosas, A. (2009). Bitter taste perception in Neanderthals through the analysis of the *TAS2R38* gene. *Biology Letters*, *5*(6), 809–811. https://doi.org/10.1098/rsbl.2009.0532

Page 25. *People vary.*

87. Fox, A. L. (1932). The Relationship between Chemical Constitution and Taste. *Proceedings of the National Academy of Sciences*, *18*(1), 115–120. https://doi.org/10.1073/pnas.18.1.115

88. Harris, H., & Kal, us, H. (1949). The measurement of taste sensitivity to phenylthiourea (P.T.C.). *Annals of Eugenics*, *15*(1), 24–31. https://doi.org/10.1111/j.1469-1809.1949.tb02419.x

89. Reddy, B. M., Rao, D. C., & MacCluer, J. W. (1989). Phenylthiocarbamide taste sensitivity revisited: Complete sorting test supports residual family resemblance. *Genetic Epidemiology*, *6*(3), 413–421. https://doi.org/10.1002/gepi.1370060304

Page 25. *This difference.*

90. Kim, U., Jorgenson, E., Coon, H., Leppert, M., Risch, N., & Drayna, D. (2003). Positional Cloning of the Human Quantitative Trait Locus Underlying Taste Sensitivity to Phenylthiocarbamide. *Science*, *299*(5610), 1221–1225. https://doi.org/10.1126/science.1080190

Page 25. *The bones of seven Neanderthal.*

91. Rosas Gonzalez, A., Estalrrich, A., García-Tabernero, A., Huguet, R., Lalueza-Fox, C., Ríos, L., Bastir, M., Fernández-Cascón, B., Perez-Criado, L., Rodriguez-Perez, F. J., Ferrando, A., Fernández-Cerezo, S., Sierra, E., & de la Rasilla, M. (2015). Paleoanthropological research of the neandertal fossils from
92. El Sidrón (Asturias, Spain). *Cuaternario y Geomorfología*, *29*(3–4), 77–94. https://doi.org/10.17735/cyg.v29i3-4.40066

93. Rosas, A., Ríos, L., Estalrrich, A., Liversidge, H., García-Tabernero, A., Huguet, R., Cardoso, H., Bastir, M., Lalueza-Fox, C., de la Rasilla, M., & Dean, C. (2017).

The growth pattern of Neandertals, reconstructed from a juvenile skeleton from El Sidrón (Spain). *Science*, *357*(6357), 1282–1287. https://doi.org/10.1126/science.aan6463

Page 25. *Scientists scraped the calcified tartar.*

94. Hardy, K., Buckley, S., Collins, M. J., Estalrrich, A., Brothwell, D., Copeland, L., García-Tabernero, A., García-Vargas, S., Rasilla, M., Lalueza-Fox, C., Huguet, R., Bastir, M., Santamaría, D., Madella, M., Wilson, J., Cortés, Á. F., & Rosas, A. (2012). Neanderthal medics? Evidence for food, cooking, and medicinal plants entrapped in dental calculus. *Naturwissenschaften*, *99*(8), 617–626. https://doi.org/10.1007/s00114-012-0942-0

95. Weyrich, L. S., Duchene, S., Soubrier, J., Arriola, L., Llamas, B., Breen, J., Morris, A. G., Alt, K. W., Caramelli, D., Dresely, V., Farrell, M., Farrer, A. G., Francken, M., Gully, N., Haak, W., Hardy, K., Harvati, K., Held, P., Holmes, E. C., … Cooper, A. (2017). Neanderthal behaviour, diet, and disease inferred from ancient DNA in dental calculus. *Nature*, *544*(7650), 357–361. https://doi.org/10.1038/nature21674

Page 26. *So perhaps Sid knew what he was doing.*

96. Hardy, K. (2021). Paleomedicine and the Evolutionary Context of Medicinal Plant Use. *Revista Brasileira de Farmacognosia*, *31*(1), 1–15. https://doi.org/10.1007/s43450-020-00107-4

Page 27. *We diverged from a most.*

97. Langergraber, K. E., Prüfer, K., Rowney, C., Boesch, C., Crockford, C., Fawcett, K., Inoue, E., Inoue-Muruyama, M., Mitani, J. C., Muller, M. N., Robbins, M. M., Schubert, G., Stoinski, T. S., Viola, B., Watts, D., Wittig, R. M., Wrangham, R. W., Zuberbühler, K., Pääbo, S., & Vigilant, L. (2012). Generation times in wild chimpanzees and gorillas suggest earlier divergence times in great ape and human evolution. *Proceedings of the National Academy of Sciences*, *109*(39), 15716–15721. https://doi.org/10.1073/pnas.1211740109

Page 27. *People use them to treat.*

98. Burkill, H. M. (1985). *The Useful Plants of West Tropical Africa, Vol. 1. 2nd ed.* . Kew (UK): Royal Botanical Gardens.

99. Huffman, M. A. (2001). Self-Medicative Behavior in the African Great Apes: An Evolutionary Perspective into the Origins of Human Traditional Medicine: In addition to giving us a deeper understanding of our closest living relatives, the study of great ape self-medication provides a window into the origins of herbal medicine use by humans and promises to provide new insights into ways of treating parasite infections and other serious diseases. *BioScience*, *51*(8), 651–661. https://doi.org/10.1641/0006-3568(2001)051[0651:SMBITA]2.0.CO;2

Page 27. *In 1989.*

100. Huffman, M. A., & Seifu, M. (1989). Observations on the illness and consumption of a possibly medicinal plant *Vernonia amygdalina* (Del.), by a wild chimpanzee in the Mahale Mountains National Park, Tanzania. *Primates*, *30*(1), 51–63. https://doi.org/10.1007/BF02381210

Page 28. *Over the next decade.*

101. Huffman, M. A., Gotoh, S., Turner, L. A., Hamai, M., & Yoshida, K. (1997). Seasonal trends in intestinal nematode infection and medicinal plant use among chimpanzees in the Mahale Mountains, Tanzania. *Primates*, *38*(2), 111–125. https://doi.org/10.1007/BF02382002

Page 28. *Not only is food.*

102. Rodriguez, E., & Wrangham, R. (1993). Zoopharmacognosy: The Use of Medicinal Plants by Animals. In *Phytochemical Potential of Tropical Plants* (pp. 89–105). Springer US. https://doi.org/10.1007/978-1-4899-1783-6_4

Page 28. *Gorillas and orangutans.*

103. Huffman, M. A. (1997). Current evidence for self-medication in primates: A multidisciplinary perspective. *American Journal of Physical Anthropology*, *104*(S25), 171–200. https://onlinelibrary.wiley.com/doi/abs/10.1002/(SICI)1096-8644(1997)25+%3C171::AID-AJPA7%3E3.0.CO;2-7.

104. Morrogh-Bernard, H. C. (2008). Fur-Rubbing as a Form of Self-Medication in *Pongo pygmaeus*. *International Journal of Primatology*, *29*(4), 1059–1064. https://doi.org/10.1007/s10764-008-9266-5

105. de la Fuente, M. F., Souto, A., Albuquerque, U. P., & Schiel, N. (2022). Self-medication in nonhuman primates: A systematic evaluation of the possible function of the use of medicinal plants. *American Journal of Primatology*, *84*(11). https://doi.org/10.1002/ajp.23438

Page 28. *For example, in Borneo.*

106. Morrogh-Bernard, H. C., Foitová, I., Yeen, Z., Wilkin, P., de Martin, R., Rárová, L., Doležal, K., Nurcahyo, W., & Olšanský, M. (2017). Self-medication by orangutans (*Pongo pygmaeus*) using bioactive properties of *Dracaena cantleyi*. *Scientific Reports*, *7*(1), 16653. https://doi.org/10.1038/s41598-017-16621-w

Page 29. *Indigenous people.*

107. From abstract of below reference: "In Central Kalimantan, local indigenous people use the same species as an external medication to treat their arms after a stroke, for muscular pain, and for sore bones and swellings. Morrogh-Bernard, H. C. (2008). Fur-Rubbing as a Form of Self-Medication in *Pongo pygmaeus*. *International Journal of Primatology*, *29*(4), 1059–1064. https://doi.org/10.1007/s10764-008-9266-5

Page 28. *The main toxic constituent*.

108. Gupta, D., Bleakley, B., & Gupta, R. K. (2008). Dragon's blood: Botany, chemistry and therapeutic uses. *Journal of Ethnopharmacology*, *115*(3), 361–380. https://doi.org/10.1016/j.jep.2007.10.018

109. Kougan, G. B., Miyamoto, T., Tanaka, C., Paululat, T., Mirjolet, J.-F., Duchamp, O., Sondengam, B. L., & Lacaille-Dubois, M.-A. (2010). Steroidal Saponins from Two Species of *Dracaena*. *Journal of Natural Products*, *73*(7), 1266–1270. https://doi.org/10.1021/np100153m

110. Tapondjou, L. A., Ponou, K. B., Teponno, R. B., Mbiantcha, M., Djoukeng, J. D., Nguelefack, T. B., Watcho, P., Cadenas, A. G., & Park, H.-J. (2008). In vivo anti-inflammatory effect of a new steroidal saponin, mannioside A, and its derivatives isolated from *Dracaena mannii*. *Archives of Pharmacal Research*, *31*(5), 653–658. https://doi.org/10.1007/s12272-001-1208-3

Page 28. *We use some of these plants*.

111. Konkol, K. L., & Rasmussen, S. C. (2015). *An Ancient Cleanser: Soap Production and Use in Antiquity* (pp. 245–266). https://doi.org/10.1021/bk-2015-1211.ch009

112. Martín, R. S., & Briones, R. (1999). Industrial uses and sustainable supply of *Quillaja saponaria* (Rosaceae) saponins. *Economic Botany*, *53*(3), 302–311. https://doi.org/10.1007/BF02866642

Page 28. *Remarkably, a saponin*.

113. Pulendran, B., S. Arunachalam, P., & O'Hagan, D. T. (2021). Emerging concepts in the science of vaccine adjuvants. *Nature Reviews Drug Discovery*, *20*(6), 454–475. https://doi.org/10.1038/s41573-021-00163-y

114. *Our Matrix-M™ adjuvant technology*. (n.d.). Retrieved June 29, 2023, from https://www.novavax.com/science-technology/matrix-m-adjuvant-technology

Chapter 2. Forests of Phenolics and Flavonoids

Page 30. *The chemicals leaching*. This refers to the tannins (tinting agents) and saponins (foaming agents) that many plants produce. "Root beer" from sarsaparilla root is one way this tonic was made by Indigenous and local people (from *Smilax ornata*, a plant native to Mexico and Central America) and it is possible that the saponins from this plant are responsible for the foaming effect, but see Ref. 109 below, which takes a more skeptical view given the concentrations involved. Another form of "root beer" was often made from sassafras root (*Sassafras albidum*), originally by Native Americans, until it was discovered that safrole was carcinogenic. Although some producers (e.g., Bundaberg) use sarsaparilla still, nowadays, some commercial beverage makers use saponins from other species like *Quillaja saponaria* to produce the foaming effect in some soft drinks. Sarsaparilla is both a drink and a reference to the plant, and root beer may or may not refer to sarsaparilla. For a light-hearted discussion of this issue see Ref. 111. Saponins are one, but not the only mechanism for the production of foam in blackwater rivers. Tannins in the strict sense, and phenolics in the broadest sense, contribute in a major way to the tinting of blackwater rivers.

115. Britannica, T. Editors of Encyclopaedia (2013, May 2). *sarsaparilla*. *Encyclopedia Britannica*. https://www.britannica.com/topic/sarsaparilla

116. Leung, A. Y. (1980). *Encyclopedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics*. John Wiley & Sons, New York.

117. Dietz, B., & Bolton, J. L. (2007). Botanical Dietary Supplements Gone Bad. *Chemical Research in Toxicology*, *20*(4), 586–590. https://doi.org/10.1021/tx7000527

118. *The difference between root beer and sarsaparilla*. (n.d.). Retrieved June 30, 2023, from https://www.bundaberg.com/en-us/the-difference-between-root-beer-and-sarsaparilla/

119. Janzen, D. H. (1974). Tropical Blackwater Rivers, Animals, and Mast Fruiting by the Dipterocarpaceae. *Biotropica*, *6*(2), 69. https://doi.org/10.2307/2989823

Page 31. *Nonetheless, some white wines*.

120. "Total phenolic content (absorbance at 280 nm) was higher for white wines (Picapoll and Chardonnay) fermented in oak barrels than in stainless steel vats." From:
Ibern-Gómez, M., Andrés-Lacueva, C., Lamuela-Raventós, R. M., Lao-Luque, C., Buxaderas, S., & de la Torre-Boronat, M. C. (2001). Differences in Phenolic Profile between Oak Wood and Stainless Steel Fermentation in White Wines. *American Journal of Enology and Viticulture*, *52*(2), 159–164. https://doi.org/10.5344/ajev.2001.52.2.159

Page 31. *The individual gallic acid molecules*.

121. *Tannic Acid*. (n.d.). Retrieved June 29, 2023, from https://www.acs.org/molecule-of-the-week/archive/t/tannic-acid.html

Page 31. *Although the structure is satisfying to the eye, it takes precious energy*. The general idea is that constitutive (always present) and inducible (produced after attack) chemical defenses/deterrents, toxins *sensu lato* are costly to plant fitness (survival odds and reproductive output) in the absence of enemies. In the presence of enemies these chemical defenses/deterrents enhance fitness over what it would be if the plants didn't make them or as much of them. The proximal cause of the enhanced fitness in the face of competition between plant genotypes (species) for resources (see August Pyramus de Candolle's quote "All the plants of a given country, all those of a given place, are at war with one another." in Chapter 3). Those plants able to survive and reproduce better than the others in this scenario are those that have enhanced defenses when in natural environments where attack by enemies like herbivores and microbial pathogens is *de rigueur*. The experimental, mechanistic evidence for this is strong and a few examples are given below, some of which take advantage of mutants wherein the principal chemical defense pathways are absent, or herbivores are excluded using pesticides, essentially lifting the governor on plant fitness as mediated by herbivory. The conclusion is that chemical defenses are costly to make in the absence of herbivores from a fitness perspective, and provide a benefit in the presence of herbivores generally that surmounts this cost and allows those endowed with the capacity to outcompete other plant genotypes. However, the chemical pathways to produce these chemicals and the chemicals themselves may also have other effects on the plant's biology that are divorced from the defensive function per se. Put another way, pleiotropy–the effect of one gene on more than one trait in an organism-is pervasive.

122. Schultz, J. C., & Baldwin, I. T. (1982). Oak Leaf Quality Declines in Response to Defoliation by Gypsy Moth Larvae. *Science*, *217*(4555), 149–151. https://doi.org/10.1126/science.217.4555.149

123. Coley, P. D., Bryant, J. P., & Chapin, F. S. (1985). Resource Availability and Plant Antiherbivore Defense. *Science*, *230*(4728), 895–899. https://doi.org/10.1126/science.230.4728.895

124. Mauricio, R., & Rausher, M. D. (1997). Experimental manipulation of putative selective agents provides evidence for the role of natural enemies in the evolution of plant defense. *Evolution*, *51*(5), 1435–1444. https://doi.org/10.1111/j.1558-5646.1997.tb01467.x

125. Baldwin, I. T. (1998). Jasmonate-induced responses are costly but benefit plants under attack in native populations. *Proceedings of the National Academy of Sciences*, *95*(14), 8113–8118. https://doi.org/10.1073/pnas.95.14.8113

126. Kessler, A., Halitschke, R., & Baldwin, I. T. (2004). Silencing the Jasmonate Cascade: Induced Plant Defenses and Insect Populations. *Science*, *305*(5684), 665–668. https://doi.org/10.1126/science.1096931

127. Zangerl, A. R., & Berenbaum, M. R. (2005). Increase in toxicity of an invasive weed after reassociation with its coevolved herbivore. *Proceedings of the National Academy of Sciences*, *102*(43), 15529–15532. https://doi.org/10.1073/pnas.0507805102

128. Züst, T., Joseph, B., Shimizu, K. K., Kliebenstein, D. J., & Turnbull, L. A. (2011). Using knockout mutants to reveal the growth costs of defensive traits. *Proceedings of the Royal Society B: Biological Sciences*, *278*(1718), 2598–2603. https://doi.org/10.1098/rspb.2010.2475

129. Agrawal, A. A., Hastings, A. P., Johnson, M. T. J., Maron, J. L., & Salminen, J.-P. (2012). Insect Herbivores Drive Real-Time Ecological and Evolutionary Change in Plant Populations. *Science*, *338*(6103), 113–116. https://doi.org/10.1126/science.1225977

Page 32. *Hydrolyzable tannins are derived from phenolic.* This refers to the shikimate pathway.

130. Muir, R. M., Ibáñez, A. M., Uratsu, S. L., Ingham, E. S., Leslie, C. A., McGranahan, G. H., Batra, N., Goyal, S., Joseph, J., Jemmis, E. D., & Dandekar, A. M. (2011). Mechanism of gallic acid biosynthesis in bacteria (Escherichia coli) and walnut (Juglans regia). *Plant Molecular Biology*, *75*(6), 555–565. https://doi.org/10.1007/s11103-011-9739-3

Page 32. *Condensed tannins are flavonoids made by a more recently evolved.* This refers to the phenylpropanoid pathway.

131. Chapple, C. C., Vogt, T., Ellis, B. E., & Somerville, C. R. (1992). An Arabidopsis mutant defective in the general phenylpropanoid pathway. *The Plant Cell*, *4*(11), 1413–1424. https://doi.org/10.1105/tpc.4.11.1413

Page 32. *Remarkably, gallotannins and other*.

132. Aigner, S., Remias, D., Karsten, U., & Holzinger, A. (2013). Unusual phenolic compounds contribute to ecophysiological performance in the purple-colored green alga *Zygogonium ericetorum* (Zygnematophyceae, Streptophyta) from a high-alpine habitat. *Journal of Phycology*, *49*(4), 648–660. https://doi.org/10.1111/jpy.12075

133. Newsome, A., & van Breemen, R. (2012). Characterization of the purple vacuolar pigment of *Zygogonium ericatorum* alga. *Planta Medica*, *78*(11). https://doi.org/10.1055/s-0032-1321180

Page 32. *Ultraviolet (UVB) light is highly damaging to DNA.* UVB causes dimers to form between nucleotide sequences, often along the same DNA strand of the double-helix. Common dimers are cyclobutane pyrimidine dimers that then prevent the DNA from being transcribed into RNA or being replicated into DNA. An interesting example of the real-world effects of enhanced UVB radiation on terrestrial organisms (plants) is below, which was associated with "ozone hole" over Antarctica caused by anthropogenic chlorofluorocarbons that passed over southern Southern America in 1997.

134. Rousseaux, M. C., Ballaré, C. L., Giordano, C. v., Scopel, A. L., Zima, A. M., Szwarcberg-Bracchitta, M., Searles, P. S., Caldwell, M. M., & Díaz, S. B. (1999). Ozone depletion and UVB radiation: Impact on plant DNA damage in southern South America. *Proceedings of the National Academy of Sciences*, *96*(26), 15310–15315. https://doi.org/10.1073/pnas.96.26.15310

Page 32. *UVB light rapidly dissipates.* (A) Suspended sediment (causing turbidity), pigmented phytoplankton that absorb some wavelengths of light (algae), and dissolved organic carbon (DOC) within water, absorb much of the UVB light in the water column. Yet, the variation in the degree of UVB attenuation is substantial across different bodies of both freshwater and saltwater. Moreover, there is non-trivial UVB penetration just below the surface that attenuates with depth, but the extent of this depends on many different factors. Algae growing underwater are more protected from the cumulative effects of UVB radiation on DNA damage compared to algae or plants growing on land. (B) Algae growing near the surface of the water certainly produce myriad chemicals to shield from UVB. For example, dinoflagellates that live as symbionts in corals, can be susceptible to UVB-driven DNA damage and indeed have evolved many different compounds that provide UVB protection. More generally, there is some controversy as to the importance of the higher UVB incidence on land in preventing its colonization by early life forms.

135. Dunne, R. P., & Brown, B. E. (1996). Penetration of solar UVB radiation in shallow tropical waters and its potential biological effects on coral reefs; results from the central Indian Ocean and Andaman Sea. *Marine Ecology Progress Series*, *144*(1/3), 109–118. https://www.int-res.com/articles/meps/144/m144p109.pdf.

136. Tedetti, M., & Sempéré, R. (2006). Penetration of Ultraviolet Radiation in the Marine Environment. A Review. *Photochemistry and Photobiology*, *82*(2), 389. https://doi.org/10.1562/2005-11-09-IR-733

137. V.-Balogh, K., Németh, B., & Vörös, L. (2009). Specific attenuation coefficients of optically active substances and their contribution to the underwater ultraviolet and visible light climate in shallow lakes and ponds. *Hydrobiologia*, *632*(1), 91–105. https://doi.org/10.1007/s10750-009-9830-9

138. De Mora, S., Demers, S., & Vernet, M. (Eds.). (2000). *The Effects of UV Radiation in the Marine Environment* (Cambridge Environmental Chemistry Series). Cambridge: Cambridge University Press. https://doi.org/10.1017/CBO9780511535444

139. Wiencke, C., Gómez, I., Pakker, H., Flores-Moya, A., Altamirano, M., Hanelt, D., Bischof, K., & Figueroa, F. (2000). Impact of UV-radiation on viability, photosynthetic characteristics and DNA of brown algal zoospores:implications for depth zonation. *Marine Ecology Progress Series*, *197*, 217–229. https://doi.org/10.3354/meps197217

140. Caldwell, M. M. (1971). Solar UV irradiation and the growth and development of higher plants. *Photophysiology*, 6, 131-177.

141. Karentz, D., McEuen, F. S., Land, M. C., & Dunlap, W. C. (1991). Survey of mycosporine-like amino acid compounds in Antarctic marine organisms: Potential protection from ultraviolet exposure. *Marine Biology*, *108*(1), 157–166. https://doi.org/10.1007/BF01313484

142. Garcia-Pichel, F., & Castenholz, R. W. (1993). Occurrence of UV-Absorbing, Mycosporine-Like Compounds among Cyanobacterial Isolates and an Estimate of Their Screening Capacity. *Applied and Environmental Microbiology*, *59*(1), 163–169. https://doi.org/10.1128/aem.59.1.163-169.1993

143. Banaszak, A. T., & Lesser, M. P. (2009). Effects of solar ultraviolet radiation on coral reef organisms. *Photochemical & Photobiological Sciences*, *8*(9), 1276–1294. https://doi.org/10.1039/b902763g

144. Berkner, L. v., & Marshall, L. C. (1965). History of major atmospheric components. *Proceedings of the National Academy of Sciences*, *53*(6), 1215–1226. https://doi.org/10.1073/pnas.53.6.1215

145. Cockell, C. S., & Raven, J. A. (2007). Ozone and life on the Archaean Earth. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences*, *365*(1856), 1889–1901. https://doi.org/10.1098/rsta.2007.2049

Page 32. *When Zygnematophyceae* algae.

146. Alston, R. E. (1958). An investigation of the purple vacuolar pigment of *Zygogonium ericetorum* and the status of "algal anthocyanins" and "phycoporphyrins." *American Journal of Botany*, *45*(9), 688–692. https://doi.org/10.1002/j.1537-2197.1958.tb12223.x

147. Newsome, A., & van Breemen, R. (2012). Characterization of the purple vacuolar pigment of *Zygogonium ericatorum* alga. *Planta Medica*, *78*(11). https://doi.org/10.1055/s-0032-1321180

148. Aigner, S., Remias, D., Karsten, U., & Holzinger, A. (2013). Unusual phenolic compounds contribute to ecophysiological performance in the purple-colored green alga *Zygogonium ericetorum* (Zygnematophyceae, Streptophyta) from a high-alpine habitat. *Journal of Phycology*, *49*(4), 648–660. https://doi.org/10.1111/jpy.12075

149. Herburger, K., Remias, D., & Holzinger, A. (2016). The green alga *Zygogonium ericetorum* (Zygnematophyceae, Charophyta) shows high iron and aluminium tolerance: protection mechanisms and photosynthetic performance. *FEMS Microbiology Ecology*, *92*(8), fiw103. https://doi.org/10.1093/femsec/fiw103

Page 32. *When these algae grow on ice*.

150. Remias, D., Schwaiger, S., Aigner, S., Leya, T., Stuppner, H., & Lütz, C. (2012). Characterization of an UV- and VIS-absorbing, purpurogallin-derived secondary pigment new to algae and highly abundant in *Mesotaenium berggrenii* (Zygnematophyceae, Chlorophyta), an extremophyte living on glaciers. *FEMS Microbiology Ecology*, *79*(3), 638–648. https://doi.org/10.1111/j.1574-6941.2011.01245.x

151. Yallop, M. L., Anesio, A. M., Perkins, R. G., Cook, J., Telling, J., Fagan, D., MacFarlane, J., Stibal, M., Barker, G., Bellas, C., Hodson, A., Tranter, M., Wadham, J., & Roberts, N. W. (2012). Photophysiology and albedo-changing potential of the ice algal community on the surface of the Greenland ice sheet. *The ISME Journal*, *6*(12), 2302–2313. https://doi.org/10.1038/ismej.2012.107

Page 32. *Once plants evolved on land.*

152. "Of several people who tasted the aqueous extract, several reported a bitter or astringent taste." From:
Alston, R. E. (1958). An investigation of the purple vacuolar pigment of *Zygogonium ericetorum* and the status of "algal anthocyanins" and "phycoporphyrins." *American Journal of Botany*, *45*(9), 688–692. https://doi.org/10.1002/j.1537-2197.1958.tb12223.x

153. Yallop, M. L., Anesio, A. M., Perkins, R. G., Cook, J., Telling, J., Fagan, D., MacFarlane, J., Stibal, M., Barker, G., Bellas, C., Hodson, A., Tranter, M., Wadham, J., & Roberts, N. W. (2012). Photophysiology and albedo-changing potential of the ice algal community on the surface of the Greenland ice sheet. *The ISME Journal*, *6*(12), 2302–2313. https://doi.org/10.1038/ismej.2012.107

154. Feeny, P. (1970). Seasonal Changes in Oak Leaf Tannins and Nutrients as a Cause of Spring Feeding by Winter Moth Caterpillars. *Ecology*, *51*(4), 565–581. https://doi.org/10.2307/1934037

155. Feeny, P. (1976). Plant Apparency and Chemical Defense. In *Biochemical Interaction Between Plants and Insects* (pp. 1–40). Springer US. https://doi.org/10.1007/978-1-4684-2646-5_1

156. Hay, M. E., & Fenical, W. (1988). Marine Plant-Herbivore Interactions: The Ecology of Chemical Defense. *Annual Review of Ecology and Systematics*, *19*(1), 111–145. https://doi.org/10.1146/annurev.es.19.110188.000551

157. Bernays, E. A., Driver, G. C., & Bilgener, M. (1989). *Herbivores and Plant Tannins* (pp. 263–302). https://doi.org/10.1016/S0065-2504(08)60160-9

158. Schultz, J. C., Hunter, M. D., & Appel, H. M. (1992). Antimicrobial Activity of Polyphenols Mediates Plant-Herbivore Interactions. In *Plant Polyphenols* (pp. 621–637). Springer US. https://doi.org/10.1007/978-1-4615-3476-1_35

159. Quideau, S., Feldman, K. S., & Appel, H. M. (1995). Chemistry of Gallotannin-Derived o-Quinones: Reactivity toward Nucleophiles. *The Journal of Organic Chemistry*, *60*(16), 4982–4983. https://doi.org/10.1021/jo00121a012

160. Ossipov, V., Haukioja, E., Ossipova, S., Hanhimäki, S., & Pihlaja, K. (2001). Phenolic and phenolic-related factors as determinants of suitability of mountain birch leaves to an herbivorous insect. *Biochemical Systematics and Ecology*, *29*(3), 223–240. https://doi.org/10.1016/S0305-1978(00)00069-7

Page 33. *Condensed tannins evolved more recently.* References below outline the origins of the phenylpropanoid pathway in plants and the potential antecedents of that pathway in some of their closest living algal relatives.

161. Delwiche, C. F., Graham, L. E., & Thomson, N. (1989). Lignin-Like Compounds and Sporopollen in *Coleochaete* , an Algal Model for Land Plant Ancestry. *Science*, *245*(4916), 399–401. https://doi.org/10.1126/science.245.4916.399

162. Sørensen, I., Pettolino, F. A., Bacic, A., Ralph, J., Lu, F., O'Neill, M. A., Fei, Z., Rose, J. K. C., Domozych, D. S., & Willats, W. G. T. (2011). The charophycean green algae provide insights into the early origins of plant cell walls. *The Plant Journal*, *68*(2), 201–211. https://doi.org/10.1111/j.1365-313X.2011.04686.x

163. Brillouet, J.-M., Romieu, C., Schoefs, B., Solymosi, K., Cheynier, V., Fulcrand, H., Verdeil, J.-L., & Conéjéro, G. (2013). The tannosome is an organelle forming condensed tannins in the chlorophyllous organs of Tracheophyta. *Annals of Botany*, *112*(6), 1003–1014. https://doi.org/10.1093/aob/mct168

164. de Vries, S., Fürst-Jansen, J. M. R., Irisarri, I., Dhabalia Ashok, A., Ischebeck, T., Feussner, K., Abreu, I. N., Petersen, M., Feussner, I., & de Vries, J. (2021). The evolution of the phenylpropanoid pathway entailed pronounced radiations and divergences of enzyme families. *The Plant Journal*, *107*(4), 975–1002. https://doi.org/10.1111/tpj.15387

165. Rieseberg, T. P., Dadras, A., Fürst-Jansen, J. M. R., Dhabalia Ashok, A., Darienko, T., de Vries, S., Irisarri, I., & de Vries, J. (2023). Crossroads in the evolution of plant specialized metabolism. *Seminars in Cell & Developmental Biology*, *134*, 37–58. https://doi.org/10.1016/j.semcdb.2022.03.004

Page 33. *Made of two or more catechin.*

166. Mole, S. (1993). The systematic distribution of tannins in the leaves of angiosperms: A tool for ecological studies. *Biochemical Systematics and Ecology*, *21*(8), 833–846. https://doi.org/10.1016/0305-1978(93)90096-A

167. Puupponen-Pimia, R., Nohynek, L., Meier, C., Kahkonen, M., Heinonen, M., Hopia, A., & Oksman-Caldentey, K.-M. (2001). Antimicrobial properties of

phenolic compounds from berries. *Journal of Applied Microbiology*, *90*(4), 494–507. https://doi.org/10.1046/j.1365-2672.2001.01271.x

Page 33. *In moderate amounts*.

168. Chung, K.-T., Wei, C.-I., & Johnson, M. G. (1998). Are tannins a double-edged sword in biology and health? *Trends in Food Science & Technology*, *9*(4), 168–175. https://doi.org/10.1016/S0924-2244(98)00028-4

169. Maugeri, A., Lombardo, G. E., Cirmi, S., Süntar, I., Barreca, D., Laganà, G., & Navarra, M. (2022). Pharmacology and toxicology of tannins. *Archives of Toxicology*, *96*(5), 1257–1277. https://doi.org/10.1007/s00204-022-03250-0

Page 33. *Around 10 percent*.

170. Graham, H. N. (1992). Green tea composition, consumption, and polyphenol chemistry. *Preventive Medicine*, *21*(3), 334–350. https://doi.org/10.1016/0091-7435(92)90041-F

Page 33. *The most abundant one.*

171. Bieschke, J., Russ, J., Friedrich, R. P., Ehrnhoefer, D. E., Wobst, H., Neugebauer, K., & Wanker, E. E. (2010). EGCG remodels mature α-synuclein and amyloid-β fibrils and reduces cellular toxicity. *Proceedings of the National Academy of Sciences*, *107*(17), 7710–7715. https://doi.org/10.1073/pnas.0910723107

172. Borges, C. M., Papadimitriou, A., Duarte, D. A., Lopes de Faria, J. M., & Lopes de Faria, J. B. (2016). The use of green tea polyphenols for treating residual albuminuria in diabetic nephropathy: A double-blind randomised clinical trial. *Scientific Reports*, *6*(1), 28282. https://doi.org/10.1038/srep28282

Page 33. *However, EGCG pills*.

173. Younes, M., Aggett, P., Aguilar, F., Crebelli, R., Dusemund, B., Filipič, M., Frutos, M. J., Galtier, P., Gott, D., Gundert-Remy, U., Lambré, C., Leblanc, J., Lillegaard, I. T., Moldeus, P., Mortensen, A., Oskarsson, A., Stankovic, I., Waalkens-Berendsen, I., Woutersen, R. A., … Wright, M. (2018). Scientific opinion on the safety of green tea catechins. *EFSA Journal*, *16*(4). https://doi.org/10.2903/j.efsa.2018.5239

Page 33. *I became aware of the dangers*.

174. Patel, S. S. (2013). Green tea extract: A potential cause of acute liver failure. *World Journal of Gastroenterology*, *19*(31), 5174. https://doi.org/10.3748/wjg.v19.i31.5174

Page 33. *The US National Institutes of Health*.

175. Hoofnagle, J. H. (2013). Chapter 40 - LiverTox: A website on drug-induced liver Injury. Editor(s): N. Kaplowitz, and L. D. DeLeve. *Drug-Induced Liver Disease* (3rd Edition), Academic Press, Pp. 725–732. Accessed July 3, 2023: https://doi.org/10.1016/B978-0-12-387817-5.00040-6.

Page 33. *LiverTox focuses on toxins*.

176. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; (2012-). Available from: https://www.ncbi.nlm.nih.gov/books/NBK547852/

Page 34. *Stilbenoids are one of these.* References below relate to to what extent the stilbenoid resveratrol may or may not have as an anti-aging “drug” or to treat disease. Resveratrol’s role in anti-aging via activation of sirtuins (proteins involved in metabolic activation) remains a highly contested topic in the scientific literature.

177. Howitz, K. T., Bitterman, K. J., Cohen, H. Y., Lamming, D. W., Lavu, S., Wood, J. G., Zipkin, R. E., Chung, P., Kisielewski, A., Zhang, L.-L., Scherer, B., & Sinclair, D. A. (2003). Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan. *Nature*, *425*(6954), 191–196. https://doi.org/10.1038/nature01960

178. Wood, J. G., Rogina, B., Lavu, S., Howitz, K., Helfand, S. L., Tatar, M., & Sinclair, D. (2004). Sirtuin activators mimic caloric restriction and delay ageing in metazoans. *Nature*, *430*(7000), 686–689. https://doi.org/10.1038/nature02789

179. Burnett, C., Valentini, S., Cabreiro, F., Goss, M., Somogyvári, M., Piper, M. D., Hoddinott, M., Sutphin, G. L., Leko, V., McElwee, J. J., Vazquez-Manrique, R. P., Orfila, A.-M., Ackerman, D., Au, C., Vinti, G., Riesen, M., Howard, K., Neri, C., Bedalov, A., … Gems, D. (2011). Absence of effects of Sir2 overexpression on lifespan in C. elegans and Drosophila. *Nature*, *477*(7365), 482–485. https://doi.org/10.1038/nature10296

180. Related to a trial of a proprietary formulation of resveratrol as a multiple myeloma treatment: “a mid-stage Phase II study of SRT501 in patients with multiple myeloma was suspended last May after some patients with the disease, which is a type of blood cancer, developed kidney problems.” From *Glaxo drops version of resveratrol “red wine” drug*. Reuters (Reporting by Ben Hirschler; Editing by Will Waterman): Accessed July, 3, 2023: https://www.reuters.com/article/glaxo-resveratrol/glaxo-drops-version-of-resveratrol-red-wine-drug-idUSLDE6B025W20101201.

181. Kaeberlein, M., McDonagh, T., Heltweg, B., Hixon, J., Westman, E. A., Caldwell, S. D., Napper, A., Curtis, R., DiStefano, P. S., Fields, S., Bedalov, A., & Kennedy, B. K. (2005). Substrate-specific Activation of Sirtuins by Resveratrol. *Journal of Biological Chemistry*, *280*(17), 17038–17045. https://doi.org/10.1074/jbc.M500655200

182. Schmidt, C. (2010). GSK/Sirtris compounds dogged by assay artifacts. *Nature Biotechnology*, *28*(3), 185–186. https://doi.org/10.1038/nbt0310-185

183. Hubbard, B. P., Gomes, A. P., Dai, H., Li, J., Case, A. W., Considine, T., Riera, T. v., Lee, J. E., E, S. Y., Lamming, D. W., Pentelute, B. L., Schuman, E. R., Stevens, L. A., Ling, A. J. Y., Armour, S. M., Michan, S., Zhao, H., Jiang, Y., Sweitzer, S. M., … Sinclair, D. A. (2013). Evidence for a Common Mechanism of SIRT1 Regulation by Allosteric Activators. *Science*, *339*(6124), 1216–1219. https://doi.org/10.1126/science.1231097

184. Brenner, C. (2022). Sirtuins are not conserved longevity genes. *Life Metabolism*, *1*(2), 122–133. https://doi.org/10.1093/lifemeta/loac025

185. Huynh, A. T., Nguyen, T.-T. N., Villegas, C. A., Montemorso, S., Strauss, B., Pearson, R. A., Graham, J. G., Oribello, J., Suresh, R., Lustig, B., & Wang, N. (2022). Prediction and confirmation of a switch-like region within the N-terminal domain of hSIRT1. *Biochemistry and Biophysics Reports*, *30*, 101275. https://doi.org/10.1016/j.bbrep.2022.101275

186. The 60 minutes story about the "French Paradox" and potential of resveratrol as or certain formulations of it as a drug. From the CBS website: "*This story was first published on Jan. 25, 2009. It was updated on May 21, 2009.*" Accessed July 3, 2023: https://www.cbsnews.com/news/fountain-of-youth-in-a-wine-rx/.

Page 34. *Coumarin, which underlies*. The reference below cites the salient literature and provides a good primer on the origins of warfarin and connection to moldy clover and to dicoumarol

187. Nisar, T., Sutherland-Foggio, H., & Husar, W. (2020). Rural origins of warfarin. *The Lancet Neurology*, *19*(1), 35. https://doi.org/10.1016/S1474-4422(19)30446-6

Page 34. *Warfarin is also effective as a rodenticide*.

188. Herring, G., Eagles-Smith, C. A., & Buck, J. (2017). Characterizing Golden Eagle Risk to Lead and Anticoagulant Rodenticide Exposure: A Review. *Journal of Raptor Research*, *51*(3), 273–292. https://doi.org/10.3356/JRR-16-19.1

189. Hofstadter, D. F., Kryshak, N. F., Gabriel, M. W., Wood, C. M., Wengert, G. M., Dotters, B. P., Roberts, K. N., Fountain, E. D., Kelly, K. G., Keane, J. J., Whitmore, S. A., Berigan, W. J., & Peery, M. Z. (2021). High rates of anticoagulant rodenticide exposure in California Barred Owls are associated with the wildland–urban interface. *Ornithological Applications*, *123*(4). https://doi.org/10.1093/ornithapp/duab036

190. National Park Service. (2019). *Lions in the Santa Monica Mountains*. Accessed July 3, 2023: https://www.nps.gov/samo/learn/nature/pumapage.htm.

191. Holliday, I. (2022, October 28). *B.C. making rodenticide ban permanent, ministry announces*. CTV News. https://vancouverisland.ctvnews.ca/mobile/b-c-making-rodenticide-ban-permanent-ministry-announces-1.6129885

Page 35. *As a junior in college*. The study abroad program in fall semester 1996 was run through St. John's University and the College of St. Benedict in Stearns County, Minnesota and was based at the Collège International de Cannes, in Canne, France.

192. Accessed July 3, 2023: https://www.french-in-cannes.fr/.

Page 35. *Built in 1009 CE.*

193. Accessed July 3, 2023: https://stmartinducanigou.org/.

Page 35. *After each drink.*

194. Soares, S., Ferrer-Galego, R., Brandão, E., Silva, M., Mateus, N., & Freitas, V. de. (2016). Contribution of Human Oral Cells to Astringency by Binding Salivary Protein/Tannin Complexes. *Journal of Agricultural and Food Chemistry*, *64*(41), 7823–7828. https://doi.org/10.1021/acs.jafc.6b02659

Page 35. *In our mouths*.

195. McArthur, C., Sanson, G. D., & Beal, A. M. (1995). Salivary proline-rich proteins in mammals: Roles in oral homeostasis and counteracting dietary tannin. *Journal of Chemical Ecology*, *21*(6), 663–691. https://doi.org/10.1007/BF02033455

Page 35. *When tannins bind*.

196. Torregrossa, A.-M., Nikonova, L., Bales, M. B., Villalobos Leal, M., Smith, J. C., Contreras, R. J., & Eckel, L. A. (2014). Induction of Salivary Proteins Modifies Measures of Both Orosensory and Postingestive Feedback during Exposure to a Tannic Acid Diet. *PLoS ONE*, *9*(8), e105232. https://doi.org/10.1371/journal.pone.0105232

Page 35. *Tannins can benefit the plants*. For the relationship between tannins and plant fitness see references above. Note that in large animals like us, tannins bind to proteins and may prevent absorption of nutrients but the mechanism driving toxicity in herbivorous insects is likely to be driven by tannin oxidation and other effects not directly driving malabsorption via protein-binding, although this may vary depending on the pH level found in the gut.

197. Appel, H. M. (1993). Phenolics in ecological interactions: The importance of oxidation. *Journal of Chemical Ecology*, *19*(7), 1521–1552. https://doi.org/10.1007/BF00984895

198. Felton, G. W., Donato, K. K., Broadway, R. M., & Duffey, S. S. (1992). Impact of oxidized plant phenolics on the nutritional quality of dietary protein to a noctuid herbivore, *Spodoptera exigua*. *Journal of Insect Physiology*, *38*(4), 277–285. https://doi.org/10.1016/0022-1910(92)90128-Z

199. Salminen, J., & Karonen, M. (2011). Chemical ecology of tannins and other phenolics: we need a change in approach. *Functional Ecology*, *25*(2), 325–338. https://doi.org/10.1111/j.1365-2435.2010.01826.x

200. Robbins, C. T., Hanley, T. A., Hagerman, A. E., Hjeljord, O., Baker, D. L., Schwartz, C. C., & Mautz, W. W. (1987). Role of Tannins in Defending Plants Against Ruminants: Reduction in Protein Availability. *Ecology*, *68*(1), 98–107. https://doi.org/10.2307/1938809

201. DeGabriel, J. L., Moore, B. D., Foley, W. J., & Johnson, C. N. (2009). The effects of plant defensive chemistry on nutrient availability predict reproductive success in a mammal. *Ecology*, *90*(3), 711–719. https://doi.org/10.1890/08-0940.1

Page 36. *Tannic and gallic acids were.*

202. Zboralske, F. F., Harris, P. a., Riegelman, S., Rambo, O. N., & Margulis, A. R. (1966). Toxicity Studies on Tannic acid Administered by Enema. *American Journal of Roentgenology*, *96*(2), 505–509. https://doi.org/10.2214/ajr.96.2.505

203. McAlister, W. H., Anderson, M. S., Bloomberg, G. R., & Margulis, A. R. (1963). Lethal Effects of Tannic Acid in the Barium Enema. *Radiology*, *80*(5), 765–773. https://doi.org/10.1148/80.5.765

204. Lucke, H. H., Hodge, K. E., & Patt, N. L. (1963). Fatal Liver Damage after Barium Enemas Containing Tannic Acid. *Canadian Medical Association Journal*, *89*(22), 1111–1114. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1921838/pdf/canmedaj01024-0002.pdf.

Page 36. *If you live around oak trees*.

205. Stone, G. N., & Cook, J. M. (1998). The structure of cynipid oak galls: patterns in the evolution of an extended phenotype. *Proceedings of the Royal Society of London. Series B: Biological Sciences*, *265*(1400), 979–988. https://doi.org/10.1098/rspb.1998.0387

206. Redfern, M. (2011). *Plant galls*. London, UK: HarperCollins Publishers.

Page 36. *These are oak galls, or oak apples.*

207. Bronner, N. (1992). The role of nutritive cells in the nutrition of cynipids and cecidomyiids. *Biology of insect-induced galls*. Oxford University Press, Oxford, pp 118–140.

Page 36. *The galls are neoplasms.*

208. White, P. R. (1951). Neoplastic Growth in Plants. *The Quarterly Review of Biology*, *26*(1), 1–16. https://doi.org/10.1086/397879

Page 36. *Like some cervical cancers.*

209. zur Hausen, H., de Villiers, E.-M., & Gissmann, L. (1981). Papillomavirus infections and human genital cancer. *Gynecologic Oncology*, *12*(2), S124–S128. https://doi.org/10.1016/0090-8258(81)90067-6

210. Boshart, M., Gissmann, L., Ikenberg, H., Kleinheinz, A., Scheurlen, W., & zur Hausen, H. (1984). A new type of papillomavirus DNA, its presence in genital cancer biopsies and in cell lines derived from cervical cancer. *The EMBO Journal*, *3*(5), 1151–1157. https://doi.org/10.1002/j.1460-2075.1984.tb01944.x

Page 36. *In oaks, the galls are induced.*

211. Stone, G. N., & Schönrogge, K. (2003). The adaptive significance of insect gall morphology. *Trends in Ecology & Evolution*, *18*(10), 512–522. https://doi.org/10.1016/S0169-5347(03)00247-7

212. Egan, S. P., Hood, G. R., Martinson, E. O., & Ott, J. R. (2018). Cynipid gall wasps. *Current Biology*, *28*(24), R1370–R1374. https://doi.org/10.1016/j.cub.2018.10.028

Page 36. *Through largely unknown mechanisms.*

213. Hearn, J., Blaxter, M., Schönrogge, K., Nieves-Aldrey, J.-L., Pujade-Villar, J., Huguet, E., Drezen, J.-M., Shorthouse, J. D., & Stone, G. N. (2019). Genomic dissection of an extended phenotype: Oak galling by a cynipid gall wasp. *PLOS Genetics*, *15*(11), e1008398. https://doi.org/10.1371/journal.pgen.1008398

Page 36. *As the oak gall grows.*

214. Cornell, H. V. (1983). The Secondary Chemistry and Complex Morphology of Galls Formed by the Cynipinae (Hymenoptera): Why and How? *The American Midland Naturalist*, *110*(2), 225–234. https://doi.org/10.2307/2425263

Page 36. *The oak tree produces.*

215. Feeny, P. (1970). Seasonal Changes in Oak Leaf Tannins and Nutrients as a Cause of Spring Feeding by Winter Moth Caterpillars. *Ecology*, *51*(4), 565–581. https://doi.org/10.2307/1934037

Page 37. *We tried to reconcile*.

216. The Declaration of Independence. "He has excited domestic insurrections amongst us, and has endeavoured to bring on the inhabitants of our frontiers, the merciless Indian Savages, whose known rule of warfare, is an undistinguished destruction of all ages, sexes and conditions." Accessed July 4, 2023: https://www.archives.gov/founding-docs/declaration-transcript.

Page 37. *What I didn't know then*.

217. Mitchell, C. A.; Hepworth, T. C. (1904). *Inks: Their Composition and Manufacture*; Charles Griffin & Company, Ltd.: London, UK.

218. Kolar, J., Štolfa, A., Strlič, M., Pompe, M., Pihlar, B., Budnar, M., Simčič, J., & Reissland, B. (2006). Historical iron gall ink containing documents — Properties affecting their condition. *Analytica Chimica Acta*, *555*(1), 167–174. https://doi.org/10.1016/j.aca.2005.08.073

Page 38. *Roughly between 400 and 1800 CE*.

219. Stijnman, A. 2006. Iron-gall inks in history: ingredients and production. In: Kolar J, Strlič M, editors. *Iron–gall Inks: on manufacture, characterization, degradation and stabilization*. Ljubljana: National and University Library, p. 25–167 (and Appendix 4).

220. Díaz Hidalgo, R. J., Córdoba, R., Nabais, P., Silva, V., Melo, M. J., Pina, F., Teixeira, N., & Freitas, V. (2018). New insights into iron-gall inks through the use of historically accurate reconstructions. *Heritage Science*, *6*(1), 63. https://doi.org/10.1186/s40494-018-0228-8

Page 37. *Even more remarkable*. It is important to note that iron gall ink itself wasn't found in the Thanksgiving Scroll of the Dead Sea Scrolls. However, a study by Hahn et al. below showed that the ink from some scrolls does contain chemicals with spectra that are consistent with hydrolyzable tannins and that this was consistent with use of oak galls or other galls (e.g., from sumac) to make the ink. Moreover, Hahn et al. hypothesize that the protein (collagen) binding properties of tannins suggests that the tannins may indeed allow the inks to persist for such a long time. This would likely not have been the case if iron was included in the ink owing to the acidity. So, the black ink of the Dead Sea Scrolls indeed, in some cases, seems to contain hydrolyzable tannins. This is an active area of research. The relevant passages from pages 101 and 102 of that reference are as follows:

> "The solid line in fig. 3 is the first Fourier Transform Infra-Red (FTIR) spectrum of Dead Sea Scroll ink ever reported. Its shape is similar to that of natural gum. However its many peaks are sharper, suggesting the presence of tannins and aromatic compounds. Two types of vegetable tannins can be distinguished based on their infrared spectra: condensed and hydrolysable tannins. The former are of phenolic nature and do not have carboxylic groups whereas the latter (e.g.: gallic acid) do possess such groups [17,18]."

> "To our astonishment the best correspondence was found when comparing the spectra of the ink from the scroll with a sample of ours prepared according to Maimonides recipe, dating from the 12th century (grey curve) [21]. Curiously enough, Maimonides recommends adding gall nuts extract to the common ingredients of the carbon black ink, without mentioning any reason. For the preparation of our sample we used commercial Gum Arabic and oak galls. The infrared spectra obtained combining tannins with natural resin seems to fit much better the experimental results from the original ink than the spectra obtained using single type of binders. Thus, the direct addition of a tannic agent to the inks cannot be excluded: Maimonides' prescription could indicate the survival of an ancient use, whose actual reason had been forgotten. In this case the tannins would chemically bind the ink to the parchment collagen [22], explaining the surprising durability of the scroll inks as compared to the usual, physisorbed, carbon-based ink."

221. Hahn, O., Weinberg, G., Rabin, I., Wolff, T., & Masic, A. (2009). On the Origin of the Ink of the Thanksgiving Scroll (1QHodayota). *Dead Sea Discoveries*, *16*(1), 97–106. https://doi.org/10.1163/156851709X395722

Page 37. *When hydrolyzable tannins*.

222. Espina, A., Cañamares, M. V., Jurašeková, Z., & Sanchez-Cortes, S. (2022). Analysis of Iron Complexes of Tannic Acid and Other Related Polyphenols as Revealed by Spectroscopic Techniques: Implications in the Identification and Characterization of Iron Gall Inks in Historical Manuscripts. *ACS Omega*, *7*(32), 27937–27949. https://doi.org/10.1021/acsomega.2c01679

Page 38. Iron gall ink and quill pens.

223. Carvalho, D. N. 2007. Forty Centuries of Ink. Echo Library.

224. Lock, A., & Sims, J. (2015). Invoking Magna Carta: Locating Information Objects and Meaning in the 13th to 19th Centuries. Legal Information Management, 15(2), 74–85. https://doi.org/10.1017/S1472669615000249

Page 38. *Leonardo da Vinci*.

225. Kolar, J., Štolfa, A., Strlič, M., Pompe, M., Pihlar, B., Budnar, M., Simčič, J., & Reissland, B. (2006). Historical iron gall ink containing documents — Properties affecting their condition. *Analytica Chimica Acta*, *555*(1), 167–174. https://doi.org/10.1016/j.aca.2005.08.073

Page 39. *For hundreds of years*.

226. Leszczyńska, D. (2013). Historical trajectory and knowledge embeddedness: a case study in the French perfume cluster. *Management &*

Organizational History, *8*(3), 290–305. https://doi.org/10.1080/17449359.2013.804419

227. Dugan, H. (2011). *The Ephemeral History of Perfume: Scent and Sense in Early Modern England*. Baltimore: The Johns Hopkins University Press, 2011.

228. Redwood, M. (2016). *Gloves and Glove-making*. Oxford, Shire Publications Ltd.

229. Creamer, C. (2017). *A perfume devotee in the land of French fragrance*. The New York Times. Accessed July 5, 2023: https://www.nytimes.com/2017/08/08/travel/grasse-france-perfume-fragrance-gardens-capital.html.

Page 40. *Each year we collectively swallow 120 billion bitter doses*.

230. Jones, A. (2015). Starting chemistry. A. Jones (Ed.), *Chemistry: An Introduction for Medical and Health Sciences*. John Wiley & Sons, Chichester, West Sussex, England, pp. 5-6.

Page 40. *In 1763, when.*

231. Stone, E. (1763). XXXII. An account of the success of the bark of the willow in the cure of agues. In a letter to the Right Honourable George Earl of Macclesfield, President of R. S. from the Rev. Mr. Edward Stone, of Chipping-Norton in Oxfordshire. *Philosophical Transactions of the Royal Society of London*, *53*, 195–200. https://doi.org/10.1098/rstl.1763.0033

Page 41. *Proof that these chemicals*.

232. Green, P. W. C., Simmonds, M. S. J., & Blaney, W. M. (2002). Toxicity and behavioural effects of diet-borne alkaloids on larvae of the black blowfly, *Phormia regina*. *Medical and Veterinary Entomology*, *16*(2), 157–160. https://doi.org/10.1046/j.1365-2915.2002.00358.x

Page 41. *Even more remarkably*.

233. Krug, E., & Proksch, P. (1993). Influence of dietary alkaloids on survival and growth of *Spodoptera littoralis*. *Biochemical Systematics and Ecology*, *21*(8), 749–756. https://doi.org/10.1016/0305-1978(93)90087-8

Page 41. *Of course, quinine*. Although quinine was the first line of defense against malaria, notably, many populations of *Plasmodium* have evolved resistance to quinine and its derivative molecules, like chloroquine and mefloquine.

234. See the WHO Guidelines for Malaria (updated November 2022 and accessed August 27 2023): https://www.who.int/teams/global-malaria-programme/guidelines-for-malaria

Page 41. *European colonists introduced malaria*

235. Wesselhoeft, C. (1916). The discovery of the cinchona bark. *The New England Medical Gazette* L1: 349–361.

236. Wesselhoeft, C. (1916). The introduction and early use of cinchona bark. *The New England Medical Gazette* L1: 362–373.

237. Crespo, F. I. O. (1995). Fragoso, Monardes and pre-Chinchonian knowledge of Cinchona. *Archives of Natural History*, *22*(2), 169–181. https://doi.org/10.3366/anh.1995.22.2.169

238. Jaramillo-Arango, J. (1949). A Critical Review of the Basic Facts in the History of Cinchona. *Journal of the Linnean Society of London, Botany*, *53*(352), 272–311. https://doi.org/10.1111/j.1095-8339.1949.tb00419.x

239. Haggis, A. W. 1941. Fundamental errors in the early history of Cinchona. B*ulletin of the History of Medicine 10*: 417–592 https://wellcomecollection.org/works/uxa7cnzk.

Page 42. *It took ninety more years after*.

240. Jack, D. B. (1997). One hundred years of aspirin. *The Lancet*, *350*(9075), 437–439. https://doi.org/10.1016/S0140-6736(97)07087-6

Page 43. *The high concentrations of salicylates in willows*.

241. Matsuki, M., & MacLean, S. F. (1994). Effects of different leaf traits on growth rates of insect herbivores on willows. *Oecologia*, *100–100*(1–2), 141–152. https://doi.org/10.1007/BF00317141

Page 43. *The most ancient role of salicylates in plants*.

242. Raskin, I. (1992). Role of Salicylic Acid in Plants. *Annual Review of Plant Physiology and Plant Molecular Biology*, *43*(1), 439–463. https://doi.org/10.1146/annurev.pp.43.060192.002255

243. Thaler, J. S., Humphrey, P. T., & Whiteman, N. K. (2012). Evolution of jasmonate and salicylate signal crosstalk. *Trends in Plant Science*, *17*(5), 260–270. https://doi.org/10.1016/j.tplants.2012.02.010

Page 43. *I was completely shocked to learn that*.

244. Paterson, J. R., Baxter, G., Dreyer, J. S., Halket, J. M., Flynn, R., & Lawrence, J. R. (2008). Salicylic Acid sans Aspirin in Animals and Man: Persistence in Fasting and Biosynthesis from Benzoic Acid. *Journal of Agricultural and Food Chemistry*, *56*(24), 11648–11652. https://doi.org/10.1021/jf800974z

Page 43. *Salicylic acid, aspirin, and other nonsteroidal*. See: https://www.nobelprize.org/prizes/medicine/1982/summary/

245. Harding, A. (2004). Sir John Robert Vane. *The Lancet*, *364*(9451), 2090. https://doi.org/10.1016/S0140-6736(04)17571-5

246. Euler, U. S. (1935). Über die Spezifische Blutdrucksenkende Substanz des Menschlichen Prostata- und Samenblasensekretes. *Klinische Wochenschrift*, *14*(33), 1182–1183. https://doi.org/10.1007/BF01778029

247. Goldblatt, M. W. (1935). Properties of human seminal plasma. *The Journal of Physiology*, *84*(2), 208–218. https://doi.org/10.1113/jphysiol.1935.sp003269

Page 43. *Chronic inflammation is a killer*.

248. Netea, M. G., Balkwill, F., Chonchol, M., Cominelli, F., Donath, M. Y., Giamarellos-Bourboulis, E. J., Golenbock, D., Gresnigt, M. S., Heneka, M. T., Hoffman, H. M., Hotchkiss, R., Joosten, L. A. B., Kastner, D. L., Korte, M., Latz, E., Libby, P., Mandrup-Poulsen, T., Mantovani, A., Mills, K. H. G., … Dinarello, C. A. (2017). A guiding map for inflammation. *Nature Immunology*, *18*(8), 826–831. https://doi.org/10.1038/ni.3790

Page 43. *Plants also make prostaglandin-like*. Oxylipins include both prostaglandins produced by animals and jasmonates produced by plants.

249. Demole, E., Lederer, E., & Mercier, D. (1962). Isolement et détermination de la structure du jasmonate de méthyle, constituant odorant caractéristique de

l'essence de jasmin. *Helvetica Chimica Acta*, *45*(2), 675–685. https://doi.org/10.1002/hlca.19620450233

250. Creelman, R. A., & Mullet, J. E. (1997). Biosynthesis and Action of Jasmonates in Plants. *Annual Review of Plant Physiology and Plant Molecular Biology*, *48*(1), 355–381. https://doi.org/10.1146/annurev.arplant.48.1.355

251. Xie, D.-X., Feys, B. F., James, S., Nieto-Rostro, M., & Turner, J. G. (1998). *COI1* : An *Arabidopsis* Gene Required for Jasmonate-Regulated Defense and Fertility. *Science*, *280*(5366), 1091–1094. https://doi.org/10.1126/science.280.5366.1091

Page 44. *The process recalls how Paul Revere.*

252. Paraphrasing Henry Wadsworth Longfellow's poem "Paul Revere's Ride": https://poets.org/poem/paul-reveres-ride

Page 44. *And to top it all off.*

253. Thaler, J. S., Humphrey, P. T., & Whiteman, N. K. (2012). Evolution of jasmonate and salicylate signal crosstalk. *Trends in Plant Science*, *17*(5), 260–270. https://doi.org/10.1016/j.tplants.2012.02.010

Page 46. *So, you may have experienced the*.

254. Blacklock, C. J. (2001). Salicylic acid in the serum of subjects not taking aspirin. Comparison of salicylic acid concentrations in the serum of vegetarians, non-vegetarians, and patients taking low dose aspirin. *Journal of Clinical Pathology*, *54*(7), 553–555. https://doi.org/10.1136/jcp.54.7.553

Page 46. *For example, the incidence of colon cancer*.

255. Jussawalla, D. J., Deshpande, V. A., Haenszel, W., & Natekar, M. v. (1970). Differences Observed in the Site Incidence of Cancer, Between the Parsi Community and the Total Population of Greater Bombay: A Critical Appraisal. *British Journal of Cancer*, *24*(1), 56–66. https://doi.org/10.1038/bjc.1970.8

Page 46. *Much of the salicylic acid in the diet*.

256. Paterson, J. R., Srivastava, R., Baxter, G. J., Graham, A. B., & Lawrence, J. R. (2006). Salicylic Acid Content of Spices and Its Implications. *Journal of*

Agricultural and Food Chemistry, *54*(8), 2891–2896. https://doi.org/10.1021/jf058158w

257. Swain, A. R., Dutton, S. P., & Truswell, A. S. (1985). Salicylates in foods. *Journal of the American Dietetic Association*, *85*(8), 950–960. https://pubmed.ncbi.nlm.nih.gov/4019987/

Page 46. *Ironically, some people take.*

258. Antithrombotic Trialists' (ATT) Collaboration, Baigent, C., Blackwell, L., Collins, R., Emberson, J., Godwin, J., Peto, R., Buring, J., Hennekens, C., Kearney, P., Meade, T., Patrono, C., Roncaglioni, M. C., & Zanchetti, A. (2009). Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet (London, England)*, *373*(9678), 1849–1860. https://doi.org/10.1016/S0140-6736(09)60503-1

Page 46. *This practice is no longer recommended.*

259. Davidson, K. W., Barry, M. J., Mangione, C. M., Cabana, M., Chelmow, D., Coker, T. R., Davis, E. M., Donahue, K. E., Jaén, C. R., Krist, A. H., Kubik, M., Li, L., Ogedegbe, G., Pbert, L., Ruiz, J. M., Stevermer, J., Tseng, C.-W., & Wong, J. B. (2022). Aspirin use to prevent cardiovascular disease. *JAMA*, *327*(16), 1577. https://doi.org/10.1001/jama.2022.4983

Page 46. *The same now goes.*

260. Cao, Y., Nishihara, R., Wu, K., Wang, M., Ogino, S., Willett, W. C., Spiegelman, D., Fuchs, C. S., Giovannucci, E. L., & Chan, A. T. (2016). Population-wide impact of long-term use of aspirin and the risk for cancer. *JAMA Oncology*, *2*(6), 762. https://doi.org/10.1001/jamaoncol.2015.6396

261. Guo, C.-G., Ma, W., Drew, D. A., Cao, Y., Nguyen, L. H., Joshi, A. D., Ng, K., Ogino, S., Meyerhardt, J. A., Song, M., Leung, W. K., Giovannucci, E. L., & Chan, A. T. (2021). Aspirin use and risk of colorectal cancer among older adults. *JAMA Oncology*, *7*(3), 428. https://doi.org/10.1001/jamaoncol.2020.7338

262. https://www.uspreventiveservicestaskforce.org/uspstf/sites/default/files/file/supporting_documents/aspirin-cvd-prevention-final-rec-bulletin.pdf

Page 46. *In the United Kingdom alone.*

263. Li, L., Geraghty, O. C., Mehta, Z., & Rothwell, P. M. (2017). Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. *The Lancet*, *390*(10093), 490–499. https://doi.org/10.1016/S0140-6736(17)30770-5

Page 47. *Across the Northern Hemisphere*.

264. Smiley, J. T., Horn, J. M., & Rank, N. E. (1985). Ecological Effects of Salicin at Three Trophic Levels: New Problems from Old Adaptations. *Science*, *229*(4714), 649–651. https://doi.org/10.1126/science.229.4714.649

Page 47. *Many species in this plant*.

265. Kirsch, R., Vogel, H., Muck, A., Vilcinskas, A., Pasteels, J. M., & Boland, W. (2011). To be or not to be convergent in salicin-based defence in chrysomeline leaf beetle larvae: evidence from Phratora vitellinae salicyl alcohol oxidase. *Proceedings. Biological Sciences*, *278*(1722), 3225–3232. https://doi.org/10.1098/rspb.2011.0175

Page 47. *This chemical, released from a beetle gland.*

266. Smiley, J. T., Horn, J. M., & Rank, N. E. (1985). Ecological Effects of Salicin at Three Trophic Levels: New Problems from Old Adaptations. *Science*, *229*(4714), 649–651. https://doi.org/10.1126/science.229.4714.649

Page 48. *Schoolchildren in the San Francisco Bay Area*.

267. Kristof, N. (2009, August 1). How to Lick a Slug. *The New York Times*. From: https://www.nytimes.com/2009/08/02/opinion/02kristof.html

Page 48. *A garden slug in Europe*.

268. Kästner, J., von Knorre, D., Himanshu, H., Erb, M., Baldwin, I. T., & Meldau, S. (2014). Salicylic Acid, a Plant Defense Hormone, Is Specifically Secreted by a Molluscan Herbivore. *PLoS ONE*, *9*(1), e86500. https://doi.org/10.1371/journal.pone.0086500

Page 48. *In addition to providing*. See preceding reference and another that shows the suppression of jasmonate-dependent defense signaling via salicylates in slug slime is still unclear:

269. Meldau, S., Kästner, J., von Knorre, D., & Baldwin, I. T. (2014). Salicylic acid-dependent gene expression is activated by locomotion mucus of different

molluscan herbivores. *Communicative & Integrative Biology*, *7*(3), e28728. https://doi.org/10.4161/cib.28728

Page 48. *The last mentioned-plant contains.*

270. Guthrie, W. K. C. (1962). *A History of Greek Philosophy: Volume 3, The Fifth Century Enlightenment*. Cambridge University Press. https://archive.org/details/historyofgreekph0003unse/page/n5/mode/2up

271. Sullivan, J. (2001). A Note on *The Death of Socrates*. *The Classical Quarterly*, *51*(2), 608–610. https://doi.org/10.1093/cq/51.2.608

272. Gesellschaft, D. P., der Berufsvertretun, A., & Norddeutschland, A. v. (2019). *Archiv Der Pharmazie Und Berichte Der Deutschen Pharmazeutischen Gesellschaft erster band*. Creative Media Partners, LLC. https://babel.hathitrust.org/cgi/pt?id=chi.63391235&view=1up&seq=117

273. Deutsche Chemische Gesellschaft. *Berichte der Deutschen Chemischen Gesellschaft.* Berlin: Verlag Chemie. https://babel.hathitrust.org/cgi/pt?id=mdp.39015026349442&view=1up&seq=713

Page 48. *These plants, as well as those.*

274. Pathak, M. A., Daniels, F., & Fitzpatrick, T. B. (1962). The Presently Known Distribution of Furocoumarins (Psoralens) in Plants. *Journal of Investigative Dermatology*, *39*(3), 225–239. https://doi.org/10.1038/jid.1962.106

275. Berenbaum, M. (1983). Coumarins and Caterpillars: A Case for Coevolution. *Evolution*, *37*(1), 163. https://doi.org/10.2307/2408184

Page 48. *Because furanocourmarins are contained in.*

276. U.S. Food and Drug Administration. (2021, July 1). *Grapefruit Juice and Some Drugs Don't Mix*.

277. Spence, J. D. (1997). Drug interactions with grapefruit: Whose responsibility is it to warn the public? *Clinical Pharmacology & Therapeutics*, *61*(4), 395–400. https://doi.org/10.1016/S0009-9236(97)90189-2

278. Bailey, D. G., Dresser, G., & Arnold, J. M. O. (2013). Grapefruit–medication interactions: Forbidden fruit or avoidable consequences? *Canadian Medical Association Journal*, *185*(4), 309–316. https://doi.org/10.1503/cmaj.120951

Page 49. *The activity of an important drug metabolism enzyme.*

279. Guo, L. Q., Fukuda, K., Ohta, T., & Yamazoe, Y. (2000). Role of furanocoumarin derivatives on grapefruit juice-mediated inhibition of human CYP3A activity. *Drug Metabolism and Disposition: The Biological Fate of Chemicals*, *28*(7), 766–771.

280. Bailey, D., Spence, J., Munoz, C., & Arnold, J. M. O. (1991). Interaction of citrus juices with felodipine and nifedipine. *The Lancet*, *337*(8736), 268–269. https://doi.org/10.1016/0140-6736(91)90872-M

281. Wangensteen, H., Molden, E., Christensen, H., & Malterud, K. E. (2003). Identification of epoxybergamottin as a CYP3A4 inhibitor in grapefruit peel. *European Journal of Clinical Pharmacology*, *58*(10), 663–668. https://doi.org/10.1007/s00228-002-0537-3

Page 49. *A twenty-nine-year-old man*.

282. Spence, J. D. (1997). Drug interactions with grapefruit: Whose responsibility is it to warn the public? *Clinical Pharmacology & Therapeutics*, *61*(4), 395–400. https://doi.org/10.1016/S0009-9236(97)90189-2

Page 49. *In all, there are eight-five.*

283. Bailey, D., Spence, J., Munoz, C., & Arnold, J. M. O. (1991). Interaction of citrus juices with felodipine and nifedipine. *The Lancet*, *337*(8736), 268–269. https://doi.org/10.1016/0140-6736(91)90872-M

Page 49. *Furanocoumarins can also cause third-degree.*

284. Klaber, R. (1942). Phyto-photo-dermatitis. *British Journal of Dermatology*, *54*(7), 193–211. https://doi.org/10.1111/j.1365-2133.1942.tb10682.x

Page 50. *When furanocoumarin exposure is chroni*

285. Melough, M. M., & Chun, O. K. (2018). Dietary furocoumarins and skin cancer: A review of current biological evidence. *Food and Chemical Toxicology*, *122*, 163–171. https://doi.org/10.1016/j.fct.2018.10.027

Page 50. *Although I don't want to scare you*.

286. Abramowitz, A. I., Resnik, K. S., & Cohen, K. R. (1993). Margarita Photodermatitis. *New England Journal of Medicine*, *328*(12), 891–891. https://doi.org/10.1056/NEJM199303253281220

Page 50. *He recovered, but this skin disease.*

287. Seligman, P. J. (1987). Phytophotodermatitis From Celery Among Grocery Store Workers. *Archives of Dermatology*, *123*(11), 1478. https://doi.org/10.1001/archderm.1987.01660350078017

Page 50. *Another case involved.*

288. Gross, T. P., Ratner, L., de Rodriguez, O., Farrell, K. P., & Israel, E. (1987). An outbreak of phototoxic dermatitis due to limes. *American Journal of Epidemiology*, *125*(3), 509–514. https://doi.org/10.1093/oxfordjournals.aje.a114557

Page 50. *Burns have even led.*

289. Baker, B. G., Bedford, J., & Kanitkar, S. (2017). Keeping pace with the media; Giant Hogweed burns — A case series and comprehensive review. *Burns*, *43*(5), 933–938. https://doi.org/10.1016/j.burns.2016.10.018

Page 59. *Psoralen, the principal.*

290. Pathak, M. A., & Fitzpatrick, T. B. (1992). The evolution of photochemotherapy with psoralens and UVA (PUVA): 2000 BC to 1992 AD. *Journal of Photochemistry and Photobiology B: Biology*, *14*(1–2), 3–22. https://doi.org/10.1016/1011-1344(92)85080-E

Page 50. *In fact, furanocoumarins*.

291. Hönigsmann, H. (2012). History of phototherapy in dermatology. *Photochemical & Photobiological Sciences*, *12*(1), 16–21. https://doi.org/10.1039/c2pp25120e

Page 50. *In the Mediterranean region*.

292. Gauthier, Y., & Benzekri, L. (2019). Historical Aspects of Vitiligo. In *Vitiligo* (pp. 3–10). Springer International Publishing. https://doi.org/10.1007/978-3-319-62960-5_1

Page 50. *Building on knowledge*.

293. Fahmy, I. R., Abushady, H., Schönberg, A., & Sina, A. (1947). A Crystalline Principle from *Ammi majus* L. *Nature*, *160*(4066), 468–469. https://doi.org/10.1038/160468c0

294. Fahmy, I. R., & Abushady, H. (1948). The isolation and properties of ammoidin, ammidin and majudin, and their effect in the treatment of leukodermia. *Quarterly Journal of Pharmacy and Pharmacology*, *21*(4), 499–503.

Page 51. *It is also used against*.

295. Querfeld, C. (2005). Long-term Follow-up of Patients With Early-Stage Cutaneous T-Cell Lymphoma Who Achieved Complete Remission With Psoralen Plus UV-A Monotherapy. *Archives of Dermatology*, *141*(3), 305–311. https://doi.org/10.1001/archderm.141.3.305

Page 51. *A clinical trial is.*

296. Oldham, M., Yoon, P., Fathi, Z., Beyer, W. F., Adamson, J., Liu, L., Alcorta, D., Xia, W., Osada, T., Liu, C., Yang, X. Y., Dodd, R. D., Herndon, J. E., Meng, B., Kirsch, D. G., Lyerly, H. K., Dewhirst, M. W., Fecci, P., Walder, H., & Spector, N. L. (2016). X-Ray Psoralen Activated Cancer Therapy (X-PACT). *PLOS ONE*, *11*(9), e0162078. https://doi.org/10.1371/journal.pone.0162078

Page 51. *Psoralen was used sometimes*.

297. Autier, P., Doré, J.-F., Césarini, J.-P., & Boyle, P. (1997). Should subjects who used psoralen suntan activators be screened for melanoma? *Annals of Oncology*, *8*(5), 435–437. https://doi.org/10.1023/A:1008205513771

Page 51. *The dried fruits of*.

298. Pathak, M. A., & Fitzpatrick, T. B. (1992). The evolution of photochemotherapy with psoralens and UVA (PUVA): 2000 BC to 1992 AD. *Journal of Photochemistry and Photobiology B: Biology*, *14*(1–2), 3–22. https://doi.org/10.1016/1011-1344(92)85080-E\

299. Hönigsmann, H. (2012). History of phototherapy in dermatology. *Photochemical & Photobiological Sciences*, *12*(1), 16–21. https://doi.org/10.1039/c2pp25120e

Page 51. *Cow parsnip, which also produces.*

300. BRIT - Native American Ethnobotany Database. http://naeb.brit.org/uses/search/?string=Heracleum+maximum

Page 51. *As you have probably guessed.*

301. Berenbaum, M. (1978). Toxicity of a Furanocoumarin to Armyworms: A Case of Biosynthetic Escape from Insect Herbivores. *Science*, *201*(4355), 532–534. https://doi.org/10.1126/science.201.4355.532

Page 51. *For example, entomologist May Berenbaum.*

302. Berenbaum, M. (1978). Toxicity of a Furanocoumarin to Armyworms: A Case of Biosynthetic Escape from Insect Herbivores. *Science*, *201*(4355), 532–534. https://doi.org/10.1126/science.201.4355.532

303. Berenbaum, M. R., & Zangerl, A. R. (1992). Genetics of physiological and behavioral resistance to host furanocoumarins in the parsnip webworm. *Evolution*, *46*(5), 1373–1384. https://doi.org/10.1111/j.1558-5646.1992.tb01130.x

Page 52. *Berenbaum has used this.*

304. Berenbaum, M. (1983). Coumarins and Caterpillars: A Case for Coevolution. *Evolution*, *37*(1), 163. https://doi.org/10.2307/2408184

Chapter 3. Toxic, Titillating, Tumor-Killing Terpenoids

Page 53. *All the plants of a given country.*

305. De Candolle, A. P. (1820). "Géographie botanique", in Frédéric Cuvier (ed.), *Dictionnaire des sciences naturelles, vol. 18*, Paris et Strasbourg, Levrault. pp. 359-422.

Page 53. *My father died.*

306. For a discussion of the DSM-5 criteria (revised in 2021) relating to Alcohol Use Disorder (AUD) see: https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/alcohol-use-disorder-comparison-between-dsm

Page 53. *In the days after his death.* For an introduction on shirin-yoku or forest bathing see:

307. Li, Q. (2018, May 1). *'Forest Bathing' Is Great for Your Health. Here's How to Do It*. Time. https://time.com/5259602/japanese-forest-bathing/
308. Li, Qing. (2018). *Shirin-Yoku: The Art and Science of Forest Bathing*. Penguin.

Page 53 and 54. *I got what I had come for*. The quote "frosty pepper up my nose" is from Robert Louis Stevenson's poem Winter-Time:

309. Stevenson, R. L. (1885). XXXVIII. *Winter-Time*. In: *A Child's Garden of Verses*. Longmans, Green, and Company, London. See: https://en.wikisource.org/wiki/A_Child%27s_Garden_of_Verses

Late lies the wintry sun a-bed,
A frosty, fiery sleepy-head;
Blinks but an hour or two; and then,
A blood-red orange, sets again.

Before the stars have left the skies,
At morning in the dark I rise;
And shivering in my nakedness,
By the cold candle, bathe and dress.

Close by the jolly fire I sit
To warm my frozen bones a bit;
Or with a reindeer-sled, explore
The colder countries round the door.

When to go out, my nurse doth wrap
Me in my comforter and cap;
The cold wind burns my face, and blows
Its frosty pepper up my nose.

Black are my steps on silver sod;
Thick blows my frosty breath abroad;
And tree and house, and hill and lake,
Are frosted like a wedding-cake.

Page 54. *Terpenoids are the largest.*

310. Chen, K., & Baran, P. S. (2009). Total synthesis of eudesmane terpenes by site-selective C–H oxidations. *Nature*, *459*(7248), 824–828. https://doi.org/10.1038/nature08043

311. Christianson, D. W. (2017). Structural and Chemical Biology of Terpenoid Cyclases. *Chemical Reviews*, *117*(17), 11570–11648. https://doi.org/10.1021/acs.chemrev.7b00287

Page 54. *Like phenolics and flavonoids*.

312. Bobrovskiy, I., Hope, J. M., Ivantsov, A., Nettersheim, B. J., Hallmann, C., & Brocks, J. J. (2018). Ancient steroids establish the Ediacaran fossil *Dickinsonia* as one of the earliest animals. *Science*, *361*(6408), 1246–1249. https://doi.org/10.1126/science.aat7228

Page 54. *The now-extinct Dickinsonia.*

313. Sprigg, Reg. C. (1947). Early Cambrian (?) Jellyfishes from the Flinders Ranges, South Australia. *Transactions of the Royal Society of South Australia, Incorporated*, *71*, 212–224. https://www.biodiversitylibrary.org/part/82733

Page 54. *So important are terpenoids*.

314. Ourisson, G., & Nakatani, Y. (1994). The terpenoid theory of the origin of cellular life: the evolution of terpenoids to cholesterol. *Chemistry & Biology*, *1*(1), 11–23. https://doi.org/10.1016/1074-5521(94)90036-1

315. Brocks, J. J., Love, G. D., Summons, R. E., Knoll, A. H., Logan, G. A., & Bowden, S. A. (2005). Biomarker evidence for green and purple sulphur bacteria in a stratified Palaeoproterozoic sea. *Nature*, *437*(7060), 866–870. https://doi.org/10.1038/nature04068

Page 54. *Isoprene is exhaled in every breath*.

316. Gelmont, D., Stein, R. A., & Mead, J. F. (1981). Isoprene — The main hydrocarbon in human breath. *Biochemical and Biophysical Research Communications*, *99*(4), 1456–1460. https://doi.org/10.1016/0006-291X(81)90782-8

317. Sanadze, G. A. (1957). Nature of gaseous substances from the Robinia pseudoacacia leaves. *Rep Akad Nauk GruzSSR*, *19*(8), 3.

318. Sharkey, T. D., & Yeh, S. (2001). Isoprene Emission from Plants. *Annual Review of Plant Physiology and Plant Molecular Biology*, *52*(1), 407–436. https://doi.org/10.1146/annurev.arplant.52.1.407

Page 54. *Our bodies make isoprene*.

319. Stone, B. G., Besse, T. J., Duane, W. C., Dean Evans, C., & DeMaster, E. G. (1993). Effect of regulating cholesterol biosynthesis on breath isoprene excretion in men. *Lipids*, *28*(8), 705–708. https://doi.org/10.1007/BF02535990

Page 54. *We emit so much isoprene*.

320. Veres, P. R., Faber, P., Drewnick, F., Lelieveld, J., & Williams, J. (2013). Anthropogenic sources of VOC in a football stadium: Assessing human emissions in the atmosphere. *Atmospheric Environment*, *77*, 1052–1059. https://doi.org/10.1016/j.atmosenv.2013.05.076

321. Williams, J., Stönner, C., Wicker, J., Krauter, N., Derstroff, B., Bourtsoukidis, E., Klüpfel, T., & Kramer, S. (2016). Cinema audiences reproducibly vary the chemical composition of air during films, by broadcasting scene specific emissions on breath. *Scientific Reports*, *6*(1), 25464. https://doi.org/10.1038/srep25464

Page 54. *Isoprene can protect*.

322. Sharkey, T. D., Wiberley, A. E., & Donohue, A. R. (2007). Isoprene Emission from Plants: Why and How. *Annals of Botany*, *101*(1), 5–18. https://doi.org/10.1093/aob/mcm240

Page 54 and 55. *When plants release*.

323. Went, F. W. (1960). Blue Hazes in the Atmosphere. *Nature*, *187*(4738), 641–643. https://doi.org/10.1038/187641a0

Page 55. *The Blue Ridge Mountains*.

324. Claeys, M., Graham, B., Vas, G., Wang, W., Vermeylen, R., Pashynska, V., Cafmeyer, J., Guyon, P., Andreae, M. O., Artaxo, P., & Maenhaut, W. (2004). Formation of Secondary Organic Aerosols Through Photooxidation of Isoprene. *Science*, *303*(5661), 1173–1176. https://doi.org/10.1126/science.1092805

Page 55. *The amount of isoprene*.

325. Sharkey, T. D., Wiberley, A. E., & Donohue, A. R. (2007). Isoprene Emission from Plants: Why and How. *Annals of Botany*, *101*(1), 5–18. https://doi.org/10.1093/aob/mcm240

Page 55. *Nature rubber is made*.

326. *What's in a Tire*. (n.d.). U.S. Tire Manufacturers Association. Retrieved June 29, 2023, from https://www.ustires.org/whats-tire-0

Page 55. *Indigenous peoples of South America*.

327. Whaley, W. G. (1948). Rubber-The Primary Sources For American Production. *Economic Botany*, *2*(2), 198–216. https://doi.org/10.1007/BF02859004

Page 55. *Separately, the Panama rubber tree*.

328. Fox, J. G., Ashmore, W., Blitz, J. H., Gillespie, S. D., Houston, S. D., Ted J. J. Leyenaar, Marcus, J., Moore, J. D., Urban, P. A., Schortman, E. M., & Webster, D. (1996). Playing with Power: Ballcourts and Political Ritual in Southern Mesoamerica [and Comments and Reply]. *Current Anthropology*, *37*(3), 483–509. http://www.jstor.org/stable/2744545

Page 55. *The oldest stone*.

329. Hill, W. D., Blake, M., & Clark, J. E. (1998). Ball court design dates back 3,400 years. *Nature*, *392*(6679), 878–879. https://doi.org/10.1038/31837

Page 55. *It was through*.

330. Whaley, W. G. (1948). Rubber-The Primary Sources For American Production. *Economic Botany*, *2*(2), 198–216. https://doi.org/10.1007/BF02859004

Page 56. *More than twenty thousand*. This reference also supports the rest of this paragraph.

331. Agrawal, A. A., & Konno, K. (2009). Latex: A Model for Understanding Mechanisms, Ecology, and Evolution of Plant Defense Against Herbivory. *Annual Review of Ecology, Evolution, and Systematics*, *40*(1), 311–331. https://doi.org/10.1146/annurev.ecolsys.110308.120307

Page 56. *The Congo rubber vine*. This reference also supports the rest of this paragraph.

332. Neuwinger, H. D. (1996). *African Ethnobotany: Poisons and Drugs : Chemistry, Pharmacology, Toxicology*.

Page 56. *Millions of people in what is now*.

333. Nzongola-Ntalaja, G. (2002). *The Congo from Leopold to Kabila*. Zed Books. https://doi.org/10.5040/9781350223004

Page 56. *For example, at Leopold's behest*.

334. Hochschild, A. (1998). *King Leopold's Ghost: A Story of Greed, Terror, and Heroism in Colonial Africa*. Mariner Books.

Page 56. *An early act of biopiracy*.

335. Page Jackson, J. (2008). *The Thief at the End of the World: Rubber, Power, and the Seeds of Empire*. Penguin

Page 56. *Some of the rubber tree*.

336. Loadman, J. (2005). *Tears of the Tree: The Story of Rubber - A Modern Marvel*. OUP Oxford.

Page 56 and 57. *The juggernaut and the blight*.

337. Davis, W. (1997). *One river: Science, adventure and hallucinogenics in the Amazon Basin*. Simon & Schuster Londres.

Page 57. *The United States could not have*.

338. Neeleman, G. & Neeleman, R. (2017). *Rubber Soldiers: The Forgotten Army that Saved the Allies in WWII*. Schiffer Publishing, Limited.

Page 57. *My only memory*.

339. Florida. - Division of Tourism. *Banyan tree by Thomas Edison's house in Fort Myers, Florida.* 20th century. State Archives of Florida, Florida Memory. https://www.floridamemory.com/items/show/92761, accessed 5 October 2023.

Page 57. *I later learned*. These references apply to the three paragraphs that follow.

340. Finlay, M. R. (2009). *Growing American Rubber: Strategic Plants and the Politics of National Security*. Rutgers University Press. http://www.jstor.org/stable/j.ctt5hhx8h

341. American Chemical Society (1998). *United States Synthetic Rubber Program, 1939-1945: a National Historic Chemical Landmark*. http://www.acs.org/content/acs/en/education/whatischemistry/landmarks/syntheticrubber.html

342. Grandin, G. (2009). *Fordlandia: The Rise and Fall of Henry Ford's Forgotten Jungle City*. Macmillan.

343. Raymond, M. (2021). *Global isoprene rubber market forecast at $1.9 billion by 2026*. https://rubberworld.com/global-isoprene-rubber-market-forecast-at-19-billion-by-2026/?doing_wp_cron=1638733987.1943929195404052734375

Page 57. *As I learned firsthand.*

344. Agrawal, A. A., & Konno, K. (2009). Latex: A Model for Understanding Mechanisms, Ecology, and Evolution of Plant Defense Against Herbivory. *Annual Review of Ecology, Evolution, and Systematics*, *40*(1), 311–331. https://doi.org/10.1146/annurev.ecolsys.110308.120307

Page 58. *Early last year*.

345. Text message to Noah Whiteman from Karin Fyhrie on January 20, 2021

Page 58. *We had been fooled*.

346. Losos, J. (2017). *Improbable destinies: how predictable is evolution?* Penguin UK.

Page 58. *The terpenoids in the latex*.

347. Sofat, B. K., Sood, G. C., Chandel, R. D., & Mehrotra, S. K. (1972). *Euphorbia royleana* latex keratitis. *Am. J. Ophthalmol.*, *74*(4), 634–637. https://doi.org/10.1016/0002-9394(72)90825-2

348. Scott, I. U., & Karp, C. L. (1996). Euphorbia sap keratopathy: four cases and a possible pathogenic mechanism. *British Journal of Ophthalmology*, *80*(9), 823–826. https://doi.org/10.1136/bjo.80.9.823

Page 59. *Many terpenoids serve as*.

349. Pichersky, E., & Raguso, R. A. (2018). Why do plants produce so many terpenoid compounds? *New Phytologist*, *220*(3), 692–702. https://doi.org/10.1111/nph.14178

Page 60. *Mono- and sesquiterpenes are volatile*.

350. Seyfullah, L. J., Beimforde, C., Dal Corso, J., Perrichot, V., Rikkinen, J., & Schmidt, A. R. (2018). Production and preservation of resins – past and present. *Biological Reviews*, *93*(3), 1684–1714. https://doi.org/10.1111/brv.12414

Page 60. *The resin and essential oil*.

351. Régimbal, J.-M., & Collin, G. (1994). Essential Oil Analysis of Balsam Fir *Abies balsamea* (L.) Mill. *Journal of Essential Oil Research*, *6*(3), 229–238. https://doi.org/10.1080/10412905.1994.9698369

352. Mills, J. S., & White, R. (1977). Natural Resins of Art and Archaeology Their Sources, Chemistry, and Identification. *Studies in Conservation*, *22*(1), 12–31. https://doi.org/10.2307/1505670

Page 60. *The oldest amber*.

353. Bray, P. S., & Anderson, K. B. (2009). Identification of Carboniferous (320 Million Years Old) Class Ic Amber. *Science*, *326*(5949), 132–134. https://doi.org/10.1126/science.1177539

Page 60. *There is even more ancient evidence*. These references apply to the whole paragraph.

354. Hernick, L. V., Landing, E., & Bartowski, K. E. (2008). Earth's oldest liverworts—Metzgeriothallus sharonae sp. nov. from the Middle Devonian (Givetian) of eastern New York, USA. *Review of Palaeobotany and Palynology*, *148*(2–4), 154–162. https://doi.org/10.1016/j.revpalbo.2007.09.002

355. Labandeira, C. C., Tremblay, S. L., Bartowski, K. E., & VanAller Hernick, L. (2014). Middle Devonian liverwort herbivory and antiherbivore defence. *New Phytologist*, *202*(1), 247–258. https://doi.org/10.1111/nph.12643

356. Asakawa, Y. (2004). Chemosystematics of the Hepaticae. *Phytochemistry*, *65*(6), 623–669. https://doi.org/10.1016/j.phytochem.2004.01.003

357. Howard, J. J., Cazin, J., & Wiemer, D. F. (1988). Toxicity of terpenoid deterrents to the leafcutting antAtta cephalotes and its mutualistic fungus. *Journal of Chemical Ecology*, *14*(1), 59–69. https://doi.org/10.1007/BF01022531

358. Graham, L. E., Gray, J., Graham, L. E., & Gray, J. (2001). 8. The Origin, Morphology, and Ecophysiology of Early Embryophytes: Neontological and Paleontological Perspectives. In *Plants Invade the Land* (pp. 140–158). Columbia University Press. https://doi.org/10.7312/gens11160-009

359. Daeschler, E. B., Shubin, N. H., & Jenkins, F. A. (2006). A Devonian tetrapod-like fish and the evolution of the tetrapod body plan. *Nature*, *440*(7085), 757–763. https://doi.org/10.1038/nature04639

Page 61. *Pine sawfly caterpillars eat only*.

360. Eisner, T., Johnessee, J. S., Carrel, J., Hendry, L. B., & Meinwald, J. (1974). Defensive Use by an Insect of a Plant Resin. *Science*, *184*(4140), 996–999. https://doi.org/10.1126/science.184.4140.996

Page 61. *If a predator tries to attack.*

361. The Legend of Hot Tar or Pitch as a Defensive Weapon. Atzbach, R. (2015). *Castles at War: The Danish Castle Research Association "Magt, Borg og Landskab" Interdisciplinary Symposium 2013*. Atzbach, R., Meldgaard Sass Jensen, L. & Plith Lauritsen, L. (eds.). Bonn: Dr. Rudolf Habelt, p. 119-134 16 p. (Castles of the North, Vol. 1).

Page 61. *To gain the upper hand.*

362. Kelsey, R. G., Gallego, D., Sánchez-García, F. J., & Pajares, J. A. (2014). Ethanol accumulation during severe drought may signal tree vulnerability to detection and attack by bark beetles. *Canadian Journal of Forest Research*, *44*(6), 554–561. https://doi.org/10.1139/cjfr-2013-0428

Page 61. *But they do so in response to.*

363. Kimmerer, T. W., & Kozlowski, T. T. (1982). Ethylene, Ethane, Acetaldehyde, and Ethanol Production By Plants under Stress. *Plant Physiology*, *69*(4), 840–847. https://doi.org/10.1104/pp.69.4.840

Page 61. *Once a mountain pine beetle.*

364. Chiu, C. C., Keeling, C. I., & Bohlmann, J. (2018). Monoterpenyl esters in juvenile mountain pine beetle and sex-specific release of the aggregation pheromone *trans* -verbenol. *Proceedings of the National Academy of Sciences*, *115*(14), 3652–3657. https://doi.org/10.1073/pnas.1722380115

Page 62. *After all, why would.*

365. Dawkins, R. (1976). *The Selfish Gene*. Oxford University Press

366. Alcock, J. (1982). Natural Selection and Communication among Bark Beetles. *The Florida Entomologist*, *65*(1), 17–32. https://doi.org/10.2307/3494143

Page 62. *When they bore into the trunk.*

367. Safranyik, L., Wilson, B. & Others. (2007). *The mountain pine beetle: a synthesis of biology, management and impacts on lodgepole pine*. Canadian Forest Service.

Page 62. *But there can be too much.*

368. Raffa, K. F. (2014). Terpenes Tell Different Tales at Different Scales: Glimpses into the Chemical Ecology of Conifer - Bark Beetle - Microbial Interactions. *Journal of Chemical Ecology*, *40*(1), 1–20. https://doi.org/10.1007/s10886-013-0368-y

Page 62. *Bristlecone pines, including the 4,853.*

369. Bentz, B. J., Hood, S. M., Hansen, E. M., Vandygriff, J. C., & Mock, K. E. (2017). Defense traits in the long-lived Great Basin bristlecone pine and resistance to the native herbivore mountain pine beetle. *New Phytologist*, *213*(2), 611–624. https://doi.org/10.1111/nph.14191

Page 62. *From tree ring analyses.*

370. Alfaro, R., Campbell, R., Vera, P., Hawkes, B., & Shore, T. (2004). *Dendroecological Reconstruction of Mountain Pine Beetle Outbreaks in the Chilcotin Plateau of British Columbia*. Mountain Pine Beetle Symposium: Challenges and Solutions 245–256 (Natural Resources Canada, Canadian Forest Service, Pac. For. Centre Victoria).

Page 62. *For one tragic example.*

371. EHS Today Staff. *No One Knew He was There: Death in a Confined Space*. https://www.ehstoday.com/safety/article/21904364/no-one-knew-he-was-there-death-in-a-confined-space (2002).

Page 63. *Birch trees hold a special.*

372. Ķencis, T. (2011). The Latvian Mythological Space in Scholarly Time. *Archaeology, religion, and folklore in the Baltic Sea region,* 144-157

Page 63. *The poem "Birches" by Robert Frost.*

373. Frost, R. *Birches*. The Atlantic. August, 1915. See: https://www.theatlantic.com/magazine/archive/1915/08/a-group-of-poems/306620/

Page 63. *Their alabaster trunks.*

374. Krasutsky, P. A. (2006). Birch bark research and development. *Natural Product Reports*, *23*(6), 919. https://doi.org/10.1039/b606816b

Page 63. *Known since 1788.*

375. Lowitz, J. T. (1788). Über eine neue, fast benzoeartige Substanz der Birken. *Chemische Annalen 2,* 312–316.

Page 63. *More recently, betulin*.

376. Smith, P. F., Ogundele, A., Forrest, A., Wilton, J., Salzwedel, K., Doto, J., Allaway, G. P., & Martin, D. E. (2007). Phase I and II Study of the Safety, Virologic Effect, and Pharmacokinetics/Pharmacodynamics of Single-Dose 3- *O* -(3′,3′-Dimethylsuccinyl)Betulinic Acid (Bevirimat) against Human Immunodeficiency Virus Infection. *Antimicrobial Agents and Chemotherapy*, *51*(10), 3574–3581. https://doi.org/10.1128/AAC.00152-07

Page 63. *They protect the thin layer*.

377. Harvey, R. B. (1923). Relation of the Color of Bark to the Temperature of the Cambium in Winter. *Ecology*, *4*(4), 391–394. https://doi.org/10.2307/1929185

Page 64. *Betulin also deters.*

378. Bergvall, U. A., Co, M., Bergström, R., Sjöberg, P. J. R., Waldebäck, M., & Turner, C. (2013). Anti-browsing effects of birch bark extract on fallow deer. *European Journal of Forest Research*, *132*(5–6), 717–725. https://doi.org/10.1007/s10342-013-0709-y

379. Hordyjewska, A., Ostapiuk, A., Horecka, A., & Kurzepa, J. (2019). Betulin and betulinic acid: triterpenoids derivatives with a powerful biological potential. *Phytochemistry Reviews*, *18*(3), 929–951. https://doi.org/10.1007/s11101-019-09623-1

Page 64. *Paper birch lines the roofs*.

380. Turner, N. J., Ari, Y., Berkes, F., Davidson-Hunt, I., Ertug, Z. F., & Miller, A. (2009). Cultural Management of Living Trees: An International Perspective. *Journal of Ethnobiology*, *29*(2), 237–270. https://doi.org/10.2993/0278-0771-29.2.237

Page 64. *All these qualities.*

381. Densmore, F. (1928). *Uses of plants by the Chippewa Indians*. U.S. G.P.O. https://doi.org/10.5962/bhl.title.79349

Page 64. *The ancient and sacred*.

382. Blessing F. K. (1977). *The ojibway indians observed : papers of fred k. blessing jr. on the ojibway indians from the minnesota archaeologist*. Minnesota Archaeological Society.

Page 65. *Ethanol is unique*.

383. Yang, J., Son, J. H., Kim, H., Cho, S., Na, J., Yeon, Y. J., & Lee, J. (2019). Mevalonate production from ethanol by direct conversion through acetyl-CoA using recombinant Pseudomonas putida, a novel biocatalyst for terpenoid production. *Microbial Cell Factories*, *18*(1), 168. https://doi.org/10.1186/s12934-019-1213-y

Page 65. *Despite my father's AUD*. The quote "good company, good welcome, good wine, can make good people." is from William Shakespeare's Henry the Eighth.

384. Shakespeare, W. *Henry VIII*. Published in Rafael Holinshed's *Chronicles of England, Scotlande, and Irelande* 2, 1577.

Page 65. *At the same time*.

385. Baum-Baicker, C. (1985). The psychological benefits of moderate alcohol consumption: A review of the literature. *Drug and Alcohol Dependence*, *15*(4), 305–322. https://doi.org/10.1016/0376-8716(85)90008-0

386. Marchand, A., Demers, A., Durand, P., & Simard, M. (2003). The moderating effect of alcohol intake on the relationship between work strains and psychological distress. *Journal of Studies on Alcohol*, *64*(3), 419–427. https://doi.org/10.15288/jsa.2003.64.419

387. Stockwell, T., Zhao, J., Panwar, S., Roemer, A., Naimi, T., & Chikritzhs, T. (2016). Do "Moderate" Drinkers Have Reduced Mortality Risk? A Systematic Review and Meta-Analysis of Alcohol Consumption and All-Cause Mortality. *J. Stud. Alcohol Drugs*, *77*(2), 185–198. https://doi.org/10.15288/jsad.2016.77.185

388. Griswold, M. G., Fullman, N., Hawley, C., Arian, N., Zimsen, S. R. M., Tymeson, H. D., Venkateswaran, V., Tapp, A. D., Forouzanfar, M. H., Salama, J. S., Abate, K. H., Abate, D., Abay, S. M., Abbafati, C., Abdulkader, R. S., Abebe, Z., Aboyans, V., Abrar, M. M., Acharya, P., … Gakidou, E. (2018). Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*, *392*(10152), 1015–1035. https://doi.org/10.1016/S0140-6736(18)31310-2

389. John, U., Rumpf, H.-J., Hanke, M., & Meyer, C. (2021). Alcohol abstinence and mortality in a general population sample of adults in Germany: A cohort study. *PLoS Med.*, *18*(11), e1003819. https://doi.org/10.1371/journal.pmed.1003819

Page 65. *AUD is the third-leading*.

390. CDC. (2021). Deaths from excessive alcohol use in the United States. https://www.cdc.gov/alcohol/features/excessive-alcohol-deaths.html

Page 65. *Binge drinking kills*.

391. Kanny, D., Naimi, T. S., Liu, Y., Lu, H., & Brewer, R. D. (2018). Annual Total Binge Drinks Consumed by U.S. Adults, 2015. *American Journal of Preventive Medicine*, *54*(4), 486–496. https://doi.org/10.1016/j.amepre.2017.12.021

Page 66. *Brewer's yeast, which humans*.

392. Gonçalves, M., Pontes, A., Almeida, P., Barbosa, R., Serra, M., Libkind, D., Hutzler, M., Gonçalves, P., & Sampaio, J. P. (2016). Distinct Domestication Trajectories in Top-Fermenting Beer Yeasts and Wine Yeasts. *Current Biology*, *26*(20), 2750–2761. https://doi.org/10.1016/j.cub.2016.08.040

393. McGovern, P. E., Zhang, J., Tang, J., Zhang, Z., Hall, G. R., Moreau, R. A., Nuñez, A., Butrym, E. D., Richards, M. P., Wang, C., Cheng, G., Zhao, Z., & Wang, C. (2004). Fermented beverages of pre- and proto-historic China. *Proceedings of the National Academy of Sciences*, *101*(51), 17593–17598. https://doi.org/10.1073/pnas.0407921102

Page 66. *Yeast's ability to make alcohol*. In addition to rotting fruit, these yeast associate with bark and galls in nature. The"Crabtree effect" is the observation that yeast ferment ethanol even in aerobic conditions, which is unusual for yeasts.

394. de Deken, R. H. (1966). The Crabtree Effect: A Regulatory System in Yeast. *Journal of General Microbiology*, *44*(2), 149–156. https://doi.org/10.1099/00221287-44-2-149

395. Peter, J., de Chiara, M., Friedrich, A., Yue, J.-X., Pflieger, D., Bergström, A., Sigwalt, A., Barre, B., Freel, K., Llored, A., Cruaud, C., Labadie, K., Aury, J.-M., Istace, B., Lebrigand, K., Barbry, P., Engelen, S., Lemainque, A., Wincker, P., … Schacherer, J. (2018). Genome evolution across 1,011 Saccharomyces cerevisiae isolates. *Nature*, *556*(7701), 339–344. https://doi.org/10.1038/s41586-018-0030-5

396. Piskur, J., Rozpedowska, E., Polakova, S., Merico, A., & Compagno, C. (2006). How did Saccharomyces evolve to become a good brewer? *Trends in Genetics*, *22*(4), 183–186. https://doi.org/10.1016/j.tig.2006.02.002

397. Boynton, P. J., & Greig, D. (2014). The ecology and evolution of non-domesticated *Saccharomyces* species. *Yeast*, n/a-n/a. https://doi.org/10.1002/yea.3040

398. Pretorius, I. S. (2000). Tailoring wine yeast for the new millennium: novel approaches to the ancient art of winemaking. *Yeast (Chichester, England)*, *16*(8), 675–729. https://doi.org/10.1002/1097-0061(20000615)16:8<675::AID-YEA585>3.0.CO;2-B

399. Thomson, J. M., Gaucher, E. A., Burgan, M. F., de Kee, D. W., Li, T., Aris, J. P., & Benner, S. A. (2005). Resurrecting ancestral alcohol dehydrogenases from yeast. *Nature Genetics*, *37*(6), 630–635. https://doi.org/10.1038/ng1553

Page 66. *Brewer's yeast is resistant.*

400. Casey, G. P., & Ingledew, W. M. M. (1986). Ethanol Tolerance in Yeasts. *CRC Critical Reviews in Microbiology*, *13*(3), 219–280. https://doi.org/10.3109/10408418609108739

401. Snoek, T., Verstrepen, K. J., & Voordeckers, K. (2016). How do yeast cells become tolerant to high ethanol concentrations? *Current Genetics*, *62*(3), 475–480. https://doi.org/10.1007/s00294-015-0561-3

402. Williams, K. M., Liu, P., & Fay, J. C. (2015). Evolution of ecological dominance of yeast species in high-sugar environments. *Evolution*, *69*(8), 2079–2093. https://doi.org/10.1111/evo.12707

Page 67. *Unsurprisingly, fruit flies are resistant.*

403. McKenzie, J. A., & Parsons, P. A. (1972). Alcohol tolerance: An ecological parameter in the relative success of *Drosophila melanogaster* and *Drosophila simulans*. *Oecologia*, *10*(4), 373–388. https://doi.org/10.1007/BF00345738

Page 67. *If that doesn't work*.

404. Milan, N. F., Kacsoh, B. Z., & Schlenke, T. A. (2012). Alcohol Consumption as Self-Medication against Blood-Borne Parasites in the Fruit Fly. *Current Biology*, *22*(6), 488–493. https://doi.org/10.1016/j.cub.2012.01.045

Page 67. *They only do so if*.

405. Kacsoh, B. Z., Lynch, Z. R., Mortimer, N. T., & Schlenke, T. A. (2013). Fruit Flies Medicate Offspring After Seeing Parasites. *Science*, *339*(6122), 947–950. https://doi.org/10.1126/science.1229625

Page 68. *The cost of a high ethanol*.

406. Chawla, S. S., Perron, J.-M., & Radouco-Thomas, C. (1981). Effects of ingested ethanol on adult *Drosophila melanogaster* (Diptera: Drosophilidae). *The Canadian Entomologist*, *113*(4), 315–323. https://doi.org/10.4039/Ent113315-4

Page 69. *We know Darwin held this view*. The quote is derived from the letter cited below.

407. Darwin, C., & The Editors of the Darwin Correspondence Project. (2021). *The Correspondence of Charles Darwin* (F. Burkhardt & J. A. Secord, Eds.). Cambridge University Press. https://doi.org/10.1017/9781108884594

Page 69. *Ethanol is thought to*.

408. Kumar, S., Porcu, P., Werner, D. F., Matthews, D. B., Diaz-Granados, J. L., Helfand, R. S., & Morrow, A. L. (2009). The role of GABAA receptors in the acute and chronic effects of ethanol: a decade of progress. *Psychopharmacology*, *205*(4), 529–564. https://doi.org/10.1007/s00213-009-1562-z

Page 69. *It may actually bind to the*.

409. Wallner, M., Hanchar, H. J., & Olsen, R. W. (2014). Alcohol Selectivity of β3-Containing GABAA Receptors: Evidence for a Unique Extracellular Alcohol/Imidazobenzodiazepine Ro15-4513 Binding Site at the α+β- Subunit

Interface in αβ3δ GABAA Receptors. *Neurochemical Research*, *39*(6), 1118–1126. https://doi.org/10.1007/s11064-014-1243-0

410. Masiulis, S., Desai, R., Uchański, T., Serna Martin, I., Laverty, D., Karia, D., Malinauskas, T., Zivanov, J., Pardon, E., Kotecha, A., Steyaert, J., Miller, K. W., & Aricescu, A. R. (2019). GABAA receptor signalling mechanisms revealed by structural pharmacology. *Nature*, *565*(7740), 454–459. https://doi.org/10.1038/s41586-018-0832-5

411. Laverty, D., Desai, R., Uchański, T., Masiulis, S., Stec, W. J., Malinauskas, T., Zivanov, J., Pardon, E., Steyaert, J., Miller, K. W., & Aricescu, A. R. (2019). Cryo-EM structure of the human α1β3γ2 GABAA receptor in a lipid bilayer. *Nature*, *565*(7740), 516–520. https://doi.org/10.1038/s41586-018-0833-4

412. Olsen, R. W. (2018). GABAA receptor: Positive and negative allosteric modulators. *Neuropharmacology*, *136*, 10–22. https://doi.org/10.1016/j.neuropharm.2018.01.036

Page 70. *In addition to coping with physical trauma*.

413. Smith, K. Z., Smith, P. H., & Grekin, E. R. (2014). Childhood sexual abuse, distress, and alcohol-related problems: Moderation by drinking to cope. *Psychology of Addictive Behaviors*, *28*(2), 532–537. https://doi.org/10.1037/a0035381

Page 70. *Robert Dudley, my UC-Berkeley colleague*. References support the paragraphs through the end of this section on page 71.

414. Dudley, R. (2000). Evolutionary Origins of Human Alcoholism in Primate Frugivory. *The Quarterly Review of Biology*, *75*(1), 3–15. https://doi.org/10.1086/393255

415. Dudley, R. (2002). Fermenting fruit and the historical ecology of ethanol ingestion: is alcoholism in modern humans an evolutionary hangover? Addiction, 97(4), 381–388. https://doi.org/10.1046/j.1360-0443.2002.00002.x

416. Stephens, Dustin, and Robert K. Dudley. (2004). The drunken monkey hypothesis. Natural History

417. Dudley, Robert. (2014.) *The drunken monkey: why we drink and abuse alcohol*. Univ of California Press

418. Dudley, R. (2004). Ethanol, Fruit Ripening, and the Historical Origins of Human Alcoholism in Primate Frugivory. *Integrative and Comparative Biology*, *44*(4), 315–323. https://doi.org/10.1093/icb/44.4.315

419. Sánchez, F., Korine, C., Pinshow, B., & Dudley, R. (2004). The Possible Roles of Ethanol in the Relationship Between Plants and Frugivores: First Experiments with Egyptian Fruit Bats1. *Integrative and Comparative Biology*, *44*(4), 290–294. https://doi.org/10.1093/icb/44.4.290

420. Dudley, R., & Maro, A. (2021). Human Evolution and Dietary Ethanol. *Nutrients*, *13*(7), 2419. https://doi.org/10.3390/nu13072419

421. Campbell, C. J., Maro, A., Weaver, V., & Dudley, R. (2022). Dietary ethanol ingestion by free-ranging spider monkeys *(Ateles geoffroyi*). *Royal Society Open Science*, *9*(3). https://doi.org/10.1098/rsos.211729

Page 71. *We know now, thanks largely*.

422. Li, Qing.(2018). *Shirin-Yoku: The Art and Science of Forest Bathing*. Penguin.

423. Li, Q., Kobayashi, M., Wakayama, Y., Inagaki, H., Katsumata, M., Hirata, Y., Hirata, K., Shimizu, T., Kawada, T., Park, B. J., Ohira, T., Kagawa, T., & Miyazaki, Y. (2009). Effect of Phytoncide from Trees on Human Natural Killer Cell Function. *International Journal of Immunopathology and Pharmacology*, *22*(4), 951–959. https://doi.org/10.1177/039463200902200410

Page 71. *In a study of 92 alcoholics*.

424. Kuria, M. W., Ndetei, D. M., Obot, I. S., Khasakhala, L. I., Bagaka, B. M., Mbugua, M. N., & Kamau, J. (2012). The Association between Alcohol Dependence and Depression before and after Treatment for Alcohol Dependence. *ISRN Psychiatry*, *2012*, 1–6. https://doi.org/10.5402/2012/482802

425. Shin, W. S., Shin, C. S., & Yeoun, P. S. (2012). The influence of forest therapy camp on depression in alcoholics. *Environmental Health and Preventive Medicine*, *17*(1), 73–76. https://doi.org/10.1007/s12199-011-0215-0

Page 71. *We don't know for certain*.

426. Antonelli, M., Donelli, D., Carlone, L., Maggini, V., Firenzuoli, F., & Bedeschi, E. (2022). Effects of forest bathing (shinrin-yoku) on individual well-

being: an umbrella review. *International Journal of Environmental Health Research*, *32*(8), 1842–1867. https://doi.org/10.1080/09603123.2021.1919293

Page 72. *However, as Qing Li*.

427. Li, Qing. (2018). *Shirin-Yoku: The Art and Science of Forest Bathing*. Penguin.

Page 72. *One idea for the mechanism*.

428. Yamaoka, S., Tomita, T., Imaizumi, Y., Watanabe, K., & Hatanaka, A. (2005). Effects of plant-derived odors on sleep-wakefulness and circadian rhythmicity in rats. *Chemical senses*, *30 Suppl 1*, i264–i265. https://doi.org/10.1093/chemse/bjh216

Page 72. *Most likely, plants.*

429. Bown, A. W., MacGregor, K. B., & Shelp, B. J. (2006). Gamma-aminobutyrate: defense against invertebrate pests? *Trends in Plant Science*, *11*(9), 424–427. https://doi.org/10.1016/j.tplants.2006.07.002

Page 72. *With my collaborator Jia Huang*.

430. Guo, L., Qiao, X., Haji, D., Zhou, T., Liu, Z., Whiteman, N. K., & Huang, J. (2023). Convergent resistance to GABA receptor neurotoxins through plant–insect coevolution. *Nature Ecology & Evolution*, *7*(9), 1444–1456. https://doi.org/10.1038/s41559-023-02127-4

Page 72. *The neurotransmitter GABA*.

431. Dudel, J., Gryder, R., Kaji, A., Kuffler, S. W., & Potter, D. D. (1963). Gama-aminobutyric acid and other blocking compounds in Crustacea. I. Central nervous system. *Journal of Neurophysiology*, *26*(5), 721–728. https://doi.org/10.1152/jn.1963.26.5.721

Page 72. *They use it much as they*.

432. Bown, A. W., MacGregor, K. B., & Shelp, B. J. (2006). Gamma-aminobutyrate: defense against invertebrate pests? *Trends in Plant Science*, *11*(9), 424–427. https://doi.org/10.1016/j.tplants.2006.07.002

Page 72. *Alpha pinene causes a hypnotic effect*.

433. Satou, T., Kasuya, H., Maeda, K., & Koike, K. (2014). Daily Inhalation of α-Pinene in Mice: Effects on Behavior and Organ Accumulation. *Phytotherapy Research*, *28*(9), 1284–1287. https://doi.org/10.1002/ptr.5105

Page 72 and 73. *All things considered*.

434. Oh, B., Lee, K. J., Zaslawski, C., Yeung, A., Rosenthal, D., Larkey, L., & Back, M. (2017). Health and well-being benefits of spending time in forests: systematic review. *Environmental Health and Preventive Medicine*, *22*(1), 71. https://doi.org/10.1186/s12199-017-0677-9

Page 73. *In the forest bathing literature*.

435. Kohman, E. F. (1947). The Chemical Components of Onion Vapors Responsible for Wound-healing Qualities. *Science*, *106*(2765), 625–627. https://doi.org/10.1126/science.106.2765.625

Page 73. *Unfortunately, Tokin aligned himself with Lysenkoism*.

436. Dobzhansky, T. (1955). The Crisis of Soviet Biology. In *Continuity and Change in Russian and Soviet Thought* (pp. 329–346). Harvard University Press. https://doi.org/10.4159/harvard.9780674367173.c25

Page 73. *Although his reasoning was incorrect*.

437. Kohman, E. F. (1947). The Chemical Components of Onion Vapors Responsible for Wound-healing Qualities. *Science*, *106*(2765), 625–627. https://doi.org/10.1126/science.106.2765.625

Page 73. *He also presciently hypothesized*.

438. Baldwin, I. T., & Schultz, J. C. (1983). Rapid Changes in Tree Leaf Chemistry Induced by Damage: Evidence for Communication Between Plants. *Science*, *221*(4607), 277–279. https://doi.org/10.1126/science.221.4607.277

439. Rhoades, D. F. (1983). *Responses of Alder and Willow to Attack by Tent Caterpillars and Webworms: Evidence for Pheromonal Sensitivity of Willows* (pp. 55–68). https://doi.org/10.1021/bk-1983-0208.ch004

440. Kazarian, R. (1983). Some Evidence That Trees 'Communicate When in Trouble.' *Environmental Conservation*, *10*(2), 173–173. https://doi.org/10.1017/S0376892900012376

Page 73. *These messages can even be absorbed*.

441. Himanen, S. J., Blande, J. D., Klemola, T., Pulkkinen, J., Heijari, J., & Holopainen, J. K. (2010). Birch (*Betula* spp.) leaves adsorb and re-release volatiles specific to neighbouring plants – a mechanism for associational herbivore resistance? *New Phytologist*, *186*(3), 722–732. https://doi.org/10.1111/j.1469-8137.2010.03220.x

442. Baldwin, I. T., & Schultz, J. C. (1983). Rapid Changes in Tree Leaf Chemistry Induced by Damage: Evidence for Communication Between Plants. *Science*, *221*(4607), 277–279. https://doi.org/10.1126/science.221.4607.277

Page 73. *We now know*.

443. Karban, R., Shiojiri, K., Huntzinger, M., & McCall, A. C. (2006). Damage-induced resistance in sagebrush: volatiles are key to intra- and interplant communication. *Ecology*, *87*(4), 922–930. https://doi.org/10.1890/0012-9658(2006)87[922:drisva]2.0.co;2

444. Karban, R., Shiojiri, K., Ishizaki, S., Wetzel, W. C., & Evans, R. Y. (2013). Kin recognition affects plant communication and defence. *Proceedings of the Royal Society B: Biological Sciences*, *280*(1756), 20123062. https://doi.org/10.1098/rspb.2012.3062

Page 74. *Parasitoid wasps, for example*.

445. Turlings, T. C. J., Tumlinson, J. H., & Lewis, W. J. (1990). Exploitation of Herbivore-Induced Plant Odors by Host-Seeking Parasitic Wasps. *Science*, *250*(4985), 1251–1253. https://doi.org/10.1126/science.250.4985.1251

Page 75. *However, beultin, like alpha-pinene*.

446. Muceniece, R., Saleniece, K., Rumaks, J., Krigere, L., Dzirkale, Z., Mezhapuke, R., Zharkova, O., & Klusa, V. (2008). Betulin binds to gamma-aminobutyric acid receptors and exerts anticonvulsant action in mice. *Pharmacol. Biochem. Behav.*, *90*(4), 712–716. https://doi.org/10.1016/j.pbb.2008.05.015

447. Durst, T., Merali, Z., Arnason, J. T., Pablo Sanchez-Vindas, E., & Poveda-Alvarez, L. J. (2015). Anxiolytic marcgraviaceae compositions containing betulinic acid, betulinic acid derivatives, and methods. In USPTO (Ed.), *US Patent*. University of Ottawa.

https://patentimages.storage.googleapis.com/5c/b4/d6/04bc5a9fd60b7b/US20150005267A1.pdf

Page 75. *Ethanol also probably.*

448. Mihic, S. J., Ye, Q., Wick, M. J., Koltchine, V. v., Krasowski, M. D., Finn, S. E., Mascia, M. P., Valenzuela, C. F., Hanson, K. K., Greenblatt, E. P., Harris, R. A., & Harrison, N. L. (1997). Sites of alcohol and volatile anaesthetic action on GABAA and glycine receptors. *Nature*, *389*(6649), 385–389. https://doi.org/10.1038/38738

Page 75. *Additionally, naturally occurring*.

449. Olfson, E., & Bierut, L. J. (2012). Convergence of genome-wide association and candidate gene studies for alcoholism. *Alcohol. Clin. Exp. Res.*, *36*(12), 2086–2094. https://doi.org/10.1111/j.1530-0277.2012.01843.x

450. Li, D., Sulovari, A., Cheng, C., Zhao, H., Kranzler, H. R., & Gelernter, J. (2014). Association of gamma-aminobutyric acid A receptor α2 gene (GABRA2) with alcohol use disorder. *Neuropsychopharmacology*, *39*(4), 907–918. https://doi.org/10.1038/npp.2013.291

Page 76. *Fog drip brings life.*

451. Limm, E. B., Simonin, K. A., Bothman, A. G., & Dawson, T. E. (2009). Foliar water uptake: a common water acquisition strategy for plants of the redwood forest. *Oecologia*, *161*(3), 449–459. https://doi.org/10.1007/s00442-009-1400-3

Page 76. *Toxins produced by the leaves.*

452. del Moral, R., & Muller, C. H. (1969). Fog Drip: A Mechanism of Toxin Transport from *Eucalyptus globulus*. *Bulletin of the Torrey Botanical Club*, *96*(4), 467. https://doi.org/10.2307/2484065

453. Molina, A., Reigosa, M. J., & Carballeira, A. (1991). Release of allelochemical agents from litter, throughfall, and topsoil in plantations of *Eucalyptus globulus* Labill in Spain. *Journal of Chemical Ecology*, *17*(1), 147–160. https://doi.org/10.1007/BF00994428

Page 76. *The chemicals in the water.*

454. Inderjit. (1996). Plant Phenolics in Allelopathy. *Botanical Review*, *62*(2), 186–202. http://www.jstor.org/stable/4354269

455. del Moral, R., & Muller, C. H. (1970). The Allelopathic Effects of *Eucalyptus camaldulensis*. *American Midland Naturalist*, *83*(1), 254. https://doi.org/10.2307/2424020

Page 76. *By suppressing the growth*.

456. Callaway, R. M., & Ridenour, W. M. (2004). Novel weapons: invasive success and the evolution of increased competitive ability. *Frontiers in Ecology and the Environment*, *2*(8), 436–443. https://doi.org/https://doi.org/10.1890/1540-9295(2004)002[0436:NWISAT]2.0.CO;2

Page 77. *It could be the same reason*.

457. Becerra, P. I., Catford, J. A., Inderjit, Luce McLeod, M., Andonian, K., Aschehoug, E. T., Montesinos, D., & Callaway, R. M. (2018). Inhibitory effects of *Eucalyptus globulus* on understorey plant growth and species richness are greater in non-native regions. *Global Ecology and Biogeography*, *27*(1), 68–76. https://doi.org/10.1111/geb.12676

Page 77. *Nowadays, eucalyptol is used*.

458. Galan, D. M., Ezeudu, N. E., Garcia, J., Geronimo, C. A., Berry, N. M., & Malcolm, B. J. (2020). Eucalyptol (1,8-cineole): an underutilized ally in respiratory disorders? *Journal of Essential Oil Research*, *32*(2), 103–110. https://doi.org/10.1080/10412905.2020.1716867

Page 77. *In Australia, suspected eucalyptol poisoning*.

459. Day, L. M., Ozanne-Smith, J., Parsons, B. J., Dobbin, M., & Tibballs, J. (1997). Eucalyptus oil poisoning among young children: mechanisms of access and the potential for prevention. *Australian and New Zealand Journal of Public Health*, *21*(3), 297–302. https://doi.org/10.1111/j.1467-842X.1997.tb01703.x

Page 77 and 78. *Oral consumption.*

460. National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 2758, Eucalyptol. Retrieved October 5, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Eucalyptol.

461. Tibballs, J. (1995). Clinical effects and management of eucalyptus oil ingestion in infants and young children. *Medical Journal of Australia*, *163*(4), 177–180. https://doi.org/10.5694/j.1326-5377.1995.tb124516.x

Page 78. *On the other hand.*

462. MacPherson, J. (2009). The Eucalyptus in the Daily Life and Medical Practice of the Australian Aborigines. *Mankind*, *2*(6), 175–180. https://doi.org/10.1111/j.1835-9310.1939.tb00957.x

Page 78. *The successful health treatments.*

463. Goto, S., Suzuki, H., Nakagawa, T., & Shimizu, K. (2020). The Effect of Eucalyptol on Nursing Home Residents. *Scientific Reports*, *10*(1), 3996. https://doi.org/10.1038/s41598-020-61045-8

Page 78. *Blood flow throughout.*

464. Našel, C., Našel, B., Samec, P., Schindler, E., & Buchbauer, G. (1994). Functional imaging of effects of fragrances on the human brain after prolonged inhalation. *Chemical Senses*, *19*(4), 359–364. https://doi.org/10.1093/chemse/19.4.359

465. Gomes, P. B., Feitosa, M. L., Silva, M. I. G., Noronha, E. C., Moura, B. A., Venâncio, E. T., Rios, E. R. V., de Sousa, D. P., de Vasconcelos, S. M. M., Fonteles, M. M. de F., & de Sousa, F. C. F. (2010). Anxiolytic-like effect of the monoterpene 1,4-cineole in mice. *Pharmacology Biochemistry and Behavior*, *96*(3), 287–293. https://doi.org/10.1016/j.pbb.2010.05.019

Page 78. *Eucalyptol activates the "menthol receptor."*

466. Takaishi, M., Fujita, F., Uchida, K., Yamamoto, S., Sawada (Shimizu), M., Hatai (Uotsu), C., Shimizu, M., & Tominaga, M. (2012). 1,8-Cineole, a TRPM8 Agonist, is a Novel Natural Antagonist of Human TRPA1. *Molecular Pain*, *8*, 1744-8069-8–86. https://doi.org/10.1186/1744-8069-8-86

467. Bautista, D. M., Siemens, J., Glazer, J. M., Tsuruda, P. R., Basbaum, A. I., Stucky, C. L., Jordt, S.-E., & Julius, D. (2007). The menthol receptor TRPM8 is the principal detector of environmental cold. *Nature*, *448*(7150), 204–208. https://doi.org/10.1038/nature05910

Page 78. *Plants don't always use.*

468. Ramya, M., Jang, S., An, H.-R., Lee, S.-Y., Park, P.-M., & Park, P. H. (2020). Volatile Organic Compounds from Orchids: From Synthesis and Function to Gene Regulation. *International Journal of Molecular Sciences*, *21*(3), 1160. https://doi.org/10.3390/ijms21031160

469. Brand, P., Hinojosa-Díaz, I. A., Ayala, R., Daigle, M., Yurrita Obiols, C. L., Eltz, T., & Ramírez, S. R. (2020). The evolution of sexual signaling is linked to odorant receptor tuning in perfume-collecting orchid bees. *Nature Communications*, *11*(1), 244. https://doi.org/10.1038/s41467-019-14162-6

Page 79. *It seems paradoxical*.

470. Janzen, D. H. (1977). Why Don't Ants Visit Flowers? *Biotropica*, *9*(4), 252. https://doi.org/10.2307/2388142

471. Stephenson, A. G. (1981). Toxic Nectar Deters Nectar Thieves of *Catalpa speciosa*. *American Midland Naturalist*, *105*(2), 381. https://doi.org/10.2307/2424757

472. Rhoades, D. F., & Bergdahl, J. C. (1981). Adaptive Significance of Toxic Nectar. *The American Naturalist*, *117*(5), 798–803. https://doi.org/10.1086/283765

473. Stephenson, A. G. (1982). Iridoid glycosides in the nectar of *Catalpa speciosa* are unpalatable to nectar thieves. *Journal of Chemical Ecology*, *8*(7), 1025–1034. https://doi.org/10.1007/BF00987883

Page 79. *Evolution may favor plants*.

474. Raven, P. H. (1972). Why are bird-visited flowers predominantly red? *Evolution*, *26*(4), 674–674. https://doi.org/10.1111/j.1558-5646.1972.tb01975.x

475. Shrestha, M., Dyer, A. G., Boyd-Gerny, S., Wong, B. B. M., & Burd, M. (2013). Shades of red: bird-pollinated flowers target the specific colour discrimination abilities of avian vision. *New Phytologist*, *198*(1), 301–310. https://doi.org/10.1111/nph.12135

Page 79. *Some of the best-studied toxins are*.

476. Reynolds, T. (1985). The compounds in Aloë leaf exudates: a review. *Botanical Journal of the Linnean Society*, *90*(3), 157–177. https://doi.org/10.1111/j.1095-8339.1985.tb00377.x

Page 80. *Honeybees and long-billed sunbirds*.

477. Johnson, S. D., Hargreaves, A. L., & Brown, M. (2006). Dark, bitter-tasting nectar functions as a filter of flower visitors in a bird-pollinated plant. *Ecology*, *87*(11), 2709–2716. https://doi.org/10.1890/0012-9658(2006)87[2709:dbnfaa]2.0.co;2

478. Botes, C., Johnson, S. D., & Cowling, R. M. (2009). The Birds and the Bees: Using Selective Exclusion to Identify Effective Pollinators of African Tree Aloes. *International Journal of Plant Sciences*, *170*(2), 151–156. https://doi.org/10.1086/595291

Page 80. *These phenolics are also the same*.

479. Reynolds, T. (1985). The compounds in Aloë leaf exudates: a review. *Botanical Journal of the Linnean Society*, *90*(3), 157–177. https://doi.org/10.1111/j.1095-8339.1985.tb00377.x

Page 81. *The grayanotoxins in nectar are*.

480. Tiedeken, E. J., Egan, P. A., Stevenson, P. C., Wright, G. A., Brown, M. J. F., Power, E. F., Farrell, I., Matthews, S. M., & Stout, J. C. (2016). Nectar chemistry modulates the impact of an invasive plant on native pollinators. *Functional Ecology*, *30*(6), 885–893. https://doi.org/10.1111/1365-2435.12588

Page 81. *Notably, the Green historian Strabo*. The quote below this paragraph is derived from this reference as well.

481. Strabo, *Geography*, book 12, chapter 3. http://www.perseus.tufts.edu/hopper/text?doc=Perseus:text:1999.01.0198:book%3D12:chapter%3D3.

Page 81. *The Heptacomitae people of Pontus*.

482. Mayor, A. (2010). *The Poison King: The Life and Legend of Mithradates, Rome's Deadliest Enemy*. Princeton University Press. http://www.jstor.org/stable/j.ctt7t7kz

Page 81. *The poison honey may well be*.

483. Koca, I., & Koca, A. F. (2007). Poisoning by mad honey: A brief review. *Food and Chemical Toxicology*, *45*(8), 1315–1318. https://doi.org/10.1016/j.fct.2007.04.006

484. H., S. (2021, June 8). *Hunting For Hallucinogenic Honey In Nepal With The Gurung Tribe*. Homegrown. https://homegrown.co.in/homegrown-explore/hunting-for-hallucinogenic-honey-in-nepal-with-the-gurung-tribe-a-raphael-treza-film

485. Newey, A. (2014, February 27). *The ancient art of honey hunting in Nepal - in pictures*. The Guardian. https://www.theguardian.com/travel/gallery/2014/feb/27/honey-hunters-nepal-in-pictures

486. Strickland, S. S. (1982). Honey Hunting by the Gurungs of Nepal. *Bee World*, *63*(4), 153–161. https://doi.org/10.1080/0005772X.1982.11097889

487. Shrestha, T. M., Nepal, G., Shing, Y. K., & Shrestha, L. (2018). Cardiovascular, psychiatric, and neurological phenomena seen in mad honey disease: A clinical case report. *Clinical Case Reports*, *6*(12), 2355–2357. https://doi.org/10.1002/ccr3.1889

488. Pant, K. (2018). Mad honey: food, medicine or toxin? A food technology perspective. *Journal of Agriculture and Environment*, *19*, 51-58.

Page 82. *On the heels*.

489. C. Julius Caesar. *Caesar's Gallic War*. Translator. W. A. McDevitte. Translator. W. S. Bohn. 1st Edition. New York. Harper & Brothers. 1869. Harper's New Classical Library. See: https://www.perseus.tufts.edu/hopper/text?doc=Perseus%3Atext%3A1999.02.0001%3Abook%3D6%3Achapter%3D31

490. Smith, W. (n.d.). *Dictionary of Greek and Roman Biography and Mythology* (Vol. 1, p. 634). https://web.archive.org/web/20060522223104/http://www.ancientlibrary.com/smith-bio/0643.html#

Page 82. *There are two main classes*.

491. Lange, B. M., & Conner, C. F. (2021). Taxanes and taxoids of the genus Taxus – A comprehensive inventory of chemical diversity. *Phytochemistry*, *190*, 112829. https://doi.org/10.1016/j.phytochem.2021.112829

Page 82. *The compound showed promise.*

492. Fuchs, D. A., & Johnson, R. K. (1978). Cytologic evidence that taxol, an antineoplastic agent from *Taxus brevifolia*, acts as a mitotic spindle poison. *Cancer Treatment Reports*, *62*(8), 1219–1222.

493. Rowinsky EK, Donehower RC, Rosenshein NB, Ettinger DS, McGuire WP (1988). Phase II study of taxol in advanced epithelial malignancies. *Proceedings of the Association of Clinical Oncology*. 7: 136.

494. Wani, M. C., Taylor, H. L., Wall, M. E., Coggon, P., & McPhail, A. T. (1971). Plant antitumor agents. VI. Isolation and structure of taxol, a novel antileukemic and antitumor agent from Taxus brevifolia. *Journal of the American Chemical Society*, *93*(9), 2325–2327. https://doi.org/10.1021/ja00738a045

495. Wall, M. E., & Wani, M. C. (1995). Camptothecin and taxol: discovery to clinic--thirteenth Bruce F. Cain Memorial Award Lecture. *Cancer Research*, *55*(4), 753–760.

Chapter 4. Dogbane & Digitalis

Page 83. *Conveniently, a thirty-nine-mile.*

496. *Alborn-Pengilly Railroad Trail*. (n.d.). MN Department of Natural Resources. Retrieved October 4, 2023, from https://www.dnr.state.mn.us/ohv/trail_detail.html

Page 83. *I used it to enter the Sax-Zim Bog*.

497. *SAX-ZIM BOG*. (n.d.). Explore Minnesota. Retrieved October 4, 2023, from https://www.exploreminnesota.com/profile/sax-zim-bog/2501

498. *SAX-ZIM BOG*. (n.d.). Friends of Sax-Zim Bog. Retrieved October 4, 2023, from https://saxzim.org/

Page 83. *When the Laurentide Ice Sheet.*

499. Updegraff, K., Bridgham, S. D., Pastor, J., Weishampel, P., & Harth, C. (2001). RESPONSE OF CO2 AND CH4 EMISSIONS FROM PEATLANDS TO WARMING AND WATER TABLE MANIPULATION. *Ecological Applications*,

11(2), 311–326. https://doi.org/https://doi.org/10.1890/1051-0761(2001)011[0311:ROCACE]2.0.CO;2

Regarding the age of the bog, see this quote ("The peat at the bog site is approximately 3.5 m deep with a basal radiocarbon date of 10040 ± 70 yr BP.") from:

500. Weltzin, J. F., Bridgham, S. D., Pastor, J., Chen, J., & Harth, C. (2003). Potential effects of warming and drying on peatland plant community composition. *Global Change Biology*, *9*(2), 141–151. https://doi.org/https://doi.org/10.1046/j.1365-2486.2003.00571.x

Page 84. *Notoriously cold in the winter*

501. *Historic Wind Chill Temperatures in Minnesota*. (2019, January 29). MN Department of Natural Resources. https://www.dnr.state.mn.us/climate/journal/historic_windchills.html

Page 84. *I had a flashback.*

502. Brower, L. P. (1969). Ecological chemistry. *Scientific American*, *220*(2), 22–29. https://doi.org/10.1038/scientificamerican0269-22

Page 84. *Its use as an emetic.*

503. Combs, A. B., & Acosta, D. (1990). Toxic mechanisms of the heart: a review. *Toxicologic Pathology*, *18*(4 Pt 1), 583–596.

Page 84. *It turns out that*. Note that in addition to emetine, cephaeline is another alkaloid from the same plants that may even be more emetic and responsible for the emesis.

504. Lee, M. R. (2008). Ipecacuanha: the South American vomiting root. *The Journal of the Royal College of Physicians of Edinburgh*, *38*(4), 355–360.

505. Rosales-López, Catalina, Muñoz-Arrieta, Rodrigo, & Abdelnour-Esquivel, Ana. (2020). Emetine and cephaeline content in plants of Psychotria ipecacuanha in Costa Rica. *Revista Colombiana de Química*, *49*(2), 18-22. https://doi.org/10.15446/rev.colomb.quim.v49n2.78347

506. *USP Monographs: Ipecac Oral Solution*. (n.d.). Pharmacopeia Online. http://www.uspbpep.com/usp29/v29240/usp29nf24s0_m42240a.html

507. Rogers, L. (1912). The rapid cure of amoebic dysentery and hepatitis by hypodermic injections of soluble salts of emetine. *British Medical Journal*, *1*(2686), 1424–1425. https://doi.org/10.1136/bmj.1.2686.1424

508. Bleasel, M. D., & Peterson, G. M. (2020). Emetine Is Not Ipecac: Considerations for Its Use as Treatment for SARS-CoV2. *Pharmaceuticals (Basel, Switzerland)*, *13*(12). https://doi.org/10.3390/ph13120428

Page 84. *Emesis means.*

509. *Webster's Collegiate Dictionary*, 11th edition.

Page 84. *The tragic death of singer Karen Carpenter*.

510. Schmidt, R. Oct. 23, 2010. Article from *The Guardian* that cites the autopsy report: https://www.theguardian.com/books/2010/oct/24/karen-carpenter-anorexia-book-extract

Page 85. *The plant is called*.

511. PURCHAS, S. (1311) *His pilgrimes, vol. IV,* London , 1625-26.

512. Grollman, A. P., & Jarkovsky, Z. (1975). Emetine and Related Alkaloids. In J. W. Corcoran, F. E. Hahn, J. F. Snell, & K. L. Arora (Eds.), *Mechanism of Action of Antimicrobial and Antitumor Agents* (pp. 420–435). Springer Berlin Heidelberg. https://doi.org/10.1007/978-3-642-46304-4_27

Page 85. *Nowadays, however, it is a dysentery*.

513. Combs, A. B., & Acosta, D. (1990). Toxic mechanisms of the heart: a review. *Toxicologic Pathology*, *18*(4 Pt 1), 583–596.

Page 85. *As we've seen with other bright*.

514. Brower, L. P., van Brower, J., & Corvino, J. M. (1967). Plant poisons in a terrestrial food chain. *Proceedings of the National Academy of Sciences of the United States of America*, *57*(4), 893–898. https://doi.org/10.1073/pnas.57.4.893

515. Brower, L. P., Ryerson, W. N., Coppinger, L. L., & Glazier, S. C. (1968). Ecological chemistry and the palatability spectrum. *Science (New York, N.Y.)*, *161*(3848), 1349–1350. https://doi.org/10.1126/science.161.3848.1349

516. BROWER, L. P. (1984). Chemical defence in butterflies. *The Biology of Butterflies*, 109–134. https://cir.nii.ac.jp/crid/1573387448916659712

517. Agrawal, A. A., Petschenka, G., Bingham, R. A., Weber, M. G., & Rasmann, S. (2012). Toxic cardenolides: chemical ecology and coevolution of specialized plant-herbivore interactions. *The New Phytologist*, *194*(1), 28–45. https://doi.org/10.1111/j.1469-8137.2011.04049.x

Page 85. *The tropical scene*.

518. Rousseau H. (1909). *The Equatorial Jungle*. See: https://www.nga.gov/collection/art-object-page.46688.html

Page 86. *The insects then stored the toxins in their bodies*.

519. Reichstein, T., von Euw, J., Parsons, J. A., & Rothschild, M. (1968). Heart poisons in the monarch butterfly. Some aposematic butterflies obtain protection from cardenolides present in their food plants. *Science (New York, N.Y.)*, *161*(3844), 861–866. https://doi.org/10.1126/science.161.3844.861

Page 86. The "golden diadem" reference is from Miriam Rothschild when she was describing monarch butterflies and their migration from eastern North America to the oyamel fir forests of Mexico:

520. https://www.youtube.com/watch?v=fec8DCl0hgo

Page 86. *In entomologist Jim Poff's.*

521. PARSONS, J. A. (1965). A DIGITALIS-LIKE TOXIN IN THE MONARCH BUTTERFLY, DANAUS PLEXIPPUS L. *The Journal of Physiology*, *178*(2), 290–304. https://doi.org/10.1113/jphysiol.1965.sp007628

522. Reichstein, T., von Euw, J., Parsons, J. A., & Rothschild, M. (1968). Heart poisons in the monarch butterfly. Some aposematic butterflies obtain protection from cardenolides present in their food plants. *Science (New York, N.Y.)*, *161*(3844), 861–866. https://doi.org/10.1126/science.161.3844.861

523. Brower, L. P., Ryerson, W. N., Coppinger, L. L., & Glazier, S. C. (1968). Ecological chemistry and the palatability spectrum. *Science (New York, N.Y.)*, *161*(3848), 1349–1350. https://doi.org/10.1126/science.161.3848.1349

Page 88. *One of the principal toxins.*

524. Cheung, H. T. A., Watson, T. R., Lee, S. M., McChesney, M. M., & Seiber, J. N. (1986). Structure of aspecioside from the monarch butterfly larvae foodplants *Asclepias speciosa* and *A. syriaca*. *Journal of the Chemical Society, Perkin Transactions 1*, *0*, 61–65. https://doi.org/10.1039/P19860000061

Page 86. *But the caterpillars did.*

525. Brower, L. P., & Glazier, S. C. (1975). Localization of Heart Poisons in the Monarch Butterfly. *Science*, *188*(4183), 19–25. https://doi.org/10.1126/science.188.4183.19

Page 86. *In at least fourteen instances.*

526. Züst, T., Mirzaei, M. & Jander, G. (2018). *Erysimum cheiranthoides*, an ecological research system with potential as a genetic and genomic model for studying cardiac glycoside biosynthesis. *Phytochem Rev* 17, 1239–1251. https://doi.org/10.1007/s11101-018-9562-4

527. Eisner, T., Wiemer, D. F., Haynes, L. W., & Meinwald, J. (1978). Lucibufagins: Defensive steroids from the fireflies Photinus ignitus and P. marginellus (Coleoptera: Lampyridae). *Proceedings of the National Academy of Sciences of the United States of America*, *75*(2), 905–908. https://doi.org/10.1073/pnas.75.2.905

Page. 87. *In Madagascar.*

528. Campbell, G. (1991). The State and Pre-Colonial Demographic History: The Case of Nineteenth-Century Madagascar. *The Journal of African History*, *32*(3), 415–445. https://doi.org/DOI: 10.1017/S0021853700031534

Page 87. *Monarch butterflies evolved to become.*

529. Carpenter G. D. Hale, D. M. (1942). The Relative Frequency of Beak-marks on Butterflies of Different/ Edibility to Birds. *Proceedings of the Zoological Society of London*, *A111*(3–4), 223–231. https://doi.org/https://doi.org/10.1111/j.1469-7998.1942.tb08483.x

530. Holen, Ø. H. (2013). Disentangling taste and toxicity in aposematic prey. *Proceedings. Biological Sciences*, *280*(1753), 20122588. https://doi.org/10.1098/rspb.2012.2588

531. Bates, H. W. (1981). Contributions to an insect fauna of the Amazon valley (Lepidoptera: Heliconidae). *Biological Journal of the Linnean Society*, *16*(1), 41–54. https://doi.org/https://doi.org/10.1111/j.1095-8312.1981.tb01842.x

532. Brower, J. V. Z. (1960). Experimental Studies of Mimicry. IV. The Reactions of Starlings to Different Proportions of Models and Mimics. *The American Naturalist*, *94*(877), 271–282. https://doi.org/10.1086/282128

533. Allen, W., Ruxton, G., Sherratt, T., & Speed, M. (2018). *Avoiding Attack: The Evolutionary Ecology of Crypsis, Aposematism, and Mimicry*. Oxford: Oxford University Press.

534. Müller, F. (1878). *Über die vortheile der mimicry bei schmetterlingen.*

Page 87. *The toxic channel of communication that flows.*

535. Agrawal, A. (2017). *Monarchs and Milkweed: A Migrating Butterfly, a Poisonous Plant, and Their Remarkable Story of Coevolution*. Princeton University Press. https://doi.org/10.2307/j.ctvc775wc

Page 87. But the milkweeds can't uproot themselves.

536. EVETTS, L.L. and BURNSIDE, O.C. (1974). Root distribution and vegetative propagation of *Asclepias syriaca* L.. *Weed Research, 14*: 283-288. https://doi.org/10.1111/j.1365-3180.1974.tb01062.x

Page 88. *In 1953, physiology Hans.*

537. SCHATZMANN & H. J. (1953). Herzglykoside als Hemmstoffe fur den activen Kalium und Natrium-Transport durch die Erythrocytemembran. Helv. Physiol. Pharmacol. Acta 11, 346–354

Page 88. *Nearly forty years later.*

538. 2023. Jens C. Skou – Biographical. NobelPrize.org. Nobel Prize Outreach https://www.nobelprize.org/prizes/chemistry/1997/skou/facts/

Page 88. *Skou found that the cardiac.*

539. Skou, J. Chr. (1960). Further investigations on a Mg++ + Na+-activated adenosintriphosphatase, possibly related to the active, linked transport of Na+

and K+ across the nerve membrane. *Biochimica et Biophysica Acta*, *42*, 6–23. https://doi.org/https://doi.org/10.1016/0006-3002(60)90746-0

Page 88. *The bulb of the sea squill*.

540. Gentry, H. S., Verbiscar, A. J., & Banigan, T. F. (1987). Red squill (*Urginea maritima*, Liliaceae). *Economic Botany*, *41*(2), 267–282. https://doi.org/10.1007/BF02858974

Page 88. The plant has been used.

541. Stannard, J. (1974). Squill in ancient and medieval materia medica, with special reference to its employment for dropsy. *Bulletin of the New York Academy of Medicine*, *50*(6), 684–713.

Quote from:

542. *Celsus: De Medicina*. With an english translation by W. G. Spencer, M.S. (Lond.), F.R.C.S. (Eng.). In three volumes (Loeb Classical Library). 6 5/8 × 4 1/4 in. Vol. I (1935).

Page 88. *The report, titled*.

543. Withering, W. (1785). *An Account of the Foxglove and some of its Medical Uses With Practical Remarks on Dropsy and Other Diseases*. From: https://www.gutenberg.org/files/24886/24886-h/24886-h.htm

Page 90. *As digoxin became the drug of choice*. Note that the image of Mother Hutton handing the recipe to William Withering was created on January 1, 1928 by William Meade Prince.

544. Krikler, D. M. (1985). Withering and the foxglove: the making of a myth. *British Heart Journal*, *54*(3), 256–257. https://doi.org/10.1136/hrt.54.3.256

Page 90. *In the United States alone.*

545. Kane S. P. (2022). . ClinCalc DrugStats Database https://clincalc.com/DrugStats/Drugs/Digoxin.

Page 90. *It remains of the World Health Organization's*.

546. Web Annex A. World Health Organization Model List of Essential Medicines – 23rd List, 2023. In: *The selection and use of essential medicines 2023: Executive summary of the report of the 24th WHO Expert Committee on the Selection*

and Use of Essential Medicines, 24 – 28 April 2023. Geneva: World Health Organization; 2023 https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02

Page 90. *Another important cardiac glycoside*.

547. Osseo-Asare, A. D. (2008). Bioprospecting and Resistance: Transforming Poisoned Arrows into Strophantin Pills in Colonial Gold Coast, 1885–1922. *Social History of Medicine*, *21*(2), 269–290. https://doi.org/10.1093/shm/hkn025

Page 90. *The Wilé people of Burkina Faso*.

548. Fürstenwerth, H. (2018). *Ouabain - A gift from paradise*. *3*, 1–2. https://doi.org/10.15761/CDM.1000172

549. Neuwinger, H. D. (1996). *African Ethnobotany: Poisons and Drugs : Chemistry, Pharmacology, Toxicology*. CRC Press. https://doi.org/10.1021/np960638h

Page 90. *After people learned of its powers*.

550. Kirk, R. (1946). SOME VEGETABLE POISONS OF THE SUDAN. *Sudan Notes and Records*, *27*, 127–152. http://www.jstor.org/stable/41716740

Page 90. *Europeans actually first directly*. Note that utsungu is the word for bitterness in Digo and is the name for the arrow poison derived from the poison arrow tree species *Acokanthera schimperi*, which contains is ouabain.

551. Neuwinger, H. D. (1996). *African Ethnobotany: Poisons and Drugs : Chemistry, Pharmacology, Toxicology*. CRC Press. https://doi.org/10.1021/np960638h

552. Theal, G.M. (1907) *History and Ethnography of Africa South of the Zambesi – Vol. I, The Portuguese in South Africa from 1505 to 1700* London: Sonneschein.

Page 90. *Similarly, Indigenous peoples of*.

553. Shrestha, T., Kopp, B., & Bisset, N. G. (1992). The Moraceae-based dart poisons of South America. Cardiac glycosides of Maquira and Naucleopsis species. *Journal of Ethnopharmacology*, *37*(2), 129–143. https://doi.org/10.1016/0378-8741(92)90071-x

554. Kopp, B., Bauer, W. P., & Bernkop-Schnürch, A. (1992). Analysis of some Malaysian dart poisons. *Journal of Ethnopharmacology*, *36*(1), 57–62. https://doi.org/10.1016/0378-8741(92)90061-u

555. Bisset, N. G. (1979). Arrow poisons in China. Part I. *Journal of Ethnopharmacology*, *1*(4), 325–384. https://doi.org/10.1016/s0378-8741(79)80002-1

Page 90 and 91. *The maned or crested rat.*

556. Kingdon, J., Agwanda, B., Kinnaird, M., O'Brien, T., Holland, C., Gheysens, T., Boulet-Audet, M., & Vollrath, F. (2012). A poisonous surprise under the coat of the African crested rat. *Proceedings. Biological Sciences*, *279*(1729), 675–680. https://doi.org/10.1098/rspb.2011.1169

See also (toad-annointing hedgehogs and firefly-eating snakes):

557. Brodie, E. D. (1977). Hedgehogs use toad venom in their own defence. *Nature*, *268*(5621), 627–628. https://doi.org/10.1038/268627a0

558. Yoshida, T., Ujiie, R., Savitzky, A. H., Jono, T., Inoue, T., Yoshinaga, N., Aburaya, S., Aoki, W., Takeuchi, H., Ding, L., Chen, Q., Cao, C., Tsai, T.-S., Silva, A. de, Mahaulpatha, D., Nguyen, T. T., Tang, Y., Mori, N., & Mori, A. (2020). Dramatic dietary shift maintains sequestered toxins in chemically defended snakes. *Proceedings of the National Academy of Sciences of the United States of America*, *117*(11), 5964–5969. https://doi.org/10.1073/pnas.1919065117

Page 91. *I was fortunate enough.*

559. Dobler, S., Dalla, S., Wagschal, V., & Agrawal, A. A. (2012). Community-wide convergent evolution in insect adaptation to toxic cardenolides by substitutions in the Na, K-ATPase. *Proceedings of the National Academy of Sciences*, *109*(32), 13040–13045. https://www.pnas.org/content/109/32/13040.short

560. Zhen, Y., Aardema, M. L., Medina, E. M., Schumer, M., & Andolfatto, P. (2012). Parallel Molecular Evolution in an Herbivore Community. *Science*. https://doi.org/10.1126/science.1226630

Page 91. *In the end, after eight years.*

561. Karageorgi, M., Groen, S. C., Sumbul, F., Pelaez, J. N., Verster, K. I., Aguilar, J. M., Hastings, A. P., Bernstein, S. L., Matsunaga, T., Astourian, M., Guerra, G., Rico, F., Dobler, S., Agrawal, A. A., & Whiteman, N. K. (2019). Genome editing retraces the evolution of toxin resistance in the monarch butterfly. *Nature*, *574*(7778), 409–412. https://doi.org/10.1038/s41586-019-1610-8

Page 92. *In 1981*.

562. Fink, L. S., & Brower, L. P. (1981). Birds can overcome the cardenolide defence of monarch butterflies in Mexico. *Nature*, *291*(5810), 67–70. https://doi.org/10.1038/291067a0

563. Fink, L. S., Brower, L. P., Waide, R. B., & Spitzer, P. R. (1983). Overwintering Monarch Butterflies as Food for Insectivorous Birds in Mexico. *Biotropica*, *15*(2), 151–153. https://doi.org/10.2307/2387962

Page 92. *In 2021, Niels wrote to me*.

564. Groen, S. C., & Whiteman, N. K. (2021). Convergent evolution of cardiac-glycoside resistance in predators and parasites of milkweed herbivores. *Curr. Biol.*, *31*(22), R1465–R1466. https://doi.org/10.1016/j.cub.2021.10.025

Page 92. *Cardiac glycosides can bind to the sodium pump*.

565. Nyblom, M., Poulsen, H., Gourdon, P., Reinhard, L., Andersson, M., Lindahl, E., Fedosova, N., & Nissen, P. (2013). Crystal Structure of Na+, K+-ATPase in the Na+-Bound State. *Science*, *342*(6154), 123–127. https://doi.org/10.1126/science.1243352

Page 93. *Such blocking can be achieved by only*. However, it may be that there are sites outside of the binding pocket that can contribute to resistance.

566. Zhen, Y., Aardema, M. L., Medina, E. M., Schumer, M., & Andolfatto, P. (2012). Parallel Molecular Evolution in an Herbivore Community. *Science*. https://doi.org/10.1126/science.1226630

567. Dobler, S., Dalla, S., Wagschal, V., & Agrawal, A. A. (2012). Community-wide convergent evolution in insect adaptation to toxic cardenolides by

substitutions in the Na, K-ATPase. *Proceedings of the National Academy of Sciences*, *109*(32), 13040–13045. https://www.pnas.org/content/109/32/13040.short

568. Mohammadi, S., Herrera-Álvarez, S., Yang, L., Rodríguez-Ordoñez, M. D. P., Zhang, K., Storz, J. F., Dobler, S., Crawford, A. J., & Andolfatto, P. (2022). Constraints on the evolution of toxin-resistant Na,K-ATPases have limited dependence on sequence divergence. *PLoS Genetics*, *18*(8), e1010323. https://doi.org/10.1371/journal.pgen.1010323

Page 94. *The genetic change in the monarch.*

569. Karageorgi, M., Groen, S. C., Sumbul, F., Pelaez, J. N., Verster, K. I., Aguilar, J. M., Hastings, A. P., Bernstein, S. L., Matsunaga, T., Astourian, M., Guerra, G., Rico, F., Dobler, S., Agrawal, A. A., & Whiteman, N. K. (2019). Genome editing retraces the evolution of toxin resistance in the monarch butterfly. *Nature*, *574*(7778), 409–412. https://doi.org/10.1038/s41586-019-1610-8

Chapter 5. Hijacked Hormones

Page 94. *To every thing there is a season*.

570. The 1969 King James Bible, as revised by Benjamin Blayney. See: https://en.wikisource.org/wiki/Bible_(King_James)/Ecclesiastes#3:1

Page 94. *Lady Sybi, one of my favorite*. Eclampsia is specifically associated with seizure, stroke, or coma during pregnancy owing to high blood pressure and preeclampsia is the lead-up to that condition.

571. Brown, D. (2013, January 28). Lady Sybil's shocking death. *The Washington Post*. https://www.washingtonpost.com/national/health-science/lady-sybils-shocking-death/2013/01/28/c0f41e14-697a-11e2-ada3-d86a4806d5ee_story.html

Page 95. *Preeclampsia is a major public health problem.*

572. Wallis, A. B., Saftlas, A. F., Hsia, J., & Atrash, H. K. (2008). Secular Trends in the Rates of Preeclampsia, Eclampsia, and Gestational Hypertension, United

States, 1987-2004. *American Journal of Hypertension*, *21*(5), 521–526. https://doi.org/10.1038/ajh.2008.20

573. Ives, C. W., Sinkey, R., Rajapreyar, I., Tita, A. T. N., & Oparil, S. (2020). Preeclampsia—Pathophysiology and Clinical Presentations. *Journal of the American College of Cardiology*, *76*(14), 1690–1702. https://doi.org/10.1016/j.jacc.2020.08.014

Page 95. *Family history*.

574. Mayrink, J., Souza, R. T., Feitosa, F. E., Rocha Filho, E. A., Leite, D. F., Vettorazzi, J., Calderon, I. M., Sousa, M. H., Costa, M. L., Baker, P. N., Cecatti, J. G., Parpinelli, M. A., Fernandes, K. G., Guida, J. P., Santana, D. S., Barbosa, R. M., Galvao, R. B. F., Cassettari, B. F., Pfitscher, L., … Silva, M. A. (2019). Incidence and risk factors for Preeclampsia in a cohort of healthy nulliparous pregnant women: a nested case-control study. *Scientific Reports*, *9*(1), 9517. https://doi.org/10.1038/s41598-019-46011-3

575. Visintin, C., Mugglestone, M. A., Almerie, M. Q., Nherera, L. M., James, D., & Walkinshaw, S. (2010). Management of hypertensive disorders during pregnancy: summary of NICE guidance. *BMJ*, *341*(aug25 3), c2207–c2207. https://doi.org/10.1136/bmj.c2207

Page 95. *The specific causes of preeclampsia*.

576. Rasmussen, M., Reddy, M., Nolan, R., Camunas-Soler, J., Khodursky, A., Scheller, N. M., Cantonwine, D. E., Engelbrechtsen, L., Mi, J. D., Dutta, A., Brundage, T., Siddiqui, F., Thao, M., Gee, E. P. S., La, J., Baruch-Gravett, C., Santillan, M. K., Deb, S., Ame, S. M., … McElrath, T. F. (2022). RNA profiles reveal signatures of future health and disease in pregnancy. *Nature*, *601*(7893), 422–427. https://doi.org/10.1038/s41586-021-04249-w

Page 95. *Strangely, a clue to its causes.* Quotes in next few paragraphs are from this reference as well.

577. Craver, J. L., & Valdes, R. (1983). Anomalous serum digoxin concentrations in uremia. *Annals of Internal Medicine*, *98*(4), 483–484. https://doi.org/10.7326/0003-4819-98-4-483

Page 95. *"Endogenous means "from within."*

578. *Webster's Collegiate Dictionary*, 11th edition.

Page 95. *But in their report.*

579. Lowenstein, J. M. (1965). A Method for Measuring Plasma Levels of Digitalis Glycosides. *Circulation*, *31*(2), 228–233. https://doi.org/10.1161/01.CIR.31.2.228

Page 95 and 96: *The presence of glycoside-like substances.* The references also apply to the next paragraph.

580. Valdes, R., Graves, S. W., Brown, B. A., & Landt, M. (1983). Endogenous substance in newborn infants causing false positive digoxin measurements. *The Journal of Pediatrics*, *102*(6), 947–950. https://doi.org/10.1016/S0022-3476(83)80031-6

581. Graves, S. W., Valdes, R., Brown, B. A., Knight, A. B., & Craig, H. R. (1984). Endogenous digoxin-immunoreactive substance in human pregnancies. *The Journal of Clinical Endocrinology and Metabolism*, *58*(4), 748–751. https://doi.org/10.1210/jcem-58-4-748

582. Bertrand, J.-M., Langhendries, J. P., Gras, A., & Battisti, O. (1987). Digoxin-like immunoreactive substance in serum of preterm and full-term neonates. *European Journal of Pediatrics*, *146*(2), 145–146. https://doi.org/10.1007/BF02343220

583. Graves, S. W., Lincoln, K., Cook, S. L., & Seely, E. W. (1995). Digitalis-like factor and digoxin-like immunoreactive factor in diabetic women with preeclampsia, transient hypertension of pregnancy, and normotensive pregnancy. *American Journal of Hypertension*, *8*(1), 5–11. https://doi.org/10.1016/0895-7061(94)00167-A

584. Hamlyn, J. M., Blaustein, M. P., Bova, S., DuCharme, D. W., Harris, D. W., Mandel, F., Mathews, W. R., & Ludens, J. H. (1991). Identification and characterization of a ouabain-like compound from human plasma. *Proceedings of the National Academy of Sciences of the United States of America*, *88*(14), 6259–6263. https://doi.org/10.1073/pnas.88.14.6259

585. Lichtstein, D., Gati, I., Samuelov, S., Berson, D., Rozenman, Y., Landau, L., & Deutsch, J. (1993). Identification of digitalis-like compounds in human

cataractous lenses. *European Journal of Biochemistry*, *216*(1), 261–268. https://doi.org/10.1111/j.1432-1033.1993.tb18141.x

586. Bagrov, A. Y., Fedorova, O. v., Dmitrieva, R. I., Howald, W. N., Hunter, A. P., Kuznetsova, E. A., & Shpen, V. M. (1998). Characterization of a Urinary Bufodienolide Na^+,K^+-ATPase Inhibitor in Patients After Acute Myocardial Infarction. *Hypertension*, *31*(5), 1097–1103. https://doi.org/10.1161/01.HYP.31.5.1097

Page 96. *In hindsight, we might not*.

587. Gruber, K. A., Whitaker, J. M., & Buckalew, V. M. (1980). Endogenous digitalis-like substance in plasma of volume-expanded dogs. *Nature*, *287*(5784), 743–745. https://doi.org/10.1038/287743a0

588. Haiser, H. J., Gootenberg, D. B., Chatman, K., Sirasani, G., Balskus, E. P., & Turnbaugh, P. J. (2013). Predicting and Manipulating Cardiac Drug Inactivation by the Human Gut Bacterium *Eggerthella lenta*. *Science*, *341*(6143), 295–298. https://doi.org/10.1126/science.1235872

589. Flier, J. S. (1978). Ouabain-like activity in toad skin and its implications for endogenous regulation of ion transport. *Nature*, *274*(5668), 285–286. https://doi.org/10.1038/274285a0

590. Flier, J., Edwards, M. W., Daly, J. W., & Myers, C. W. (1980). Widespread Occurrence in Frogs and Toads of Skin Compounds Interacting with the Ouabain Site of Na^+, K^+-ATPase. *Science*, *208*(4443), 503–505. https://doi.org/10.1126/science.6245447

Page 96. *The use of toad venom*. From Act IV, Scene 1, line 1551.

591. Shakespeare, W. (1605). *The Tragedy of Macbeth*. Open Source Shakespeare. George Mason University. See: https://www.opensourceshakespeare.org.

Page 96. *Toad venom is the basis.*

592. Chen, K. K., & Jensen, H. (1929). Crystalline Principles From Ch'an Su, the Dried Venom of the Chinese Toad. *Experimental Biology and Medicine*, *26*(5), 378–380. https://doi.org/10.3181/00379727-26-4311

593. Hong, Z., Chan, K., & Yeung, H. W. (2011). Simultaneous Determination of Bufadienolides in the Traditional Chinese Medicine Preparation, Liu-Shen-Wan, by Liquid Chromatography. *Journal of Pharmacy and Pharmacology*, *44*(12), 1023–1026. https://doi.org/10.1111/j.2042-7158.1992.tb07086.x

594. Chen, K. K., & Kovaříková, A. (1967). Pharmacology and toxicology of toad venom. *Journal of Pharmaceutical Sciences*, *56*(12), 1535–1541. https://doi.org/10.1002/jps.2600561202

595. Morishita, S., Shoji, M., Oguni, Y., Ito, C., Higuchi, M., & Sakanashi, M. (1992). Pharmacological Actions of "Kyushin," a Drug Containing Toad Venom: Cardiotonic and Arrhythmogenic Effects, and Excitatory Effect on Respiration. *The American Journal of Chinese Medicine*, *20*(03n04), 245–256. https://doi.org/10.1142/S0192415X92000254

Page 96. *Toad venom is also used in purported.*

596. Jeffrey, R. B., Padinjarekuttu, R. R., Theodore, B., Michael, B. H., & Robert, S. H. (1996). Treatment of Toad Venom Poisoning With Digoxin-Specific Fab Fragments. *Chest*, *110*(5), 1282–1288. https://doi.org/10.1378/chest.110.5.1282

597. Gowda, R. M. (2003). Toad venom poisoning: resemblance to digoxin toxicity and therapeutic implications. *Heart*, *89*(4), 14e–114. https://doi.org/10.1136/heart.89.4.e14

Page 96. *Then there is the nine-year-old.*

598. James, G., & Thornton, S. (2019). Dare to Eat Cane Toad Eggs? *Journal of Paediatrics and Child Health*, *55*(1), 120–121. https://doi.org/10.1111/jpc.14327

599. Smith, T. W., Haber, E., Yeatman, L., & Butler, V. P. (1976). Reversal of Advanced Digoxin Intoxication with Fab Fragments of Digoxin-Specific Antibodies. *New England Journal of Medicine*, *294*(15), 797–800. https://doi.org/10.1056/NEJM197604082941501

Page 97. *There is a connection here to preeclampsia.*

600. Adair, C., Buckalew, V., Graves, S., Lam, G., Johnson, D., Saade, G., Lewis, D., Robinson, C., Danoff, T., Chauhan, N., Hopoate-Sitake, M., Porter, K., Humphrey, R., Trofatter, K., Amon, E., Ward, S., Kennedy, L., Mason, L., & Johnston, J. (2010). Digoxin Immune Fab Treatment for Severe Preeclampsia. *American Journal of Perinatology*, *27*(08), 655–662. https://doi.org/10.1055/s-0030-1249762

601. Graves, S. W., Hopoate-Sitake, M., Johnston, A., Buckalew, V., Lam, G., Mason, L., & Adair, D. (2012). PP087. Deep trial secondary analysis: Digoxin immune fab fragment treatment has additional benefits in endogenous digitalis-like factor positive preeclamptic women. *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health*, *2*(3), 287–288. https://doi.org/10.1016/j.preghy.2012.04.198

602. Lam, G. K., Hopoate-Sitake, M., Adair, C. D., Buckalew, V. M., Johnson, D. D., Lewis, D. F., Robinson, C. J., Saade, G. R., & Graves, S. W. (2013). Digoxin

antibody fragment, antigen binding (Fab), treatment of preeclampsia in women with endogenous digitalis-like factor: a secondary analysis of the DEEP Trial. *American Journal of Obstetrics and Gynecology*, *209*(2), 119.e1-119.e6. https://doi.org/10.1016/j.ajog.2013.04.010

603. AMAG Pharmaceuticals, Inc. (2016, December 20-2022, March 4) *Study of the Efficacy and Safety of AMAG-423 (Digoxin Immune Fab) in Antepartum Subjects With Severe Preeclampsia.* https://clinicaltrials.gov/ct2/show/NCT03008616.

Page 97. *Our bodies do appear*.

604. Baecher, S., Kroiss, M., Fassnacht, M., & Vogeser, M. (2014). No endogenous ouabain is detectable in human plasma by ultra-sensitive UPLC-MS/MS. *Clinica Chimica Acta*, *431*, 87–92. https://doi.org/10.1016/j.cca.2014.01.038

605. Blaustein, M. P. (2015). Letter to the Editor concerning Baecher et al. (Clin Chim Acta 2014;431:87–92). *Clinica Chimica Acta*, *448*, 248–249. https://doi.org/10.1016/j.cca.2015.07.011

606. Blaustein, M. P. (2014). Why isn't endogenous ouabain more widely accepted? *American Journal of Physiology-Heart and Circulatory Physiology*, *307*(5), H635–H639. https://doi.org/10.1152/ajpheart.00404.2014

607. Fedorova, O. v., Zernetkina, V. I., Shilova, V. Y., Grigorova, Y. N., Juhasz, O., Wei, W., Marshall, C. A., Lakatta, E. G., & Bagrov, A. Y. (2015). Synthesis of an Endogenous Steroidal Na Pump Inhibitor Marinobufagenin, Implicated in Human Cardiovascular Diseases, Is Initiated by CYP27A1 via Bile Acid Pathway. *Circulation: Cardiovascular Genetics*, *8*(5), 736–745. https://doi.org/10.1161/CIRCGENETICS.115.001217

608. Greene, L. A., & Tischler, A. S. (1976). Establishment of a noradrenergic clonal line of rat adrenal pheochromocytoma cells which respond to nerve growth factor. *Proceedings of the National Academy of Sciences*, *73*(7), 2424–2428. https://doi.org/10.1073/pnas.73.7.2424

609. Komiyama, Y., Dong, X. H., Nishimura, N., Masaki, H., Yoshika, M., Masuda, M., & Takahashi, H. (2005). A novel endogenous digitalis, telocinobufagin, exhibits elevated plasma levels in patients with terminal renal failure. *Clinical Biochemistry*, *38*(1), 36–45. https://doi.org/10.1016/j.clinbiochem.2004.08.005

610. Schneider, R., Antolovic, R., Kost, H., Sich, B., Kirch, U., Tepel, M., Zidek, W., & Schoner, W. (1998). Proscillaridin A Immunoreactivity: Its Purification, Transport in Blood By A Specific Binding Protein And Its Correlation With Blood Pressure. *Clinical and Experimental Hypertension*, *20*(5–6), 593–599. https://doi.org/10.3109/10641969809053237

611. Chasalow, F., & Pierce-Cohen, L. (2018). Ionotropin is the mammalian digoxin-like material (DLM). It is a phosphocholine ester of a steroid with 23 carbon atoms. *Steroids*, *136*, 63–75. https://doi.org/10.1016/j.steroids.2018.03.001

Page 98. *Although nobody knew it at the time.*

612. Allen, W. M., & Ehrenstein, M. (1944). 10-Nor-Progesterone, a Physiologically Active Lower Homolog of Progesterone. *Science*, *100*(2594), 251–252. https://doi.org/10.1126/science.100.2594.251

613. EHRENSTEIN, M. (1944). INVESTIGATIONS ON STEROIDS. VIII. LOWER HOMOLOGS OF HORMONES OF THE PREGNANE SERIES: 10-NOR-11-DESOXY-CORTICOSTERONE ACETATE AND 10-NORPROGESTERONE [1]. *The Journal of Organic Chemistry*, *09*(5), 435–456. https://doi.org/10.1021/jo01187a009

614. Djerassi, C. (2006). Chemical birth of the pill. *American Journal of Obstetrics and Gynecology*, *194*(1), 290–298. https://doi.org/10.1016/j.ajog.2005.06.010

Page 98. *Progesterone is called the pregnancy.*

615. Christensen, A., Bentley, G., Cabrera, R., Ortega, H., Perfito, N., Wu, T., & Micevych, P. (2012). Hormonal Regulation of Female Reproduction. *Hormone and Metabolic Research*, *44*(08), 587–591. https://doi.org/10.1055/s-0032-1306301

Page 99. *In the early 1940s.*

616. *The Nobel Prize in Physiology or Medicine 1950*. NobelPrize.org. https://www.nobelprize.org/prizes/medicine/1950/summary/

617. Sarett, L. H. (1946). Partial synthesis of pregnene-4-triol-17(beta), 20(beta), 21-dione-3,11 and pregnene-4-diol-17(beta), 21-trione-3,11,20 monoacetate. *The Journal of Biological Chemistry*, *162*, 601–631.

618. Pines, S. H. (2004). The Merck Bile Acid Cortisone Process: The Next-to-Last Word. *Organic Process Research & Development*, *8*(5), 708–724. https://doi.org/10.1021/op030050z

Page 99. *Such adrenal gland hormones were given.* See reference below regarding Ingle's note that: "Attention focused on a rumor that Germany was buying beef adrenal glands in South America for the purpose of making adrenal cortical extract. It was said that the extract was being used to counteract the hypoxia of Luftwaffe pilots to permit them to fly at higher altitudes."

619. Ingle, D. J. (1974). Edward C. Kendall. *Biographical Memoirs. National Academy of Sciences (U.S.)*, *47*, 249–290.

Page 99. *In 1940, chemists Russel Marker*.

620. Marker, R. E., & Krueger, J. (1940). Sterols. CXII. Sapogenins. XLI. The Preparation of Trillin and its Conversion to Progesterone. *Journal of the American Chemical Society*, *62*(12), 3349–3350. https://doi.org/10.1021/ja01869a023

621. Chevallier, A. (1996). *The encyclopedia of medicinal plants.*

622. 塚本赳夫, 上農義雄, & 太田次作. (1937). ヂオスゲニンの構造に就て (II). 藥學雜誌, *57*(11), 985–991. https://doi.org/10.1248/yakushi1881.57.11_985

Page 99. *Knowing that there were relatives*

623. American Chemical Society, Sociedad Química de México (1999). *The "Marker Degradation" and Creation of the Mexican Steroid Hormone Industry, 1938-1945: An International Historic Chemical Landmark : University Park, Pennsylvania, October 1, 1999, Mexico City, December 1, 1999*. American Chemical Society.

Page 99. *The goal was to use.*

624. Pederson, T. (2015). Carl Djerassi (1923–2015). *Current Biology*, *25*(7), R263–R264. https://doi.org/10.1016/j.cub.2015.02.030

Page 100. *The Syntex team*.

625. Soto Laveaga, G. (2009). *Jungle Laboratories*. Duke University Press. https://doi.org/10.1215/9780822391968

Page 100. *Barbasco, it should be noted.*

626. Kamen-Kaye, D. (1977). ICHTHYOTOXIC PLANTS AND THE TERM "BARBASCO." *Botanical Museum Leaflets, Harvard University*, *25*(2), 71–90. http://www.jstor.org/stable/41762777

Page 100. *Just a year after arriving*.

627. Djerassi, C., Rosenkranz, G., Romo, J., Pataki, J., & Kaufmann, St. (1950). Steroids. VIII. [1,2] The Dienone—Phenol Rearrangement in the Steroid Series. Synthesis of a New Class of Estrogens. *Journal of the American Chemical Society*, *72*(10), 4540–4544. https://doi.org/10.1021/ja01166a056

628. Djerassi, C. (2006). Chemical birth of the pill. *American Journal of Obstetrics and Gynecology*, *194*(1), 290–298. https://doi.org/10.1016/j.ajog.2005.06.010

Page 100. *Like Allen and Ehernetsein*.

629. Miramontes, L., Rosenkranz, G., & Djerassi, C. (1951). STEROIDS. XXII. THE SYNTHESIS OF 19-NORPROGESTERONE. *Journal of the American Chemical Society*, *73*(7), 3540–3541. https://doi.org/10.1021/ja01151a547

Page 100. *The laboratory notebook.*

630. Djerassi, C. (2006). Chemical birth of the pill. *American Journal of Obstetrics and Gynecology*, *194*(1), 290–298. https://doi.org/10.1016/j.ajog.2005.06.010

631. Djerassi, C. (2001). *This Man's Pill: Reflections on the 50th Birthday of the Pill*. Oxford University Press

Page 101. *Great minds often think alike.*

632. Colton, F. B. (1992). Steroids and "the Pill": early steroid research at Searle. *Steroids*, *57*(12), 624–630. https://doi.org/10.1016/0039-128X(92)90015-2

633. Djerassi, C. (2006). Chemical birth of the pill. *American Journal of Obstetrics and Gynecology*, *194*(1), 290–298. https://doi.org/10.1016/j.ajog.2005.06.010

Page 101. *Soybeans have now replaced*. Note, however, that the production of other hormone analogs used in contraceptive pill formulations are fully synthetic.

634. Hogg, J. A. (1992). Steroids, the steroid community, and Upjohn in perspective: a profile of innovation. *Steroids*, *57*(12), 593–616. https://doi.org/10.1016/0039-128X(92)90013-Y

635. Sundararaman, P., & Djerassi, C. (1977). A convenient synthesis of progesterone from stigmasterol. *The Journal of Organic Chemistry*, *42*(22), 3633–3634. https://doi.org/10.1021/jo00442a044

Page 102. *Indeed, if you search*.

636. Fugh-Berman, A. (1999, January 1). *Wild Yam Cream, Diosgenin, and Natural Progesterone: What Can They Really Do for You?* National Women's Health Network. https://nwhn.org/wild-yam-cream-diosgenin-and-natural-progesterone-what-can-they-really-do-for-you/

Page 102. *In 1935, entomologist and physiologist Gottfried Fraenkel*. It was simultaneously discovered by V.B. Wigglesworth, see reference below.

637. Fraenkel, G. (1935). A hormone causing pupation in the blowfly *calliphora erythrocephala*. *Proceedings of the Royal Society of London. Series B - Biological Sciences*, *118*(807), 1–12. https://doi.org/10.1098/rspb.1935.0044

638. Wigglesworth, V. B. (1934). The Physiology of Ecdysis in Bhodnius Prolixus (Hemiptera). II. Factors controlling Moulting and 'Metamorphosis.' *Journal of Cell Science*, *S2-77*(306), 191–222. https://doi.org/10.1242/jcs.s2-77.306.191

Page 103. *Using flies that grew from*. See this quote from page 172 of the reference below: "His life and future scientific activity were immediately influenced by the fly, *Calliphora erythrocephala*, that he saw come in through an open window and deposit its eggs on a small piece of meat. He watched the larvae emerge from the eggs and grow and–amid all the difficulties of a new language, a new culture, a new family, almost no salary, and using the most primitive tools–conceived the idea that, within a period of two months, resulted in the discovery of the blood-borne factor we now know to be the insect molting hormone, ecdysterone."

639. Ladd Prosser, C., S. Friedman, and J. H. Willis. (1990). *Gottfried Samuel Fraenkel 1901–1984*. Biographical Memoir. National Academy of Sciences, Washington, D.C. See: https://nap.nationalacademies.org/read/1652/chapter/10

Page 103. *Some plants endogenously*.

640. Báthory, M., Tóth, I., Szendrei, K., & Reisch, J. (1982). Ecdysteroids in Spinacia oleracea and Chenopodium bonus-henricus. *Phytochemistry*, *21*(1), 236–238. https://doi.org/10.1016/0031-9422(82)80057-5

641. Lee, E., Liu, Y. T., Solomon, P. H., & Nakanishi, K. (1976). Stereospecific conversion of diosgenin to .alpha.-ecdysone. *Journal of the American Chemical Society*, *98*(6), 1634–1635. https://doi.org/10.1021/ja00422a086

642. Marion-Poll, F., Calas, D., Darazy-Choubaya, D., Faucher, C., & Descoins, C. (2009). Tasting toxicants as bitter: phytoecdysteroids. *SEB Experimental Biology Series*, *63*, 127–138.

643. Dinan, L., Bourne, P. C., Meng, Y., Sarker, S. D., Tolentino, R. B., & Whiting, P. (2001). Assessment of natural products in the *Drosophila melanogaster* B(II) cell bioassay for ecdysteroid agonist and antagonist activities. *Cellular and Molecular Life Sciences*, *58*(2), 321–342. https://doi.org/10.1007/PL00000859

644. de Geyter, E., Swevers, L., Soin, T., Geelen, D., & Smagghe, G. (2012). Saponins do not affect the ecdysteroid receptor complex but cause membrane permeation in insect culture cell lines. *Journal of Insect Physiology*, *58*(1), 18–23. https://doi.org/10.1016/j.jinsphys.2011.09.005

Page 103. *In fact, 20E may have been*.

645. Parr, M., Botrè, F., Naß, A., Hengevoss, J., Diel, P., & Wolber, G. (2014). Ecdysteroids: A novel class of anabolic agents? *Biology of Sport*, *32*(2), 169–173. https://doi.org/10.5604/20831862.1144420

646. Tóth, N., Szabó, A., Kacsala, P., Héger, J., & Zádor, E. (2008). 20-Hydroxyecdysone increases fiber size in a muscle-specific fashion in rat. *Phytomedicine*, *15*(9), 691–698. https://doi.org/10.1016/j.phymed.2008.04.015

Page 103. *To find out, the World Anti-Doping Agency*.

647. Isenmann, E., Ambrosio, G., Joseph, J. F., Mazzarino, M., de la Torre, X., Zimmer, P., Kazlauskas, R., Goebel, C., Botrè, F., Diel, P., & Parr, M. K. (2019). Ecdysteroids as non-conventional anabolic agent: performance enhancement by ecdysterone supplementation in humans. *Archives of Toxicology*, *93*(7), 1807–1816. https://doi.org/10.1007/s00204-019-02490-x

Page 103. *However, a word of caution is in order*.

648. Wilborn, C. D., Taylor, L. W., Campbell, B. I., Kerksick, C., Rasmussen, C. J., Greenwood, M., & Kreider, R. B. (2006). Effects of Methoxyisoflavone, Ecdysterone, and Sulfo-Polysaccharide Supplementation on Training

Adaptations in Resistance-Trained Males. *Journal of the International Society of Sports Nutrition*, *3*(2). https://doi.org/10.1186/1550-2783-3-2-19

Page 104. *When the estrogen receptor beta*.

649. Parr, M. K., Zhao, P., Haupt, O., Ngueu, S. T., Hengevoss, J., Fritzemeier, K. H., Piechotta, M., Schlörer, N., Muhn, P., Zheng, W., Xie, M., & Diel, P. (2014). Estrogen receptor beta is involved in skeletal muscle hypertrophy induced by the phytoecdysteroid ecdysterone. *Molecular Nutrition & Food Research*, *58*(9), 1861–1872. https://doi.org/10.1002/mnfr.201300806

Page 104. *There are some potential downsides*.

650. Dinan, L., & Lafont, R. (2006). Effects and applications of arthropod steroid hormones (ecdysteroids) in mammals. *Journal of Endocrinology*, *191*(1), 1–8. https://doi.org/10.1677/joe.1.06900

651. Lu, M., Wang, P., Ge, Y., Dworkin, L., Brem, A., Liu, Z., & Gong, R. (2018). Activation of mineralocorticoid receptor by ecdysone, an adaptogenic and anabolic ecdysteroid, promotes glomerular injury and proteinuria involving overactive GSK3β pathway signaling. *Scientific Reports*, *8*(1), 12225. https://doi.org/10.1038/s41598-018-29483-7

Page 104. *In addition to being active all winter*.

652. Rose, R. K., & Dueser, R. D. (1980). Lifespan of Virginia Meadow Voles. *Journal of Mammalogy*, *61*(4), 760–763. https://doi.org/10.2307/1380335

653. Jameson, E. W. J.. (1947). Natural history of the prairie vole (Mammalian genus *Microtus*). *Misc. Publ. Mus. Nat. Hist., Univ. of Kansas* 1: 125–151.

Page 104. *It turns out*.

654. Negus, N. C., & Berger, P. J. (1977). Experimental Triggering of Reproduction in a Natural Population of *Microtus montanus*. *Science*, *196*(4295), 1230–1231. https://doi.org/10.1126/science.323977

Page 105. *These boom-and-bust cycles*.

655. Negus, N. C., & Berger, P. J. (1972). *Environmental factors and reproductive processes in mammalian populations* in: Biology of Reproduction: Basic and Clinical

Studies (J. T. Velardo and B. A. Kasprow, eds.), Third Pan American Congress on Anatomy, New Orleans, Louisiana, pp. 89-98.

Page 105. *The Norwegian language.*

656. Amundsen, B., & Bazilchuk, N. (2015, September 4). *Rodent population swings remain a mystery*. sciencenorway.no. https://sciencenorway.no/animal-world-ecology-forskningno/rodent-population-swings-remain-a-mystery/1421846

Page 105. *Grasses account for about.*

657. Christenhusz, M.J.M.; Byng, J.W. (2016). The number of known plants species in the world and its annual increase. *Phytotaxa*, *261*(3), 201. https://doi.org/10.11646/phytotaxa.261.3.1

Page 105. *We rely on grasses more than.*

658. DeWet, J. M. J. (1981). Grasses and the Culture History of Man. *Annals of the Missouri Botanical Garden*, *68*(1), 87. https://doi.org/10.2307/2398812

659. Gibson, D.J., (2009). *Grasses and grassland ecology*. Oxford University Press.

660. Alexandratos N, Bruinsma J. (2012). *World agriculture towards 2030/2050: the 2012 revision* (vol. ESA Workin).

Page 105. *One of the most effective.*

661. Frey, M., Chomet, P., Glawischnig, E., Stettner, C., Grün, S., Winklmair, A., Eisenreich, W., Bacher, A., Meeley, R. B., Briggs, S. P., Simcox, K., & Gierl, A. (1997). Analysis of a Chemical Plant Defense Mechanism in Grasses. *Science*, *277*(5326), 696–699. https://doi.org/10.1126/science.277.5326.696

Page 105. *Grasses use DIMBOA to defend.*

662. Vicari, M., & Bazely, D. R. (1993). Do grasses fight back? The case for antiherbivore defences. *Trends in Ecology & Evolution*, *8*(4), 137–141. https://doi.org/10.1016/0169-5347(93)90026-L

663. Wouters, F. C., Blanchette, B., Gershenzon, J., & Vassão, D. G. (2016). Plant defense and herbivore counter-defense: benzoxazinoids and insect herbivores. *Phytochemistry Reviews*, *15*(6), 1127–1151.

664.
665. https://doi.org/10.1007/s11101-016-9481-1
666. Jander, G. (2014). Revisiting Plant-Herbivore Co-Evolution in the Molecular Biology Era. In *Annual Plant Reviews* (pp. 361–384). Wiley. https://doi.org/10.1002/9781118829783.ch11

667. Frey, M., Schullehner, K., Dick, R., Fiesselmann, A., & Gierl, A. (2009). Benzoxazinoid biosynthesis, a model for evolution of secondary metabolic pathways in plants. *Phytochemistry*, *70*(15–16), 1645–1651. https://doi.org/10.1016/j.phytochem.2009.05.012

668. Kokubo, Y., Nishizaka, M., Ube, N., Yabuta, Y., Tebayashi, S., Ueno, K., Taketa, S., & Ishihara, A. (2017). Distribution of the tryptophan pathway-derived defensive secondary metabolites gramine and benzoxazinones in Poaceae. *Bioscience, Biotechnology, and Biochemistry*, *81*(3), 431–440. https://doi.org/10.1080/09168451.2016.1256758

669. Meihls, L. N., Handrick, V., Glauser, G., Barbier, H., Kaur, H., Haribal, M. M., Lipka, A. E., Gershenzon, J., Buckler, E. S., Erb, M., Köllner, T. G., & Jander, G. (2013). Natural Variation in Maize Aphid Resistance Is Associated with 2,4-Dihydroxy-7-Methoxy-1,4-Benzoxazin-3-One Glucoside Methyltransferase Activity . *The Plant Cell*, *25*(6), 2341–2355. https://doi.org/10.1105/tpc.113.112409

670. Barry, D., Alfaro, D., & Darrah, L. L. (1994). Relation of European Corn Borer (Lepidoptera: Pyralidae) Leaf-Feeding Resistance and Dimboa Content in Maize. *Environmental Entomology*, *23*(1), 177–182. https://doi.org/10.1093/ee/23.1.177

671. Poloni, A., & Schirawski, J. (2014). Red Card for Pathogens: Phytoalexins in Sorghum and Maize. *Molecules*, *19*(7), 9114–9133. https://doi.org/10.3390/molecules19079114

Page 106. *These grass-feeding herbivores can*.

672. Sikder, M. M., Vestergård, M., Kyndt, T., Fomsgaard, I. S., Kudjordjie, E. N., & Nicolaisen, M. (2021). Benzoxazinoids selectively affect maize root-associated nematode taxa. *Journal of Experimental Botany*, *72*(10), 3835–3845. https://doi.org/10.1093/jxb/erab104

673. Zhang, X., van Doan, C., Arce, C. C. M., Hu, L., Gruenig, S., Parisod, C., Hibbard, B. E., Hervé, M. R., Nielson, C., Robert, C. A. M., Machado, R. A. R., &

Erb, M. (2019). Plant defense resistance in natural enemies of a specialist insect herbivore. *Proceedings of the National Academy of Sciences*, *116*(46), 23174–23181. https://doi.org/10.1073/pnas.1912599116

674. Friebe, A., Klever, W., Sikora, R., & Schnabl, H. (1998). Allelochemicals in Root Exudates of Maize. In *Phytochemical Signals and Plant – Microbe Interactions* (pp. 71–93). Springer US. https://doi.org/10.1007/978-1-4615-5329-8_5

675. Robert, C. A. M., Veyrat, N., Glauser, G., Marti, G., Doyen, G. R., Villard, N., Gaillard, M. D. P., Köllner, T. G., Giron, D., Body, M., Babst, B. A., Ferrieri, R. A., Turlings, T. C. J., & Erb, M. (2012). A specialist root herbivore exploits defensive metabolites to locate nutritious tissues. *Ecology Letters*, *15*(1), 55–64. https://doi.org/10.1111/j.1461-0248.2011.01708.x

Page 106. *In 1981, researchers discovered that*.

676. Sanders, E. H., Gardner, P. D., Berger, P. J., & Negus, N. C. (1981). 6-Methoxybenzoxazolinone: A Plant Derivative That Stimulates Reproduction in *Microtus montanus*. *Science*, *214*(4516), 67–69. https://doi.org/10.1126/science.7025209

Page 106. *A close look at the chemical structure of 6-MBOA*.

677. Yuwiler, A., & Winters, W. D. (1985). Effects of 6-methoxy-2-benzoxazolinone on the pineal melatonin generating system. *The Journal of Pharmacology and Experimental Therapeutics*, *233*(1), 45–50.

678. Dai, X., Jiang, L. Y., Han, M., Ye, M. H., Wang, A. Q., Wei, W. H., & Yang, S. M. (2016). Reproductive responses of male Brandt's voles (Lasiopodomys brandtii) to 6-methoxybenzoxazolinone (6-MBOA) under short photoperiod. *The Science of Nature*, *103*(3–4), 29. https://doi.org/10.1007/s00114-016-1347-2

Page 106. *Melatonin is an essential hormone*.

679. Lerner, A. B., Case, J. D., Takahashi, Y., Lee, T. H., & Mori, W. (1958). Isolation of melatonin, the pineal gland factor that lightens melanocytes. *Journal of the American Chemical Society*, *80*(10), 2587–2587. https://doi.org/10.1021/ja01543a060

680. Reiter, R. J. (1993). The melatonin rhythm: both a clock and a calendar. *Experientia*, *49*(8), 654–664. https://doi.org/10.1007/BF01923947

Page 106. *Millions of people use melatonin*.

681. Wunsch N-G. (2021). Sales of melatonin 2020. New York, NY: Statista; https://www.statista.com/statistics/1267421/sales-of-melatonin-in-the-united-states/

682. Kuehn, B. M. (2022). Climbing Melatonin Use for Insomnia Raises Safety Concerns. *JAMA*, *328*(7), 605. https://doi.org/10.1001/jama.2022.11506

Page 106. *Melatonin is made by plants too.*

683. Hattori, A., Migitaka, H., Iigo, M., Itoh, M., Yamamoto, K., Ohtani-Kaneko, R., Hara, M., Suzuki, T., & Reiter, R. J. (1995). Identification of melatonin in plants and its effects on plasma melatonin levels and binding to melatonin receptors in vertebrates. *Biochemistry and Molecular Biology International*, *35*(3), 627–634.

684. Dubbels, R., Reiter, R. J., Klenke, E., Goebel, A., Schnakenberg, E., Ehlers, C., Schiwara, H. W., & Schloot, W. (1995). Melatonin in edible plants identified by radioimmunoassay and by high performance liquid chromatography-mass spectrometry. *Journal of Pineal Research*, *18*(1), 28–31. https://doi.org/10.1111/j.1600-079X.1995.tb00136.x

685. Kolář, J., Macháčková, I., Eder, J., Prinsen, E., Van Dongen, W., Van Onckelen, H., & Illnerová, H. (1997). Melatonin: occurrence and daily rhythm in Chenopodium rubrum. *Phytochemistry*, *44*(8), 1407-1413. https://doi.org/10.1016/S0031-9422(96)00568-7

686. Back, K. (2021). Melatonin metabolism, signaling and possible roles in plants. *The Plant Journal*, *105*(2), 376–391. https://doi.org/10.1111/tpj.14915

Page 106. *Voles given 6-MBOA.*

687. Berger, P. J., Negus, N. C., & Rowsemitt, C. N. (1987). Effect of 6-Methoxybenzoxazolinone on Sex Ratio and Breeding Performance in Microtus Montanus1. *Biology of Reproduction*, *36*(2), 255–260. https://doi.org/10.1095/biolreprod36.2.255

Page 106. *Researchers have theorized that 6-MBOA*.

688. Dai, X., Jiang, L. Y., Han, M., Ye, M. H., Wang, A. Q., Wei, W. H., & Yang, S. M. (2016). Reproductive responses of male Brandt's voles (Lasiopodomys

brandtii) to 6-methoxybenzoxazolinone (6-MBOA) under short photoperiod. *The Science of Nature*, *103*(3–4), 29. https://doi.org/10.1007/s00114-016-1347-2

Page 107. *How might the connection between 6-MBOA*.

689. Sanders, E. H., Gardner, P. D., Berger, P. J., & Negus, N. C. (1981). 6-Methoxybenzoxazolinone: A Plant Derivative That Stimulates Reproduction in *Microtus montanus*. *Science*, *214*(4516), 67–69. https://doi.org/10.1126/science.7025209

690. Epstein, W. W., Rowsemitt, C. N., Berger, P. J., & Negus, N. C. (1986). Dynamics of 6-methoxybenzoxazolinone in winter wheat. *Journal of Chemical Ecology*, *12*(10), 2011–2020. https://doi.org/10.1007/BF01041950

691. Negus, N. C., Berger, P. J., & Pinter, A. J. (1992). Phenotypic plasticity of the montane vole (*Microtus montanus*) in unpredictable environments. *Canadian Journal of Zoology*, *70*(11), 2121–2124. https://doi.org/10.1139/z92-285

692. Negus, N. C., Berger, P. J., & Brown, B. W. (1986). Microtine population dynamics in a predictable environment. *Canadian Journal of Zoology*, *64*(3), 785–792. https://doi.org/10.1139/z86-117

Page 107. *Remarkably, although voles don't.*

693. Berger, P. J., Sanders, E. H., Gardner, P. D., & Negus, N. C. (1977). Phenolic Plant Compounds Functioning as Reproductive Inhibitors in *Microtus montanus*. *Science*, *195*(4278), 575–577. https://doi.org/10.1126/science.319531

694. Negus, N. C., Berger, P. J., & Forslund, L. G. (1977). Reproductive strategy of *Microtus montanus*. *Journal of Mammalogy*, *58*(3), 347–353.

Chapter 6. Abiding Alkaloids

Page 109. *Over the winter break*. We walked trails in the Huckleberry Botanic Regional Preserve.

695. See: https://www.ebparks.org/parks/huckleberry

Page 109. *I knew the tree was used by the Yuki*.

696. Chesnut, V.K., (1902). *Plants used by the Indians of Mendocino County, California*. US Government Printing Office.

697. Budner, A. (2016, October 17). How to Enjoy a Fall Taste of Bay Laurel. *Bay Nature*. https://baynature.org/article/taste-bay-laurel/

698. Benemei, S., Appendino, G., & Geppetti, P. (2010). Pleasant natural scent with unpleasant effects: Cluster headache-like attacks triggered by *Umbellularia californica*. *Cephalalgia*, *30*(6), 744–746. https://doi.org/10.1111/j.1468-2982.2009.01988.x

699. Nassini, R., Materazzi, S., Vriens, J., Prenen, J., Benemei, S., de Siena, G., la Marca, G., Andrè, E., Preti, D., Avonto, C., Sadofsky, L., di Marzo, V., de Petrocellis, L., Dussor, G., Porreca, F., Taglialatela-Scafati, O., Appendino, G., Nilius, B., & Geppetti, P. (2012). The 'headache tree' via umbellulone and TRPA1 activates the trigeminovascular system. *Brain*, *135*(2), 376–390. https://doi.org/10.1093/brain/awr272

700. Drake, M. E., & Stuhr, E. T. (1935). Some pharmacological and bactericidal properties of umbellulone*,1,2. *The Journal of the American Pharmaceutical Association (1912)*, *24*(3), 196–207. https://doi.org/10.1002/jps.3080240304

701. Heamy, J. P. (1875). *Oreodaphne californica*, Nees., Nat. Ord. Laudaceae. *American Journal of Pharmacy (1835-1907)*, vol. 47, 105.

Page 110. *Every year on Christmas Day*.

702. Roman, A. (n.d.). *Cinnamon Rolls*. New York Times Cooking. Retrieved October 5, 2023, from https://cooking.nytimes.com/recipes/1018490-cinnamon-rolls

Page 110. *These days*.

703. Ravindran, P. N., & Nirmal-Babu, K. (2003). Introduction. In P. N. Ravindran, K. Nirmal-Babu, & M. Shylaja (Eds.), *Cinnamon and Cassia* (pp. 1–13). CRC Press. https://doi.org/10.1201/9780203590874

Page 110. *The chemical activates the same capsaicin*. This is incorrect. Cinnamaldeyde primarily activates the wasabi receptor TRPA1, not TRPV1.

704. Zurborg, S., Yurgionas, B., Jira, J. A., Caspani, O., & Heppenstall, P. A. (2007). Direct activation of the ion channel TRPA1 by Ca2+. *Nature Neuroscience*, *10*(3), 277–279. https://doi.org/10.1038/nn1843

Page 110. *Capsaicin produces the heat we feel.*

705. Caterina, M. J., Schumacher, M. A., Tominaga, M., Rosen, T. A., Levine, J. D., & Julius, D. (1997). The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature*, *389*(6653), 816–824. https://doi.org/10.1038/39807

Page 112. *I knew which smell receptors*.

706. Izquierdo, C., Gómez-Tamayo, J. C., Nebel, J.-C., Pardo, L., & Gonzalez, A. (2018). Identifying human diamine sensors for death related putrescine and cadaverine molecules. *PLOS Computational Biology*, *14*(1), e1005945. https://doi.org/10.1371/journal.pcbi.1005945

707. Hussain, A., Saraiva, L. R., Ferrero, D. M., Ahuja, G., Krishna, V. S., Liberles, S. D., & Korsching, S. I. (2013). High-affinity olfactory receptor for the death-associated odor cadaverine. *Proceedings of the National Academy of Sciences*, *110*(48), 19579–19584. https://doi.org/10.1073/pnas.1318596110

Page 115. *Piperidine forms the basis of many alkaloids*.

708. Watson, P. S., Jiang, B., & Scott, B. (2000). A Diastereoselective Synthesis of 2,4-Disubstituted Piperidines: Scaffolds for Drug Discovery. *Organic Letters*, *2*(23), 3679–3681. https://doi.org/10.1021/ol006589o

709. Abdelshaheed, M. M., Fawzy, I. M., El-Subbagh, H. I., & Youssef, K. M. (2021). Piperidine nucleus in the field of drug discovery. *Future Journal of Pharmaceutical Sciences*, *7*(1), 188. https://doi.org/10.1186/s43094-021-00335-y

Page 115. *Its precursor molecules*. More specifically, cadaverine (via decarboxylation of lysine) is a precursor of piperidine and putrescine of pyrrolidine (via decarboxylation of ornithine or arginine).

710. Schmidt-Glenewinkel, T., Nomura, Y., & Giacobini, E. (1977). The conversion of lysine into piperidine, cadaverine, and pipecolic acid in the brain and other organs of the mouse. *Neurochemical Research*, *2*(6), 619–637. https://doi.org/10.1007/BF0096377

711. Yamamoto, S., Itano, H., Kataoka, H., & Makita, M. (1982). Gas-liquid chromatographic method for analysis of di- and polyamines in foods. *Journal of Agricultural and Food Chemistry*, *30*(3), 435–439. https://doi.org/10.1021/jf00111a006

712. Sigrist, R., Costa, B. Z. da, Marsaioli, A. J., & de Oliveira, L. G. (2015). Nature-inspired enzymatic cascades to build valuable compounds. *Biotechnology Advances*, *33*(5), 394–411. https://doi.org/10.1016/j.biotechadv.2015.03.010

Page 115. *So powerfully repugnant*.

713. Pinel, J. P. J., Gorzalka, B. B., & Ladak, F. (1981). Cadaverine and putrescine initiate the burial of dead conspecifics by rats. *Physiology & Behavior*, *27*(5), 819–824. https://doi.org/10.1016/0031-9384(81)90048-2

Page 115. *These so-called biogenic*.

714. Halász, A., Baráth, Á., Simon-Sarkadi, L., & Holzapfel, W. (1994). Biogenic amines and their production by microorganisms in food. *Trends in Food Science & Technology*, *5*(2), 42–49. https://doi.org/10.1016/0924-2244(94)90070-1

715. Brown, M. H. (1982). *Meat Microbiology*. Appl. Sci., London

716. Whitehead, T. R., Price, N. P., Drake, H. L., & Cotta, M. A. (2008). Catabolic Pathway for the Production of Skatole and Indoleacetic Acid by the Acetogen *Clostridium drakei* , *Clostridium scatologenes* , and Swine Manure. *Applied and Environmental Microbiology*, *74*(6), 1950–1953. https://doi.org/10.1128/AEM.02458-07

Page 115. *Humans avoid the smell of death*.

717. Mussap, C. J. (2019). The Plague Doctor of Venice. *Internal Medicine Journal*, *49*(5), 671–676. https://doi.org/10.1111/imj.14285

718. Pan, K., Goel, A., Akin, L. R., & Patel, S. R. (2020). Through Plagues and Pandemics: The Evolution of Medical Face Masks. *Rhode Island Medical Journal (2013)*, *103*(10), 72–75.

Page 115. *Our disdain for these smells*.

719. Izquierdo, C., Gómez-Tamayo, J. C., Nebel, J.-C., Pardo, L., & Gonzalez, A. (2018). Identifying human diamine sensors for death related putrescine and

cadaverine molecules. *PLOS Computational Biology*, *14*(1), e1005945. https://doi.org/10.1371/journal.pcbi.1005945

Page 115 and 116. *Flies have their own*.

720. Hussain, A., Zhang, M., Üçpunar, H. K., Svensson, T., Quillery, E., Gompel, N., Ignell, R., & Grunwald Kadow, I. C. (2016). Ionotropic Chemosensory Receptors Mediate the Taste and Smell of Polyamines. *PLOS Biology*, *14*(5), e1002454. https://doi.org/10.1371/journal.pbio.1002454

Page 116. *Cadaverine, putrescine, and the related*.

721. Ladero, V., Calles-Enriquez, M., Fernandez, M., & A. Alvarez, M. (2010). Toxicological Effects of Dietary Biogenic Amines. *Current Nutrition & Food Science*, *6*(2), 145–156. https://doi.org/10.2174/157340110791233256

722. Scientific Opinion on risk based control of biogenic amine formation in fermented foods. (2011). *EFSA Journal*, *9*(10), 2393. https://doi.org/10.2903/j.efsa.2011.2393

723. Alvarez, M. A., & Moreno-Arribas, M. V. (2014). The problem of biogenic amines in fermented foods and the use of potential biogenic amine-degrading microorganisms as a solution. *Trends Food Sci. Technol.*, *39*(2), 146–155. https://doi.org/10.1016/j.tifs.2014.07.007

724. del Rio, B., Redruello, B., Linares, D. M., Ladero, V., Ruas-Madiedo, P., Fernandez, M., Martin, M. C., & Alvarez, M. A. (2019). The biogenic amines putrescine and cadaverine show in vitro cytotoxicity at concentrations that can be found in foods. *Sci. Rep.*, *9*(1), 120. https://doi.org/10.1038/s41598-018-36239-w

Page 116. *Skatole lives up to its name*.

725. Dickinson, E. O., Spencer, G. R., & Gorham, J. R. (1967). Experimental induction of an acute respiratory syndrome in cattle resembling bovine pulmonary emphysema. *Vet. Rec.*, *80*(16), 487–489. https://doi.org/10.1136/vr.80.16.487

Page 116. *At low concentrations*.

726. Furia, T.E.; Bellanca, N. (1975). *Fenaroli's Handbook of Flavor Ingredients*; CRC Press, Inc.: Boca Raton, FL, USA; Volume 2

727. Zgarbová, E., & Vrzal, R. (2023). Skatole: A thin red line between its benefits and toxicity. *Biochimie*, *208*, 1–12. https://doi.org/10.1016/j.biochi.2022.12.014

Page 116. *Now we can see*.

728. Harper, D. (n.d.). Etymology of Intoxicated. Online Etymology Dictionary. Retrieved Oct 6, 2023from https://www.etymonline.com/word/intoxicated

729. Merriam-Webster. (n.d.). Intoxicate. In Merriam-Webster.com dictionary. Retrieved October 6, 2023, from https://www.merriam-webster.com/dictionary/intoxicate

Page 116. *Adding it to the diets*.

730. Hofer, S. J., Simon, A. K., Bergmann, M., Eisenberg, T., Kroemer, G., & Madeo, F. (2022). Mechanisms of spermidine-induced autophagy and geroprotection. *Nature Aging*, *2*(12), 1112–1129. https://doi.org/10.1038/s43587-022-00322-9

Page 116. *In human cells*.

731. Eisenberg, T., Knauer, H., Schauer, A., Büttner, S., Ruckenstuhl, C., Carmona-Gutierrez, D., Ring, J., Schroeder, S., Magnes, C., Antonacci, L., Fussi, H., Deszcz, L., Hartl, R., Schraml, E., Criollo, A., Megalou, E., Weiskopf, D., Laun, P., Heeren, G., … Madeo, F. (2009). Induction of autophagy by spermidine promotes longevity. *Nature Cell Biology*, *11*(11), 1305–1314. https://doi.org/10.1038/ncb1975

Page 116. *One effect of spermidine*.

732. Liang, Y., Piao, C., Beuschel, C. B., Toppe, D., Kollipara, L., Bogdanow, B., Maglione, M., Lützkendorf, J., See, J. C. K., Huang, S., Conrad, T. O. F., Kintscher, U., Madeo, F., Liu, F., Sickmann, A., & Sigrist, S. J. (2021). eIF5A hypusination, boosted by dietary spermidine, protects from premature brain aging and mitochondrial dysfunction. *Cell Reports*, *35*(2), 108941. https://doi.org/10.1016/j.celrep.2021.108941

733. Madeo, F., Eisenberg, T., Pietrocola, F., & Kroemer, G. (2018). Spermidine in health and disease. *Science*, *359*(6374). https://doi.org/10.1126/science.aan2788

734. Schroeder, S., Hofer, S. J., Zimmermann, A., Pechlaner, R., Dammbrueck, C., Pendl, T., Marcello, G. M., Pogatschnigg, V., Bergmann, M., Müller, M., Gschiel, V., Ristic, S., Tadic, J., Iwata, K., Richter, G., Farzi, A., Üçal, M., Schäfer, U., Poglitsch, M., … Madeo, F. (2021). Dietary spermidine improves cognitive function. *Cell Rep.*, *35*(2), 108985. https://doi.org/10.1016/j.celrep.2021.108985

735. Pekar, T., Bruckner, K., Pauschenwein-Frantsich, S., Gschaider, A., Oppliger, M., Willesberger, J., Ungersbäck, P., Wendzel, A., Kremer, A., Flak, W., Wantke, F., & Jarisch, R. (2021). The positive effect of spermidine in older adults suffering from dementia. *Wiener Klinische Wochenschrift*, *133*(9–10), 484–491. https://doi.org/10.1007/s00508-020-01758-y

Page 117. *The smell of death.*

736. Prosser, C. L., Friedman, S., & Willis, J. H. (1990). Gottfried Samuel Fraenkel: April 23, 1901-October 26, 1984. *Biographical Memoirs. National Academy of Sciences (U.S.)*, *59*, 169–195.

Page 117. *Over half of all insect species.*

737. Schoonhoven, L.M., Van Loon, J.J. and Dicke, M. (2005). *Insect-plant biology*. Oxford university press.

Page 117. *Yet the vast majority of herbivorous insect.*

738. Brues, C. T. (1924). The Specificity of Food-Plants in the Evolution of Phytophagous Insects. *The American Naturalist*, *58*(655), 127–144. https://doi.org/10.1086/279965

739. Bernays, E. A. (1998). Evolution of Feeding Behavior in Insect Herbivores. *BioScience*, *48*(1), 35–44. https://doi.org/10.2307/1313226

Page 117. *Fraenkel wanted to.*

740. Fraenkel, G. (1953). The nutritional value of green plants for insects. in *Transactions of the IXth International Congress of Entomology*. W. Junk, The Hague, The Netherlands 90–100

Page 118. *A big hint came from.*

741. Hartmann, T. (2008). The lost origin of chemical ecology in the late 19th century. *Proceedings of the National Academy of Sciences*, *105*(12), 4541–4546. https://doi.org/10.1073/pnas.0709231105

Page 118. *Fraenkel then tested the idea.*

742. Fraenkel, G. S. (1959). The Raison d'Être of Secondary Plant Substances. *Science*, *129*(3361), 1466–1470. https://doi.org/10.1126/science.129.3361.1466

Page 119. *In "Butterflies and Plants: A study in Coevolution"*

743. Ehrlich, P. R., & Raven, P. H. (1964). Butterflies and Plants: A Study in Coevolution. *Evolution*, *18*(4), 586. https://doi.org/10.2307/2406212

Page 118. *Hence the term coevolution.*

744. Thompson, J. N. (2009). *The Coevolutionary Process*. University of Chicago Press.

745. Janzen, D. H. (1980). When is it Coevolution? *Evolution*, *34*(3), 611–612. https://doi.org/10.1111/j.1558-5646.1980.tb04849.x

Page 119. *This process may explain.*

746. Fordyce, J. A. (2010). Host shifts and evolutionary radiations of butterflies. *Proceedings of the Royal Society B: Biological Sciences*, *277*(1701), 3735–3743. https://doi.org/10.1098/rspb.2010.0211

747. Edger, P. P., Heidel-Fischer, H. M., Bekaert, M., Rota, J., Glöckner, G., Platts, A. E., Heckel, D. G., Der, J. P., Wafula, E. K., Tang, M., Hofberger, J. A., Smithson, A., Hall, J. C., Blanchette, M., Bureau, T. E., Wright, S. I., dePamphilis, C. W., Eric Schranz, M., Barker, M. S., … Wheat, C. W. (2015). The butterfly plant arms-race escalated by gene and genome duplications. *Proceedings of the National Academy of Sciences*, *112*(27), 8362–8366. https://doi.org/10.1073/pnas.1503926112

Page 119. *May Berenbaum's studies.*

748. Berenbaum, M. (1983). Coumarins and Caterpillars: A Case for Coevolution. *Evolution*, *37*(1), 163. https://doi.org/10.2307/2408184

749. Martin, L. J. (2012, April 16). *The Co-Evolution of Insects, Plants and a Career*. Scientific American. https://blogs.scientificamerican.com/guest-blog/the-co-evolution-of-insects-plants-and-a-career/

Page 119 and 120. *Although they agreed*.

750. Bernays, E., & Graham, M. (1988). On the Evolution of Host Specificity in Phytophagous Arthropods. *Ecology*, *69*(4), 886–892. https://doi.org/10.2307/1941237

Page 120. *There isn't always an "orgy of mutual benefaction."* See page 95 in reference below.

751. May, R. M. (1981). *Theoretical Ecology: Principles and Applications*. Blackwell.

Page 121. *Plants, which can be robbed*.

752. Irwin, R. E., Bronstein, J. L., Manson, J. S., & Richardson, L. (2010). Nectar Robbing: Ecological and Evolutionary Perspectives. *Annual Review of Ecology, Evolution, and Systematics*, *41*(1), 271–292. https://doi.org/10.1146/annurev.ecolsys.110308.120330

Page 122. *It tastes just like Nerds candy*. More specifically, the malic acid in Nerds candy is also found typically among the most abundant organic acids in honey bee pollen. There are other organic acids in pollen, which may vary in concentration depending on floral source, such as oxalic acid, tartaric acid, succinic acid, and citric acid

753. *Nerds Candy*. (n.d.). Retrieved October 5, 2023, from https://www.nerdscandy.com/nerds

754. Çelik, S., Gerçek, Y. C., Özkök, A., & Ecem Bayram, N. (2022). Organic acids and their derivatives: minor components of bee pollen, bee bread, royal jelly and bee venom. *European Food Research and Technology*, *248*(12), 3037–3057. https://doi.org/10.1007/s00217-022-04110-y

Page 121. *Small arums like the*.

755. Smith, B. N., & Meeuse, B. J. D. (1966). Production of Volatile Amines and Skatole at Anthesis in Some *Arum* Lily Species. *Plant Physiology*, *41*(2), 343–347. https://doi.org/10.1104/pp.41.2.343

Page 121. *In Sumatra, the titan arum*.

756. Kite, G. C., & Hetterschieid, W. L. A. (1997). Inflorescence odours of Amorphophallus and Pseudodracontium (Araceae). *Phytochemistry*, *46*(1), 71–75. https://doi.org/10.1016/S0031-9422(97)00221-5

757. Barthlott, W., Szarzynski, J., Vlek, P., Lobin, W., & Korotkova, N. (2009). A torch in the rain forest: thermogenesis of the Titan arum (*Amorphophallus titanum*). *Plant Biology*, *11*(4), 499–505. https://doi.org/10.1111/j.1438-8677.2008.00147.x

Page 122. *Bouquets of anise, banana, booze*.

758. Kite, G. C., & Hetterschieid, W. L. A. (1997). Inflorescence odours of Amorphophallus and Pseudodracontium (Araceae). *Phytochemistry*, *46*(1), 71–75. https://doi.org/10.1016/S0031-9422(97)00221-5

Page 122. *Neuroethologist Marcus Stensmyr*.

759. Stökl, J., Strutz, A., Dafni, A., Svatos, A., Doubsky, J., Knaden, M., Sachse, S., Hansson, B. S., & Stensmyr, M. C. (2010). A Deceptive Pollination System Targeting Drosophilids through Olfactory Mimicry of Yeast. *Current Biology*, *20*(20), 1846–1852. https://doi.org/10.1016/j.cub.2010.09.033

Page 123. *Children can also be*.

760. Maree, A., Hashavya, S., Gross, I., Asaf, Y., & Bentur, Y. (2020). Arum palaestinum poisoning: revenge of the witch. *European Journal of Pediatrics*, *179*(10), 1553–1557. https://doi.org/10.1007/s00431-020-03648-x

Page 123. *If enough tissue is ingested*.

761. Cumpston, K. L., Vogel, S. N., Leikin, J. B., & Erickson, T. B. (2003). Acute airway compromise after brief exposure to a Dieffenbachia plant. *The Journal of Emergency Medicine*, *25*(4), 391–397. https://doi.org/10.1016/j.jemermed.2003.02.005

Page 123. *Although not an alkaloid, oxalate*.

762. Palmieri, F., Estoppey, A., House, G. L., Lohberger, A., Bindschedler, S., Chain, P. S. G., & Junier, P. (2019). *Oxalic acid, a molecule at the crossroads of*

bacterial-fungal interactions (pp. 49–77). https://doi.org/10.1016/bs.aambs.2018.10.001

Page 124. *This pattern repeats itself*.

763. Cipollini, M. L., & Levey, D. J. (1997). Secondary Metabolites Of Fleshy Vertebrate-Dispersed Fruits: Adaptive Hypotheses And Implications For Seed Dispersal. *The American Naturalist*, *150*(3), 346–372. https://doi.org/10.1086/286069

Page 124. *If broken open*.

764. Nakamura, Y., Yoshimoto, M., Murata, Y., Shimoishi, Y., Asai, Y., Park, E. Y., Sato, K., & Nakamura, Y. (2007). Papaya Seed Represents a Rich Source of Biologically Active Isothiocyanate. *Journal of Agricultural and Food Chemistry*, *55*(11), 4407–4413. https://doi.org/10.1021/jf070159w

765. Janzen, D. H. (1969). Seed-eaters versus seed size, number, toxicity and dispersal. *Evolution*, *23*(1), 1–27. https://doi.org/10.1111/j.1558-5646.1969.tb03489.x

Page 125. *Depending on the gut passage time*.

766. Howe, H. F., & Smallwood, J. (1982). Ecology of Seed Dispersal. *Annual Review of Ecology and Systematics*, *13*(1), 201–228. https://doi.org/10.1146/annurev.es.13.110182.001221

767. Nathan, R., Schurr, F. M., Spiegel, O., Steinitz, O., Trakhtenbrot, A., & Tsoar, A. (2008). Mechanisms of long-distance seed dispersal. *Trends in Ecology & Evolution*, *23*(11), 638–647. https://doi.org/10.1016/j.tree.2008.08.003

768. Herrera, C. M. (1985). Determinants of Plant-Animal Coevolution: The Case of Mutualistic Dispersal of Seeds by Vertebrates. *Oikos*, *44*(1), 132. https://doi.org/10.2307/3544054

769. Platt, S. G., Elsey, R. M., Liu, H., Rainwater, T. R., Nifong, J. C., Rosenblatt, A. E., Heithaus, M. R., & Mazzotti, F. J. (2013). Frugivory and seed dispersal by crocodilians: an overlooked form of saurochory? *Journal of Zoology*, *291*(2), 87–99. https://doi.org/10.1111/jzo.12052

770. Gottsberger, G. (1978). Seed Dispersal by Fish in the Inundated Regions of Humaita, Amazonia. *Biotropica*, *10*(3), 170. https://doi.org/10.2307/2387903

771. Anderson, J. T., Nuttle, T., Saldaña Rojas, J. S., Pendergast, T. H., & Flecker, A. S. (2011). Extremely long-distance seed dispersal by an overfished Amazonian frugivore. *Proceedings of the Royal Society B: Biological Sciences*, *278*(1723), 3329–3335. https://doi.org/10.1098/rspb.2011.0155

Page 125. *As a UMSL graduate student*. Work on toucans in South America is highlighted below in addition to her previous work on hornbills in Africa.

772. Holbrook, K. M., & Loiselle, B. A. (2009). Dispersal in a Neotropical tree, *Virola flexuosa* (Myristicaceae): Does hunting of large vertebrates limit seed removal? *Ecology*, *90*(6), 1449–1455. https://doi.org/10.1890/08-1332.1

773. Karubian, J., Browne, L., Bosque, C., Carlo, T., Galetti, M., Loiselle, B. A., ... & Wikelski, M. (2012). Seed dispersal by neotropical birds: emerging patterns and underlying processes. *Ornitologia Neotropical*, *23*, 9-14.

774. Holbrook, K. M. (2011). Home Range and Movement Patterns of Toucans: Implications for Seed Dispersal. *Biotropica*, *43*(3), 357–364. https://doi.org/10.1111/j.1744-7429.2010.00710.x

775. Holbrook, K. M., Smith, T. B., & Hardesty, B. D. (2002). Implications of long-distance movements of frugivorous rain forest hornbills. *Ecography*, *25*(6), 745–749. https://doi.org/10.1034/j.1600-0587.2002.250610.x

Page 125. *From the seed's perspective*.

776. Janzen, D. H. (1970). Herbivores and the Number of Tree Species in Tropical Forests. *The American Naturalist*, *104*(940), 501–528. https://doi.org/10.1086/282687

777. Connell, J. H. (1971). On the role of natural enemies in preventing competitive exclusion in some marine animals and in rain forest trees. *Dynamics of populations*

Page 125. *Some nutmeg seeds*.

778. Huang, Y., Tan, J. M. W. L., Kini, R. M., & Ho, S. H. (1997). Toxic and antifeedant action of nutmeg oil against Tribolium castaneum (Herbst) and Sitophilus zeamais Motsch. *Journal of Stored Products Research*, *33*(4), 289–298. https://doi.org/10.1016/S0022-474X(97)00009-X

Page 125. *In the human body*.

779. Shulgin, A. T. (1966). Possible Implication of Myristicin as a Psychotropic Substance. *Nature*, *210*(5034), 380–384. https://doi.org/10.1038/210380a0

780. Shulgin, A. T., Sargent, T., & Naranjo, C. (1973). Animal Pharmacology and Human Psychopharmacology of 3-Methoxy-4,5-Methylenedioxyphenylisopropylamine (MMDA). *Pharmacology*, *10*(1), 12–18. https://doi.org/10.1159/000136416

781. Yang, K. H., Han, B. H., & Palamar, J. J. (2022). Past-year hallucinogen use in relation to psychological distress, depression, and suicidality among US adults. *Addictive Behaviors*, *132*, 107343. https://doi.org/10.1016/j.addbeh.2022.107343

Page 125. *The physician Andrew Weil.*

782. Weil, A. T. (1965). Nutmeg as a narcotic. *Economic Botany*, *19*(3), 194–217. https://doi.org/10.1007/BF02914307

Page 126. *However, in smaller doses.*

783. van Gils, C., & Cox, P. A. (1994). Ethnobotany of nutmeg in the Spice Islands. *Journal of Ethnopharmacology*, *42*(2), 117–124. https://doi.org/10.1016/0378-8741(94)90105-8

784. Sihotang, V. B. L., Yang, G., Chi, X., & Huang, L. (2018). The ethnobotanical survey of clove, pepper, and nutmeg and their utilization by Chinese and Indonesian people. *Journal of Tropical Biology & Conservation (JTBC)*, *15*, 15â-27.

Page 126. *Amphetamines generally work.*

785. Robertson, S. D., Matthies, H. J. G., & Galli, A. (2009). A Closer Look at Amphetamine-Induced Reverse Transport and Trafficking of the Dopamine and Norepinephrine Transporters. *Molecular Neurobiology*, *39*(2), 73–80. https://doi.org/10.1007/s12035-009-8053-4

786. Sulzer, D., Sonders, M. S., Poulsen, N. W., & Galli, A. (2005). Mechanisms of neurotransmitter release by amphetamines: A review. *Progress in Neurobiology*, *75*(6), 406–433. https://doi.org/10.1016/j.pneurobio.2005.04.003

787. Fleckenstein, A. E., Volz, T. J., Riddle, E. L., Gibb, J. W., & Hanson, G. R. (2007). New Insights into the Mechanism of Action of Amphetamines. *Annual Review of Pharmacology and Toxicology*, *47*(1), 681–698. https://doi.org/10.1146/annurev.pharmtox.47.120505.105140

Page 126. *Amphetamines are also made.*

788. Zheng, Q., Mu, X., Pan, S., Luan, R., & Zhao, P. (2023). Ephedrae herba: A comprehensive review of its traditional uses, phytochemistry, pharmacology, and toxicology. *Journal of Ethnopharmacology*, *307*, 116153. https://doi.org/10.1016/j.jep.2023.116153

789. Hattori, Y., Ishii, K., Yanai, K., & Endoh, M. (2023). The large part German medicine has played in the development of experimental pharmacology in Japan. *Naunyn-Schmiedeberg's Archives of Pharmacology*, *396*(1), 35–42. https://doi.org/10.1007/s00210-022-02308-1

790. Morelli, M., & Tognotti, E. (2021). Brief history of the medical and non-medical use of amphetamine-like psychostimulants. *Experimental Neurology*, *342*, 113754. https://doi.org/10.1016/j.expneurol.2021.113754

791. Casey, S. (2019). Early elixirs: From Meji wonder to modern meth. Australian Pharmacist, 38(5), 82. https://search.informit.org/doi/10.3316/informit.555845870419950

Page 125 and 126. *Therefore, in 2005.*

792. *CMEA (Combat Methamphetamine Epidemic Act of 2005)*. (2005). U. S. Department of Justice, Drug Enforcement Administration, Diversion Control Division. https://www.deadiversion.usdoj.gov/meth/index.html

Page 127. *In 2020, some 2.5 million people.*

793. Elfein, J. (2023, July 31). *Number of Americans who used methamphetamine in the past year 2009-2021*. Statista. https://www.statista.com/statistics/611697/methamphetamine-use-during-past-year-in-the-us/

794. *Stimulant Overdose*. (2023, August 23). Centers of Disease Control and Prevention. https://www.cdc.gov/drugoverdose/deaths/stimulant-overdose.html

795. Substance Abuse and Mental Health Services Administration. (2021). *Key substance use and mental health indicators in the United States: Results from the 2020 National Survey on Drug Use and Health* (HHS Publication No. PEP21-07-01-003, NSDUH Series H-56). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from https://www.samhsa.gov/data/. See: https://www.samhsa.gov/data/report/2020-nsduh-annual-national-report

Page 127. *The combination of meth.*

796. Centers for Disease Control and Prevention. (2020). *Increase in Fatal Drug Overdoses Across the United States Driven by Synthetic Opioids Before and During the COVID-19 Pandemic*. Health Alert Network. https://emergency.cdc.gov/han/2020/han00438.asp

Page 127. *Like ma huang, a plant called khat.*

797. Giannini, A. J., Burge, H., Shaheen, J. M., & Price, W. A. (1986). Khat: Another Drug of Abuse? *Journal of Psychoactive Drugs*, *18*(2), 155–158. https://doi.org/10.1080/02791072.1986.10471395

798. Balint, E. E., Falkay, G., & Balint, G. A. (2009). Khat – a controversial plant. *Wiener Klinische Wochenschrift*, *121*(19–20), 604–614. https://doi.org/10.1007/s00508-009-1259-7

799. Al-Mugahed, L. (2008). Khat chewing in Yemen: turning over a new leaf. *Bulletin of the World Health Organization*, *86*(10), 741–742. https://doi.org/10.2471/BLT.08.011008

800. Haile, D., & Lakew, Y. (2015). Khat Chewing Practice and Associated Factors among Adults in Ethiopia: Further Analysis Using the 2011 Demographic and Health Survey. *PLOS ONE*, *10*(6), e0130460. https://doi.org/10.1371/journal.pone.0130460

Page 127. *Cathinones work on the brain.*

801. Baumann, M. H., Walters, H. M., Niello, M., & Sitte, H. H. (2018). Neuropharmacology of Synthetic Cathinones. In H. H. Maurer & S. D. Brandt (Eds.), *New Psychoactive Substances : Pharmacology, Clinical, Forensic and Analytical Toxicology* (pp. 113–142). Springer International Publishing. https://doi.org/10.1007/164_2018_178

Page 127. *Another set of alkaloids, on the other hand.*

802. Kelmendi, B., Kaye, A. P., Pittenger, C., & Kwan, A. C. (2022). Psychedelics. *Current Biology*, *32*(2), R63–R67. https://doi.org/10.1016/j.cub.2021.12.009

803. Sheldrake, M. (2020). The 'enigma' of Richard Schultes, Amazonian hallucinogenic plants, and the limits of ethnobotany. *Social Studies of Science*, *50*(3), 345–376. https://doi.org/10.1177/0306312720920362

804. Schultes, R. E.; Hofmann A. (1979). *Plants of the Gods: Origins of Hallucinogenic Use. New York: McGraw-Hill. ISBN 0-07-056089-7.*

805. Schultes R. E. (1970). *The New World Indians and their hallucinogenic plants*.

806. Davis W. (1996). *One River: Explorations and Discoveries in the Amazon Rain Forest*. Simon and Schuster, Inc.

Page 128. *One such alkaloid*.

807. Agurell, S., Holmstedt, B., Lindgren, J.-E., Schultes, R. E., Lindberg, A. A., Jansen, G., Lamm, B., & Samuelsson, B. (1969). Alkaloids in Certain Species of Virola and Other South American Plants of Ethnopharmacologic Interest. *Acta Chemica Scandinavica*, *23*, 903–916. https://doi.org/10.3891/acta.chem.scand.23-0903

808. Schultes, R. E. (1969). *Virola* as an orally administered hallucinogen. *Botanical Museum Leaflets, Harvard University*, *22*(6), 229–240. http://www.jstor.org/stable/41753106

809. Roberts, M. F. (1998). *Alkaloids* (M. F. Roberts & M. Wink, Eds.). Springer US. https://doi.org/10.1007/978-1-4757-2905-4

Page 128. *DMT and other related tryptamines*.

810. Manske, R. H. F. (1931). A SYNTHESIS OF THE METHYLTRYPTAMINES AND SOME DERIVATIVES. *Canadian Journal of Research*, *5*(5), 592–600. https://doi.org/10.1139/cjr31-097

811. Carbonaro, T. M., & Gatch, M. B. (2016). Neuropharmacology of N,N-dimethyltryptamine. *Brain Research Bulletin*, *126*, 74–88. https://doi.org/10.1016/j.brainresbull.2016.04.016

812. Smith, T. A. (1977). Tryptamine and related compounds in plants. *Phytochemistry*, *16*(2), 171–175. https://doi.org/10.1016/S0031-9422(00)86778-3

813. McKenna, D., & Riba, J. (2018). New World Tryptamine Hallucinogens and the Neuroscience of Ayahuasca. In A. L. Halberstadt, F. X. Vollenweider, & D. E. Nichols (Eds.), *Behavioral Neurobiology of Psychedelic Drugs* (pp. 283–311). Springer Berlin Heidelberg. https://doi.org/10.1007/7854_2016_472

814. Bigwood, J., & Ott, J. (1997, November). DMT. *Head Magazine*. https://web.archive.org/web/20060127003553/http://jeremybigwood.net/JBsPUBS/DMT/

Page 128. *The tryptamines bufotenine.*

815. Chilton, W. S., Bigwood, J., & Jensen, R. E. (1979). Psilocin, Bufotenine and Serotonin: Historical and Biosynthetic Observations. *Journal of Psychedelic Drugs*, *11*(1–2), 61–69. https://doi.org/10.1080/02791072.1979.10472093

816. Sherwood, A. M., Claveau, R., Lancelotta, R., Kaylo, K. W., & Lenoch, K. (2020). Synthesis and Characterization of 5-MeO-DMT Succinate for Clinical Use. *ACS Omega*, *5*(49), 32067–32075. https://doi.org/10.1021/acsomega.0c05099

817. Carpenter, D. E. (2020). 5-MeO-DMT: The 20-Minute Psychoactive Toad Experience That's Transforming Lives. *Forbes Magazine*. https://www.forbes.com/sites/davidcarpenter/2020/02/02/5-meo-dmt-the-20-minute-psychoactive-toad-experience-thats-transforming-lives/

818. Pachter , I. J., Zacharias, D. E., & Ribeiro , O. (1959). Indole Alkaloids of *Acer saccharinum* (the Silver Maple), *Dictyoloma incanescens*, *Piptadenia colubrina*, and *Mimosa hostilis*. *The Journal of Organic Chemistry*, *24*(9), 1285–1287. https://doi.org/10.1021/jo01091a032

819. Torres CM, Repke DB (2006). *Anadenanthera*: visionary plant of ancient South America. Routledge, London.

Page 128. *Magic mushrooms contain the tryptamine.*

820. Reynolds, H. T., Vijayakumar, V., Gluck-Thaler, E., Korotkin, H. B., Matheny, P. B., & Slot, J. C. (2018). Horizontal gene cluster transfer increased hallucinogenic mushroom diversity. *Evolution Letters*, *2*(2), 88–101. https://doi.org/10.1002/evl3.42

821. Guzman, G. (2005). Species Diversity of the Genus Psilocybe (Basidiomycotina, Agaricales, Strophariaceae) in the World Mycobiota, with Special Attention to Hallucinogenic Properties. *International Journal of Medicinal Mushrooms*, *7*(1–2), 305–332. https://doi.org/10.1615/IntJMedMushr.v7.i12.280

822. Beug, M. W., & Bigwood, J. (1982). Psilocybin and psilocin levels in twenty species from seven genera of wild mushrooms in the Pacific Northwest, U.S.A. *Journal of Ethnopharmacology*, *5*(3), 271–285. https://doi.org/10.1016/0378-8741(82)90013-7

823. Hofmann, A., Heim, R., Brack, A., & Kobel, H. (1958). [Psilocybin, a psychotropic substance from the Mexican mushroom Psilicybe mexicana Heim]. *Experientia*, *14*(3), 107–109. https://doi.org/10.1007/BF02159243

824. Hofmann, A., Frey, A., Ott, H., Petrzilka, Th., & Troxler, F. (1958). Konstitutionsaufklärung und Synthese von Psilocybin. *Experientia*, *14*(11), 397–399. https://doi.org/10.1007/BF02160424

825. Hofmann A. (1971). Teonanacatl and Ololuiqui and Ololuiqui, two ancient magic drugs of Mexico. *Bulletin of Narcotics*. XXIII:3–14. https://www.unodc.org/unodc/en/data-and-analysis/bulletin/bulletin_1971-01-01_1_page003.html

Page 128. *The danger of using extracts of toad glands.*

826. Davis, W., & Weil, A. T. (1992). Identity of a New World Psychoactive Toad. *Ancient Mesoamerica*, *3*(1), 51–59. https://doi.org/10.1017/S0956536100002297

827. Weil, A. T., & Davis, W. (1994). *Bufo alvarius*: a potent hallucinogen of animal origin. *Journal of Ethnopharmacology*, *41*(1–2), 1–8. https://doi.org/10.1016/0378-8741(94)90051-5

828. Romero, S. (2023, June 22). Demand for This Toad's Psychedelic Toxin Is Booming. Some Warn That's Bad for the Toad. *New York Times*. https://www.nytimes.com/2022/03/20/us/toad-venom-psychedelic.html

Page 128. *However, some Indigenous.*

829. See this quote "However, the purpose of these ancient practices has not been fully clarified, and evidence of use as a medicine is scarce. Therefore, it cannot be ruled out that the present use of toad secretion is of more recent origin." from
Uthaug, M. v., Lancelotta, R., van Oorsouw, K., Kuypers, K. P. C., Mason, N., Rak, J., Šuláková, A., Jurok, R., Maryška, M., Kuchař, M., Páleníček, T., Riba, J., & Ramaekers, J. G. (2019). A single inhalation of vapor from dried toad secretion containing 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting is related to sustained enhancement of satisfaction with life, mindfulness-related capacities, and a decrement of psychopathological symptoms. *Psychopharmacology*, *236*(9), 2653–2666. https://doi.org/10.1007/s00213-019-05236-w

830. See this quote: "Still, some of the most influential figures in the Bufo scene have promoted Indigenous connections. Dr. Octavio Rettig, a physician from Guadalajara, Mexico, said he introduced the substance to the Seri people in northwestern Mexico in 2011 in a bid to combat crystal meth addiction. "After they got the medicine, they started to put the puzzle together," said Dr. Rettig, 43, citing what he believes was a rescue of the Seri's "lost traditions." "They recognized the benefits of the toad medicine." From:
Romero, S. (2023, June 22). Demand for This Toad's Psychedelic Toxin Is Booming. Some Warn That's Bad for the Toad. *New York Times*. https://www.nytimes.com/2022/03/20/us/toad-venom-psychedelic.html

831. Davis, A. K., So, S., Lancelotta, R., Barsuglia, J. P., & Griffiths, R. R. (2019). 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) used in a naturalistic group setting is associated with unintended improvements in depression and anxiety. *Am. J. Drug Alcohol Abuse*, *45*(2), 161–169. https://doi.org/10.1080/00952990.2018.1545024

Page 128. *In fact, the practice of smoking toad venom.*

832. Most, A. (1983). *Bufo Alvarius: The Psychedelic Toad of the Sonora Desert*. https://archive.org/details/bufoalvariusbooklet_202006

Page 129. *While there were ancient paintings.*

833. de Rios, M. D., Alger, N., Crumrine, N. R., Furst, P. T., Harman, R. C., Hellmuth, N. M., Hopkins, N. A., King, W. C., Koss, J. D., La Barre, W., Landar, H. J., Long, J. K., Proskouriakoff, T., Rubel, A. J., Samaranch, F., J. Eric S.

Thompson, & Wescott, R. W. (1974). The Influence of Psychotropic Flora and Fauna on Maya Religion [and Comments and Reply]. *Current Anthropology*, *15*(2), 147–164. http://www.jstor.org/stable/2740991

834. Kennedy, A. B. (1982). *Ecce Bufo*: The Toad in Nature and in Olmec Iconography. *Current Anthropology*, *23*(3), 273–290. https://doi.org/10.1086/202831

Page 129. *DMTs bind to our*.

835. Aghajanian, G. K., Foote, W. E., & Sheard, M. H. (1968). Lysergic Acid Diethylamide: Sensitive Neuronal Units in the Midbrain Raphe. *Science*, *161*(3842), 706–708. https://doi.org/10.1126/science.161.3842.706

836. Glennon, R. A., Titeler, M., & Young, R. (1986). Structure-activity relationships and mechanism of action of hallucinogenic agents based on drug discrimination and radioligand binding studies. *Psychopharmacology Bulletin*, *22*(3), 953–958.

837. Glennon, R. A., & Gessner, P. K. (1979). Serotonin receptor binding affinities of tryptamine analogs. *Journal of Medicinal Chemistry*, *22*(4), 428–432. https://doi.org/10.1021/jm00190a014

838. González-Maeso, J., Weisstaub, N. v., Zhou, M., Chan, P., Ivic, L., Ang, R., Lira, A., Bradley-Moore, M., Ge, Y., Zhou, Q., Sealfon, S. C., & Gingrich, J. A. (2007). Hallucinogens Recruit Specific Cortical 5-HT2A Receptor-Mediated Signaling Pathways to Affect Behavior. *Neuron*, *53*(3), 439–452. https://doi.org/10.1016/j.neuron.2007.01.008

839. López-Giménez, J. F., & González-Maeso, J. (2018). Hallucinogens and Serotonin 5-HT2A Receptor-Mediated Signaling Pathways. *Current Topics in Behavioral Neurosciences*, *36*, 45–73. https://doi.org/10.1007/7854_2017_478

840. Vollenweider, F. X., Vollenweider-Scherpenhuyzen, M. F. I., Bäbler, A., Vogel, H., & Hell, D. (1998). Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. *NeuroReport*, *9*(17), 3897–3902. https://doi.org/10.1097/00001756-199812010-00024

Page 129. *The velvet bean*.

841. Pulikkalpura, H., Kurup, R., Mathew, P. J., & Baby, S. (2015). Levodopa in *Mucuna pruriens* and its degradation. *Scientific reports*, *5*, 11078. https://doi.org/10.1038/srep11078

842. Neuwinger, H.D. (1998). Alkaloids in Arrow Poisons. In: Roberts, M.F., Wink, M. (eds) *Alkaloids*. Springer, Boston, MA. https://doi.org/10.1007/978-1-4757-2905-4_3

Page 129. *Across the Atlantic.*

843. Torres, C. M., & Repke, D. B. (2014). *Anadenanthera: visionary plant of ancient South America*. Routledge.

844. Altschul, S. R. (1972). *The genus Anadenanthera in Amerindian cultures.* Mass., Harvard University.

845. Knobloch, P. J. (2000). Wari Ritual Power at Conchopata: An Interpretation of *Anadenanthera Colubrina* Iconography. *Latin American Antiquity*, *11*(4), 387–402. https://doi.org/10.2307/972003

846. Bélisle, V. (2019). Hallucinogens and Altered States of Consciousness in Cusco, Peru: A Path to Local Power during Wari State Expansion. *Cambridge Archaeological Journal, 29*(3), 375-391. doi:10.1017/S0959774319000015

Page 129 and 130. *Butotenine, probably derived from Anadenanthera.*

847. Miller, M. J., Albarracin-Jordan, J., Moore, C., & Capriles, J. M. (2019). Chemical evidence for the use of multiple psychotropic plants in a 1,000-year-old ritual bundle from South America. *Proceedings of the National Academy of Sciences of the United States of America*, *116*(23), 11207–11212. https://doi.org/10.1073/pnas.1902174116

Page 130 and 131. *DMT is also the principal.* These references apply to the next three paragraphs.

848. Holmstedt, B., & Lindgren, J. (1967). Chemical constituents and pharmacology of South American snuffs. *Psychopharmacology Bulletin*, *4*(3), 16.

849. Spruce, R (1908). *Notes of a Botanist on the Amazon and Andes (two volumes).* Macmillian, London. Reprinted by Johnson Reprint, New York, 1970.

850. Rivier, L., & Lindgren, J.-E. (1972). "Ayahuasca," the South American hallucinogenic drink: An ethnobotanical and chemical investigation. *Economic Botany*, *26*(2), 101–129. https://doi.org/10.1007/BF02860772

851. Schultes, R. E. (1980). *The botany and chemistry of hallucinogens.* Thomas.

852. Schultes, R. E. (1957). The identity of the malpighiaceous narcotics of South America. *Botanical Museum Leaflets, Harvard University*, *18*(1), 1-56. http://www.jstor.org/stable/41762183

853. Pinkley, H. v. (1969). Plant admixtures to Ayahuasca, the South American hallucinogenic drink. *Lloydia*, *32*(3), 305–314.

854. McKenna, D. J., Towers, G. H. N., & Abbott, F. (1984). Monoamine oxidase inhibitors in South American hallucinogenic plants: Tryptamine and β-carboline constituents of Ayahuasca. *Journal of Ethnopharmacology*, *10*(2), 195–223. https://doi.org/10.1016/0378-8741(84)90003-5

855. Callaway, J. C., McKenna, D. J., Grob, C. S., Brito, G. S., Raymon, L. P., Poland, R. E., Andrade, E. N., Andrade, E. O., & Mash, D. C. (1999). Pharmacokinetics of Hoasca alkaloids in healthy humans. *Journal of Ethnopharmacology*, *65*(3), 243–256. https://doi.org/10.1016/S0378-8741(98)00168-8

856. McKenna, D., & Riba, J. (2018). New World Tryptamine Hallucinogens and the Neuroscience of Ayahuasca. In A. L. Halberstadt, F. X. Vollenweider, & D. E. Nichols (Eds.), *Behavioral Neurobiology of Psychedelic Drugs* (pp. 283–311). Springer Berlin Heidelberg. https://doi.org/10.1007/7854_2016_472

857. Callaway, J. C. (2005). Various Alkaloid Profiles in Decoctions of *Banisteriopsis Caapi*. *Journal of Psychoactive Drugs*, *37*(2), 151–155. https://doi.org/10.1080/02791072.2005.10399796

Page 131. *In contrast, when toad venom is smoked*.

858. Davis, A. K., Barsuglia, J. P., Lancelotta, R., Grant, R. M., & Renn, E. (2018). The epidemiology of 5-methoxy- *N, N* -dimethyltryptamine (5-MeO-DMT) use: Benefits, consequences, patterns of use, subjective effects, and reasons for consumption. *Journal of Psychopharmacology*, *32*(7), 779–792. https://doi.org/10.1177/0269881118769063

859. Barsuglia, J., Davis, A. K., Palmer, R., Lancelotta, R., Windham-Herman, A.-M., Peterson, K., Polanco, M., Grant, R., & Griffiths, R. R. (2018). Intensity of Mystical Experiences Occasioned by 5-MeO-DMT and Comparison With a Prior Psilocybin Study. *Frontiers in Psychology*, *9*. https://doi.org/10.3389/fpsyg.2018.02459

860. Uthaug, M. V., Lancelotta, R., Ortiz Bernal, A. M., Davis, A. K., & Ramaekers, J. G. (2020). A comparison of reactivation experiences following vaporization and intramuscular injection (IM) of synthetic *5-methoxy-N,N-dimethyltryptamine* (5-MeO-DMT) in a naturalistic setting. *Journal of Psychedelic Studies, 4*(2), 104–113. https://doi.org/10.1556/2054.2020.00123

861. Brush, D. E., Bird, S. B., & Boyer, E. W. (2004). Monoamine Oxidase Inhibitor Poisoning Resulting from Internet Misinformation on Illicit Substances. *Journal of Toxicology: Clinical Toxicology*, *42*(2), 191–195. https://doi.org/10.1081/CLT-120030949

Page 131. *Psilocin is ultimately detoxified*.

862. Lenz, C., Dörner, S., Trottmann, F., Hertweck, C., Sherwood, A., & Hoffmeister, D. (2022). Assessment of Bioactivity-Modulating Pseudo-Ring Formation in Psilocin and Related Tryptamines. *ChemBioChem*, *23*(13). https://doi.org/10.1002/cbic.202200183

863. Blei, F., Dörner, S., Fricke, J., Baldeweg, F., Trottmann, F., Komor, A., Meyer, F., Hertweck, C., & Hoffmeister, D. (2020). Simultaneous Production of Psilocybin and a Cocktail of β-Carboline Monoamine Oxidase Inhibitors in "Magic" Mushrooms. *Chemistry – A European Journal*, *26*(3), 729–734. https://doi.org/10.1002/chem.201904363

864. Lenz, C., Sherwood, A., Kargbo, R., & Hoffmeister, D. (2021). Taking Different Roads: <scp>l</scp> -Tryptophan as the Origin of *Psilocybe* Natural Products. *ChemPlusChem*, *86*(1), 28–35. https://doi.org/10.1002/cplu.202000581

Page 131. Nowhere were *Psilocybe* and the many.

865. Schultes, R. E. (1940). Teonanacatl: The Narcotic Mushroom of the Aztecs. *American Anthropologist*, *42*(3), 429–443. http://www.jstor.org/stable/663232

866. Hofmann A. (1971). Teonanacatl and Ololuiqui and Ololuiqui, two ancient magic drugs of Mexico. *Bulletin of Narcotics*. XXIII:3–14.

https://www.unodc.org/unodc/en/data-and-analysis/bulletin/bulletin_1971-01-01_1_page003.html

867. Singer, R. (1958). Mycological Investigations on Teonanacatl, the Mexican Hallucinogenic Mushroom. Part I. The History of Teonanacatl, Field Work and Culture Work. *Mycologia*, *50*(2), 239. https://doi.org/10.2307/3756196

868. Singer, R., & Smith, A. H. (1958). Mycological Investigations on Teonanacatl, the Mexican Hallucinogenic Mushroom. Part II. A Taxonomic Monograph of Psilocybe, Section Caerulescentes. *Mycologia*, *50*(2), 262. https://doi.org/10.2307/3756197

869. Weber, H. P., & Petcher, T. J. (1974). Crystal structures of the Teonanácatl hallucinogens. Part I. Psilocybin $C_{12}H_{17}N_2O_4P$. *J. Chem. Soc., Perkin Trans. 2*, *8*, 942–946. https://doi.org/10.1039/P29740000942

870. Petcher, T. J., & Weber, H. P. (1974). Crystal structures of the Teonanácatl hallucinogens. Part II. Psilocin, $C_{12}H_{15}N_2O$. *J. Chem. Soc., Perkin Trans. 2*, *8*, 946–948. https://doi.org/10.1039/P29740000946

Page 131. *Two other important serotonin*. The next two paragraphs rely on the references below.

871. de Groot, A. N. J. A., van Dongen, P. W. J., Vree, T. B., Hekster, Y. A., & van Roosmalen, J. (1998). Ergot Alkaloids. *Drugs*, *56*(4), 523–535. https://doi.org/10.2165/00003495-199856040-00002

872. Lee, M. R. (2009). The history of ergot of rye (Claviceps purpurea) I: from antiquity to 1900. *The Journal of the Royal College of Physicians of Edinburgh*, *39*(2), 179-184.

873. Hofmann, A., & Ott, J. (1983). *LSD, my problem child: Reflections on sacred drugs, mysticism, and science* (p. 224). Los Angeles, CA: JP Tarcher.

Page 132. *Mescaline is found only*.

874. Jay, M. (2019). *Mescaline: a global history of the first psychedelic*. Yale University Press.

875. Gurschler, I. (2019). The fourfold discovery of Mescaline (1896–1919). *Monatshefte Für Chemie - Chemical Monthly*, *150*(5), 941–947. https://doi.org/10.1007/s00706-019-02444-0

876. Dobkin, M. (1968). Trichocereus pachanoi—A mescaline cactus used in folk healing in Peru. *Economic Botany*, *22*(2), 191–194. https://doi.org/10.1007/BF02860562

877. Ma, W. W., Jiang, X. Y., Cooks, R. G., McLaughlin, J. L., Gibson, A. C., Zeylemaker, F., & Ostolaza, C. N. (1986). Cactus Alkaloids, LXI. Identification of Mescaline and Related Compounds in Eight Additional Species Using Tlc and Ms/ms. *Journal of Natural Products*, *49*(4), 735–737. https://doi.org/10.1021/np50046a050

878. Watkins, J. L., Li, Q., Yeaman, S., & Facchini, P. J. (2023). Elucidation of the mescaline biosynthetic pathway in peyote (*Lophophora williamsii*). *The Plant Journal*. https://doi.org/10.1111/tpj.16447

879. Carod-Artal, F. J., & Vázquez-Cabrera, C. B. (2006). [Mescaline and the San Pedro cactus ritual: archaeological and ethnographic evidence in northern Peru]. *Revista de Neurologia*, *42*(8), 489–498.

880. Ogunbodede, O., McCombs, D., Trout, K., Daley, P., & Terry, M. (2010). New mescaline concentrations from 14 taxa/cultivars of Echinopsis spp. (Cactaceae) ("San Pedro") and their relevance to shamanic practice. *Journal of Ethnopharmacology*, *131*(2), 356–362. https://doi.org/10.1016/j.jep.2010.07.021

881. Davis, E. W. (1983). SACRED PLANTS OF THE SAN PEDRO CULT. *Botanical Museum Leaflets, Harvard University*, *29*(4), 367–386. http://www.jstor.org/stable/41762855

882. El-Seedi, H. R., Smet, P. A. G. M. de, Beck, O., Possnert, G., & Bruhn, J. G. (2005). Prehistoric peyote use: Alkaloid analysis and radiocarbon dating of archaeological specimens of Lophophora from Texas. *Journal of Ethnopharmacology*, *101*(1–3), 238–242. https://doi.org/10.1016/j.jep.2005.04.022

Page 132 and 133. *Most of the DMTs*.

883. U. S. Drug Enforcement Agency. (2023). Controlled Substances. https://www.deadiversion.usdoj.gov/schedules/orangebook/c_cs_alpha.pdf

Page 133. *Why psychedelic alkaloids*. Tangential evidence of anti-herbivore or anti-pathogen from related alkaloids is below (although not all are psychedelic).

884. Thomas, J. C., Saleh, E. F., Alammar, N., & Akroush, A. M. (1998). The Indole Alkaloid Tryptamine Impairs Reproduction in Drosophila melanogaster.

Journal of Economic Entomology, *91*(4), 841–846. https://doi.org/10.1093/jee/91.4.841

885. Miles, D. H., Ly, A. M., Randle, S. A., Hedin, P. A., & Burks, M. L. (1987). Alkaloidal insect antifeedants from Virola calophylla Warb. *Journal of Agricultural and Food Chemistry*, *35*(5), 794–797. https://doi.org/10.1021/jf00077a037

Page 133. *Among the plants.*

886. Simpson, B. H., Jolly, R. D., & Thomas, S. H. M. (1969). *Phalaris arundinacea* as a cause of deaths and incoordination in sheep. *New Zealand Veterinary Journal*, *17*(12), 240–244. https://doi.org/10.1080/00480169.1969.33837

887. Ulvund, M. J. (1985). Chronic Poisoning in a Lamb Grazing *Phalaris arundinacea*. *Acta Veterinaria Scandinavica*, *26*(2), 286–288. https://doi.org/10.1186/BF03546558

888. Marten, G. C., Jordan, R. M., & Hovin, A. W. (1976). Biological Significance of Reed Canarygrass Alkaloids and Associated Palatability Variation to Grazing Sheep and Cattle. *Agronomy Journal*, *68*(6), 909–914. https://doi.org/10.2134/agronj1976.00021962006800060017x

889. Culvenor, C., Dal Bon, R., & Smith, L. (1964). The occurrence of indolealkylamine alkaloids in *Phalaris tuberosa* L. and *P. arundinacea* L. *Australian Journal of Chemistry*, *17*(11), 1301. https://doi.org/10.1071/CH9641301

890. Marten, G. C. (1973). Alkaloids in reed canarygrass. *Anti-quality components of forages*, *4*, 15-31. https://doi.org/10.2135/cssaspecpub4.c2

891. Read, E., Reddy, P., Rendell, D., & Rochfort, S. (2020). Changes in field concentrations of five phalaris alkaloids and their association with toxicity in pastures of Victoria, Australia. *Crop and Pasture Science*, *71*(4), 389. https://doi.org/10.1071/CP19293

892. Alden, R., Hackney, B., Weston, L. A., & Quinn, J. C. (2014). Phalaris Toxicoses in Australian Livestock Production Systems: Prevalence, Aetiology and Toxicology. *Journal of Toxins*, *1*(1). https://doi.org/10.13188/2328-1723.1000003

893. Rendig, V., Cooper, D., Dunbar, J., Lawrence, C., Clawson, W., Bushnell, R., & McComb, E. (1976). Phalaris "staggers" in California. *California agriculture*, *30*(6), 8-10.

894. Wilkinson, S. (1958). 428. 5-Methoxy-N-methyltryptamine: a new indole alkaloid from Phalaris arundinacea L. *Journal of the Chemical Society (Resumed)*, 2079. https://doi.org/10.1039/jr9580002079

895. Ahlborg, U., Holmstedt, B., & Lindgren, J. E. (1968). Fate and metabolism of some hallucinogenic indolealkylamines. *Advances in Pharmacology*, *6*(Pt B), 213–229. https://doi.org/10.1016/s1054-3589(08)60320-8

896. Gallagher, C. H., Koch, J. H., & Hoffman, H. (1967). Electro-myographic studies on sheep injected with the n,n-dimethylated tryptamine alkaloids ofphalaris tuberosa. *International Journal of Neuropharmacology*, *6*(3), 223-IN10. https://doi.org/10.1016/0028-3908(67)90009-3

897. Brito-da-Costa, A. M., Dias-da-Silva, D., Gomes, N. G. M., Dinis-Oliveira, R. J., & Madureira-Carvalho, Á. (2020). Toxicokinetics and Toxicodynamics of Ayahuasca Alkaloids N,N-Dimethyltryptamine (DMT), Harmine, Harmaline and Tetrahydroharmine: Clinical and Forensic Impact. *Pharmaceuticals*, *13*(11), 334. https://doi.org/10.3390/ph13110334

Page 133. *For magic mushrooms and psilocybin*.

898. Levine, W. G. (1967). Formation of blue oxidation product from psilocybin. *Nature*, *215*(5107), 1292–1293. https://doi.org/10.1038/2151292a0

899. Lenz, C., Wick, J., Braga, D., García-Altares, M., Lackner, G., Hertweck, C., Gressler, M., & Hoffmeister, D. (2020). Injury-Triggered Blueing Reactions of *Psilocybe* “Magic” Mushrooms. *Angewandte Chemie International Edition*, *59*(4), 1450–1454. https://doi.org/10.1002/anie.201910175

900. Leopoldini, M., Marino, T., Russo, N., & Toscano, M. (2004). Antioxidant Properties of Phenolic Compounds: H-Atom versus Electron Transfer Mechanism. *The Journal of Physical Chemistry A*, *108*(22), 4916–4922. https://doi.org/10.1021/jp037247d

901. Barbehenn, R. v., & Peter Constabel, C. (2011). Tannins in plant–herbivore interactions. *Phytochemistry*, *72*(13), 1551–1565. https://doi.org/10.1016/j.phytochem.2011.01.040

Page 133 and 134. *Although this defense theory*.

902. Reynolds, H. T., Vijayakumar, V., Gluck-Thaler, E., Korotkin, H. B., Matheny, P. B., & Slot, J. C. (2018). Horizontal gene cluster transfer increased hallucinogenic mushroom diversity. *Evolution Letters*, *2*(2), 88–101. https://doi.org/10.1002/evl3.42

903. Meyer, M., & Slot, J. (2023). The evolution and ecology of psilocybin in nature. *Fungal Genetics and Biology*, *167*, 103812. https://doi.org/10.1016/j.fgb.2023.103812

904. Spiteller, P. (2008). Chemical Defence Strategies of Higher Fungi. *Chemistry - A European Journal*, *14*(30), 9100–9110. https://doi.org/10.1002/chem.200800292

905. Bunyard, B., & Foote, B. A. (1990). Biological notes on *Drosophila guttifera* (Diptera: Drosophilidae), a consumer of mushrooms. *Entomological News*, *101*(3), 161-163.

906. Boyce, G. R., Gluck-Thaler, E., Slot, J. C., Stajich, J. E., Davis, W. J., James, T. Y., Cooley, J. R., Panaccione, D. G., Eilenberg, J., de Fine Licht, H. H., Macias, A. M., Berger, M. C., Wickert, K. L., Stauder, C. M., Spahr, E. J., Maust, M. D., Metheny, A. M., Simon, C., Kritsky, G., … Kasson, M. T. (2019). Psychoactive plant- and mushroom-associated alkaloids from two behavior modifying cicada pathogens. *Fungal Ecology*, *41*, 147–164. https://doi.org/10.1016/j.funeco.2019.06.002

907. Lovett, B., Macias, A., Stajich, J. E., Cooley, J., Eilenberg, J., de Fine Licht, H. H., & Kasson, M. T. (2020). Behavioral betrayal: How select fungal parasites enlist living insects to do their bidding. *PLOS Pathogens*, *16*(6), e1008598. https://doi.org/10.1371/journal.ppat.1008598

Page 134. *Some scientists have proposed*.

908. Lev-Yadun, S., & Halpern, M. (2007). Ergot (*Claviceps purpurea*)-An aposematic fungus. *Symbiosis* 43: 105–108.

909. Wäli, P. P., Wäli, P. R., Saikkonen, K., & Tuomi, J. (2013). Is the Pathogenic Ergot Fungus a Conditional Defensive Mutualist for Its Host Grass? *PLoS ONE*, *8*(7), e69249. https://doi.org/10.1371/journal.pone.0069249

Page 134. *A similar question exists for mescaline*.

910. Lin, J., Yang, S., Ji, J., Xiang, P., Wu, L., & Chen, H. (2023). Natural or artificial: An example of topographic spatial distribution analysis of mescaline in cactus plants by matrix-assisted laser desorption/ionization mass spectrometry imaging. *Frontiers in Plant Science*, *14*. https://doi.org/10.3389/fpls.2023.1066595

911. Newbold, R., de Silva, S., & Terry, M. (2020). Correlation of mescaline concentrations in Lophophora williamsii (Cactaceae) with rib numbers and diameter of crown (U.S.A.). *Journal of the Botanical Research Institute of Texas*, *14*(1), 103–120. https://doi.org/10.17348/jbrit.v14.i1.901

912. Levin, D. A., & York, B. M. (1978). The toxicity of plant alkaloids: an Ecogeographic perspective. *Biochemical Systematics and Ecology*, *6*(1), 61–76. https://doi.org/10.1016/0305-1978(78)90026-1

913. Sogawa, K. (1971). Preliminary assay of antifeeding chemicals for the brown planthopper, *Nilaparvata lugens* (Stal)(Hemiptera: Delphacidae). *Applied entomology and zoology*, *6*(4), 215-218.

914. Corio, C., Soto, I. M., Carreira, V., Padró, J., Betti, M. I. L., & Hasson, E. (2013). An alkaloid fraction extracted from the cactus *Trichocereus terscheckii* affects fitness in the cactophilic fly *Drosophila buzzatii* (Diptera: Drosophilidae). *Biological Journal of the Linnean Society*, *109*(2), 342–353. https://doi.org/10.1111/bij.12036

915. Padró, J., Carreira, V., Corio, C., Hasson, E., & Soto, I. M. (2014). Host alkaloids differentially affect developmental stability and wing vein canalization in cactophilic *Drosophila buzzatii*. *Journal of Evolutionary Biology*, *27*(12), 2781–2797. https://doi.org/10.1111/jeb.12537

916. Soto, I. M., Carreira, V. P., Corio, C., Padró, J., Soto, E. M., & Hasson, E. (2014). Differences in Tolerance to Host Cactus Alkaloids in Drosophila koepferae and D. buzzatii. *PLoS ONE*, *9*(2), e88370. https://doi.org/10.1371/journal.pone.0088370

Page 134. *The visual hallucinations*.

917. Siegel, R. K., & Jarvik, M. E. (1980). DMT self-administration by monkeys in isolation. *Bulletin of the Psychonomic Society*, *16*(2), 117–120. https://doi.org/10.3758/BF03334456

918. Alex Boese. (2016, September 5). *Bravo Smokes — The Lettuce Cigarette*. Weird Universe.

https://www.weirduniverse.net/blog/comments/bravo_smokes_lettuce_cigarette

Page 135. *Even more astounding*.

919. Franzen, FR., & Gross, H. (1965). Tryptamine, N,N-Dimethyltryptamine, N,N-Dimethyl-5-hydroxytryptamine and 5-Methoxytryptamine in Human Blood and Urine. *Nature*, *206*(4988), 1052–1052. https://doi.org/10.1038/2061052a0

920. Barker, S. A., McIlhenny, E. H., & Strassman, R. (2012). A critical review of reports of endogenous psychedelic N, N-dimethyltryptamines in humans: 1955–2010. *Drug Testing and Analysis*, *4*(7–8), 617–635. https://doi.org/10.1002/dta.422

921. Kärkkäinen, J., Forsström, T., Tornaeus, J., Wähälä, K., Kiuru, P., Honkanen, A., Stenman, U. -H., Turpeinen, U., & Hesso, A. (2005). Potentially hallucinogenic 5-hydroxytryptamine receptor ligands bufotenine and dimethyltryptamine in blood and tissues. *Scandinavian Journal of Clinical and Laboratory Investigation*, *65*(3), 189–199. https://doi.org/10.1080/00365510510013604

922. Dean, J. G., Liu, T., Huff, S., Sheler, B., Barker, S. A., Strassman, R. J., Wang, M. M., & Borjigin, J. (2019). Biosynthesis and Extracellular Concentrations of N,N-dimethyltryptamine (DMT) in Mammalian Brain. *Scientific Reports*, *9*(1), 9333. https://doi.org/10.1038/s41598-019-45812-w

923. Dean, J. G., Liu, T., Huff, S., Sheler, B., Barker, S. A., Strassman, R. J., Wang, M. M., & Borjigin, J. (2019). Biosynthesis and Extracellular Concentrations of N,N-dimethyltryptamine (DMT) in Mammalian Brain. *Scientific Reports*, *9*(1), 9333. https://doi.org/10.1038/s41598-019-45812-w

Page 135. *However, natural and some synthetic*.

924. McClure-Begley, T. D., & Roth, B. L. (2022). The promises and perils of psychedelic pharmacology for psychiatry. *Nature Reviews Drug Discovery*, *21*(6), 463–473. https://doi.org/10.1038/s41573-022-00421-7

925. Marks, M., & Cohen, I. G. (2021). Psychedelic therapy: a roadmap for wider acceptance and utilization. *Nature Medicine*, *27*(10), 1669–1671. https://doi.org/10.1038/s41591-021-01530-3

926. Kwan, A. C., Olson, D. E., Preller, K. H., & Roth, B. L. (2022). The neural basis of psychedelic action. *Nature Neuroscience*, *25*(11), 1407–1419. https://doi.org/10.1038/s41593-022-01177-4

927. McGuire, A. L., Lynch, H. F., Grossman, L. A., & Cohen, I. G. (2023). Pressing regulatory challenges for psychedelic medicine. *Science*, *380*(6643), 347–350. https://doi.org/10.1126/science.adg1324

928. Pollan, M. (2019). *How to change your mind: What the new science of psychedelics teaches us about consciousness, dying, addiction, depression, and transcendence*. Penguin.

Page 136. *A small placebo-controlled trial using ayahuasca*.

929. Palhano-Fontes, F., Barreto, D., Onias, H., Andrade, K. C., Novaes, M. M., Pessoa, J. A., Mota-Rolim, S. A., Osório, F. L., Sanches, R., dos Santos, R. G., Tófoli, L. F., de Oliveira Silveira, G., Yonamine, M., Riba, J., Santos, F. R., Silva-Junior, A. A., Alchieri, J. C., Galvão-Coelho, N. L., Lobão-Soares, B., … Araújo, D. B. (2019). Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. *Psychological Medicine*, *49*(4), 655–663. https://doi.org/10.1017/S0033291718001356

Page 136. *LSD showed great promise*.

930. Krebs, T. S., & Johansen, P.-Ø. (2012). Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials. *Journal of Psychopharmacology*, *26*(7), 994–1002. https://doi.org/10.1177/0269881112439253

Page 136. *Up until 2022*.

931. Johnson, M. W., Garcia-Romeu, A., Cosimano, M. P., & Griffiths, R. R. (2014). Pilot study of the 5-HT $_{2A}$ R agonist psilocybin in the treatment of tobacco addiction. *Journal of Psychopharmacology*, *28*(11), 983–992. https://doi.org/10.1177/0269881114548296

932. Bogenschutz, M. P., Podrebarac, S. K., Duane, J. H., Amegadzie, S. S., Malone, T. C., Owens, L. T., Ross, S., & Mennenga, S. E. (2018). Clinical Interpretations of Patient Experience in a Trial of Psilocybin-Assisted Psychotherapy for Alcohol Use Disorder. *Frontiers in Pharmacology*, *9*. https://doi.org/10.3389/fphar.2018.00100

Page 137. *Then in September 2022*.

933. O'Donnell, K. C., Mennenga, S. E., Owens, L. T., Podrebarac, S. K., Baron, T., Rotrosen, J., Ross, S., Forcehimes, A. A., & Bogenschutz, M. P. (2022). Psilocybin for alcohol use disorder: Rationale and design considerations for a randomized controlled trial. *Contemporary Clinical Trials*, *123*, 106976. https://doi.org/10.1016/j.cct.2022.106976

934. Bogenschutz, M. P., Ross, S., Bhatt, S., Baron, T., Forcehimes, A. A., Laska, E., Mennenga, S. E., O'Donnell, K., Owens, L. T., Podrebarac, S., Rotrosen, J., Tonigan, J. S., & Worth, L. (2022). Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients With Alcohol Use Disorder. *JAMA Psychiatry*, *79*(10), 953. https://doi.org/10.1001/jamapsychiatry.2022.2096

Page 137. *Crucially, we now know.*

935. Tsai, G., & Coyle, J. T. (1998). The Role of Glutamatergic Neurotransmission in the Pathophysiology of Alcoholism. *Annual Review of Medicine*, *49*(1), 173–184. https://doi.org/10.1146/annurev.med.49.1.173

936. Moussawi, K., & Kalivas, P. W. (2010). Group II metabotropic glutamate receptors (mGlu2/3) in drug addiction. *European Journal of Pharmacology*, *639*(1–3), 115–122. https://doi.org/10.1016/j.ejphar.2010.01.030

937. Meinhardt, M. W., Hansson, A. C., Perreau-Lenz, S., Bauder-Wenz, C., Stählin, O., Heilig, M., Harper, C., Drescher, K. U., Spanagel, R., & Sommer, W. H. (2013). Rescue of Infralimbic mGluR $_2$ Deficit Restores Control Over Drug-Seeking Behavior in Alcohol Dependence. *The Journal of Neuroscience*, *33*(7), 2794–2806. https://doi.org/10.1523/JNEUROSCI.4062-12.2013

Page 138. *These glutamate receptors.*

938. Meinhardt, M. W., Pfarr, S., Fouquet, G., Rohleder, C., Meinhardt, M. L., Barroso-Flores, J., Hoffmann, R., Jeanblanc, J., Paul, E., Wagner, K., Hansson, A. C., Köhr, G., Meier, N., von Bohlen und Halbach, O., Bell, R. L., Endepols, H., Neumaier, B., Schönig, K., Bartsch, D., … Sommer, W. H. (2021). Psilocybin targets a common molecular mechanism for cognitive impairment and increased craving in alcoholism. *Science Advances*, *7*(47). https://doi.org/10.1126/sciadv.abh2399

939. Meinhardt, M. W., & Sommer, W. H. (2023). Schrooms against booze: Potential of mycotherapy for the treatment of AUD. *Neuropsychopharmacology*, *48*(1), 211–212. https://doi.org/10.1038/s41386-022-01446-7

940. González-Maeso, J., Ang, R. L., Yuen, T., Chan, P., Weisstaub, N. v., López-Giménez, J. F., Zhou, M., Okawa, Y., Callado, L. F., Milligan, G., Gingrich, J. A., Filizola, M., Meana, J. J., & Sealfon, S. C. (2008). Identification of a serotonin/glutamate receptor complex implicated in psychosis. *Nature*, *452*(7183), 93–97. https://doi.org/10.1038/nature06612

941. Benneyworth, M. A., Xiang, Z., Smith, R. L., Garcia, E. E., Conn, P. J., & Sanders-Bush, E. (2007). A Selective Positive Allosteric Modulator of Metabotropic Glutamate Receptor Subtype 2 Blocks a Hallucinogenic Drug Model of Psychosis. *Molecular Pharmacology*, *72*(2), 477–484. https://doi.org/10.1124/mol.107.035170

Page 138. *For some people*. Note that the association between psychedelic use and certain mental health disorders most recently was found to be weak. Note as well that there is one study proposing use of psychedelics to treat schizophrenia.

942. Huber, B. (n.d.). *What do we know about the risks of psychedelics?* Michael Pollan. Retrieved October 6, 2023, from https://michaelpollan.com/psychedelics-risk-today/

943. Smith, D. G. (2023, February 20). Psychedelics Are a Promising Therapy, but They Can Be Dangerous for Some. *The New York Times*.

944. Lebedev, A. v., Acar, K., Garzón, B., Almeida, R., Råback, J., Åberg, A., Martinsson, S., Olsson, A., Louzolo, A., Pärnamets, P., Lövden, M., Atlas, L., Ingvar, M., & Petrovic, P. (2021). Psychedelic drug use and schizotypy in young adults. *Scientific Reports*, *11*(1), 15058. https://doi.org/10.1038/s41598-021-94421-z

945. Morton, E., Sakai, K., Ashtari, A., Pleet, M., Michalak, E. E., & Woolley, J. (2023). Risks and benefits of psilocybin use in people with bipolar disorder: An international web-based survey on experiences of 'magic mushroom' consumption. *Journal of Psychopharmacology*, *37*(1), 49–60. https://doi.org/10.1177/02698811221131997

946. Bender, D., & Hellerstein, D. J. (2022). Assessing the risk–benefit profile of classical psychedelics: a clinical review of second-wave psychedelic research. *Psychopharmacology*, *239*(6), 1907–1932. https://doi.org/10.1007/s00213-021-06049-6

947. Yaden, D. B., Potash, J. B., & Griffiths, R. R. (2022). Preparing for the Bursting of the Psychedelic Hype Bubble. *JAMA Psychiatry*, *79*(10), 943. https://doi.org/10.1001/jamapsychiatry.2022.2546

948. Wolf, G., Singh, S., Blakolmer, K., Lerer, L., Lifschytz, T., Heresco-Levy, U., Lotan, A., & Lerer, B. (2023). Could psychedelic drugs have a role in the treatment of schizophrenia? Rationale and strategy for safe implementation. *Molecular Psychiatry*, *28*(1), 44–58. https://doi.org/10.1038/s41380-022-01832-z

Page 138. *As I've pointed out*.

949. Narby, J., & Pizuri, R. C. (2021). *Plant teachers: Ayahuasca, tobacco, and the pursuit of knowledge*. New World Library.

Chapter 7. Caffeine and Nicotine

Page 139. *At lower doses.*

950. Lieberman, H. R., Wurtman, R. J., Emde, G. G., Roberts, C., & Coviella, I. L. (1987). The effects of low doses of caffeine on human performance and mood. *Psychopharmacology*, *92*(3), 308–312. https://doi.org/10.1007/BF00210835

Page 139. *At higher doses*.

951. Daly, J. W., & Fredholm, B. B. (1998). Caffeine--an atypical drug of dependence. *Drug Alcohol Depend.*, *51*(1–2), 199–206. https://doi.org/10.1016/s0376-8716(98)00077-5

Page 139. *I made the switch*.

952. Tverdal, A., Selmer, R., Cohen, J. M., & Thelle, D. S. (2020). Coffee consumption and mortality from cardiovascular diseases and total mortality: Does the brewing method matter? *Eur. J. Prev. Cardiol.*, *27*(18), 1986–1993. https://doi.org/10.1177/2047487320914443

Page 139 and 140. *The increased mortality risk*.

953. Thelle, D. S. (1995). Coffee, tea and coronary heart disease. *Current Opinion in Lipidology*, *6*(1), 25–27. https://doi.org/10.1097/00041433-199502000-00006

954. van Dusseldorp, M., Katan, M. B., van Vliet, T., Demacker, P. N., & Stalenhoef, A. F. (1991). Cholesterol-raising factor from boiled coffee does not

pass a paper filter. *Arterioscler. Thromb.*, *11*(3), 586–593. https://doi.org/10.1161/01.atv.11.3.586

955. Weusten-Van der Wouw, M. P., Katan, M. B., Viani, R., Huggett, A. C., Liardon, R., Liardon, R., Lund-Larsen, P. G., Thelle, D. S., Ahola, I., & Aro, A. (1994). Identity of the cholesterol-raising factor from boiled coffee and its effects on liver function enzymes. *J. Lipid Res.*, *35*, 721–733. https://www.ncbi.nlm.nih.gov/pubmed/7911820

Page 140. *The offending terpenoids*.

956. Weusten-Van der Wouw, M. P., Katan, M. B., Viani, R., Huggett, A. C., Liardon, R., Liardon, R., Lund-Larsen, P. G., Thelle, D. S., Ahola, I., & Aro, A. (1994). Identity of the cholesterol-raising factor from boiled coffee and its effects on liver function enzymes. *J. Lipid Res.*, *35*, 721–733. https://www.ncbi.nlm.nih.gov/pubmed/7911820

957. Urgert, R., & Katan, M. B. (1997). The cholesterol-raising factor from coffee beans. *Annu. Rev. Nutr.*, *17*, 305–324. https://doi.org/10.1146/annurev.nutr.17.1.305

958. de Roos, B., van Tol, A., Urgert, R., Scheek, L. M., van Gent, T., Buytenhek, R., Princen, H. M., & Katan, M. B. (2000). Consumption of French-press coffee raises cholesteryl ester transfer protein activity levels before LDL cholesterol in normolipidaemic subjects. *J. Intern. Med.*, *248*(3), 211–216. https://doi.org/10.1046/j.1365-2796.2000.00728.x

Page 140. *The mechanism*.

959. Ricketts, M.-L., Boekschoten, M. v., Kreeft, A. J., Hooiveld, G. J. E. J., Moen, C. J. A., Müller, M., Frants, R. R., Kasanmoentalib, S., Post, S. M., Princen, H. M. G., Porter, J. G., Katan, M. B., Hofker, M. H., & Moore, D. D. (2007). The Cholesterol-Raising Factor from Coffee Beans, Cafestol, as an Agonist Ligand for the Farnesoid and Pregnane X Receptors. *Molecular Endocrinology*, *21*(7), 1603–1616. https://doi.org/10.1210/me.2007-0133

Page 140. *Scandinavian boiled coffee*.

960. Urgert, R., van der Weg, G., Kosmeijer-Schuil, T. G., van de Bovenkamp, P., Hovenier, R., & Katan, M. B. (1995). Levels of the Cholesterol-Elevating Diterpenes Cafestol and Kahweol in Various Coffee Brews. *Journal of Agricultural and Food Chemistry*, *43*(8), 2167–2172. https://doi.org/10.1021/jf00056a039

961. Gross, G., Jaccaud, E., & Huggett, A. C. (1997). Analysis of the content of the diterpenes cafestol and kahweol in coffee brews. *Food Chem. Toxicol.*, *35*(6), 547–554. https://doi.org/10.1016/s0278-6915(96)00123-8

962. Urgert, R., & Katan, M. B. (1997). The cholesterol-raising factor from coffee beans. *Annu. Rev. Nutr.*, *17*, 305–324. https://doi.org/10.1146/annurev.nutr.17.1.305

963. Ratnayake, W. M., Hollywood, R., O'Grady, E., & Stavric, B. (1993). Lipid content and composition of coffee brews prepared by different methods. *Food Chem. Toxicol.*, *31*(4), 263–269. https://doi.org/10.1016/0278-6915(93)90076-b

Page 140. *Instead of an absence of evidence*.

964. Urgert, R., van der Weg, G., Kosmeijer-Schuil, T. G., van de Bovenkamp, P., Hovenier, R., & Katan, M. B. (1995). Levels of the Cholesterol-Elevating Diterpenes Cafestol and Kahweol in Various Coffee Brews. *Journal of Agricultural and Food Chemistry*, *43*(8), 2167–2172. https://doi.org/10.1021/jf00056a039

Page 140. *However, there is a catch*.

965. Ratnayake, W. M., Hollywood, R., O'Grady, E., & Stavric, B. (1993). Lipid content and composition of coffee brews prepared by different methods. *Food Chem. Toxicol.*, *31*(4), 263–269. https://doi.org/10.1016/0278-6915(93)90076-b

Page 141. *Although speculative*.

966. Eulitz, M., Kölling-Speer, I., & Speer, K. (2009). Effect of the water feeding onto the brew and the filter cake using a household coffee maker. In *22nd International Conference on Coffee Science, ASIC 2008, Campinas, SP, Brazil, 14-19 September, 2008* (pp. 492-495). Association Scientifique Internationale du Café (ASIC).

Page 141. *I know what you are going*.

967. Albanese, D., di Matteo, M., Poiana, M., & Spagnamusso, S. (2009). Espresso coffee (EC) by POD: Study of thermal profile during extraction process and influence of water temperature on chemical–physical and sensorial properties. *Food Research International*, *42*(5–6), 727–732. https://doi.org/10.1016/j.foodres.2009.02.027

Page 142. *A UK study followed.*

968. Liu, D., Li, Z.-H., Shen, D., Zhang, P.-D., Song, W.-Q., Zhang, W.-T., Huang, Q.-M., Chen, P.-L., Zhang, X.-R., & Mao, C. (2022). Association of Sugar-Sweetened, Artificially Sweetened, and Unsweetened Coffee Consumption With All-Cause and Cause-Specific Mortality. *Annals of Internal Medicine*, *175*(7), 909–917. https://doi.org/10.7326/M21-2977

Page 142. *This study comports.*

969. Poole, R., Kennedy, O. J., Roderick, P., Fallowfield, J. A., Hayes, P. C., & Parkes, J. (2017). Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. *BMJ*, j5024. https://doi.org/10.1136/bmj.j5024

Page 142. *Finally, there was a big downside.*

970. Poole, R., Kennedy, O. J., Roderick, P., Fallowfield, J. A., Hayes, P. C., & Parkes, J. (2017). Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. *BMJ*, j5024. https://doi.org/10.1136/bmj.j5024

Page 142. *One explanation is that for most.*

971. Fukushima, Y., Ohie, T., Yonekawa, Y., Yonemoto, K., Aizawa, H., Mori, Y., Watanabe, M., Takeuchi, M., Hasegawa, M., Taguchi, C., & Kondo, K. (2009). Coffee and Green Tea As a Large Source of Antioxidant Polyphenols in the Japanese Population. *Journal of Agricultural and Food Chemistry*, *57*(4), 1253–1259. https://doi.org/10.1021/jf802418j

972. Król, K., Gantner, M., Tatarak, A., & Hallmann, E. (2020). The content of polyphenols in coffee beans as roasting, origin and storage effect. *European Food Research and Technology*, *246*(1), 33–39. https://doi.org/10.1007/s00217-019-03388-9

973. Ovaskainen, M.-L., Törrönen, R., Koponen, J. M., Sinkko, H., Hellström, J., Reinivuo, H., & Mattila, P. (2008). Dietary Intake and Major Food Sources of Polyphenols in Finnish Adults3. *The Journal of Nutrition*, *138*(3), 562–566. https://doi.org/10.1093/jn/138.3.562

974. Nardini, M., Cirillo, E., Natella, F., & Scaccini, C. (2002). Absorption of Phenolic Acids in Humans after Coffee Consumption. *Journal of Agricultural and Food Chemistry*, *50*(20), 5735–5741. https://doi.org/10.1021/jf0257547

Page 142. *The potential protective*.

975. Scalbert, A., Manach, C., Morand, C., Rémésy, C., & Jiménez, L. (2005). Dietary Polyphenols and the Prevention of Diseases. *Critical Reviews in Food Science and Nutrition*, *45*(4), 287–306. https://doi.org/10.1080/1040869059096

976. Freedman, N. D., Park, Y., Abnet, C. C., Hollenbeck, A. R., & Sinha, R. (2012). Association of Coffee Drinking with Total and Cause-Specific Mortality. *New England Journal of Medicine*, *366*(20), 1891–1904. https://doi.org/10.1056/NEJMoa1112010

977. Gunter, M. J., Murphy, N., Cross, A. J., Dossus, L., Dartois, L., Fagherazzi, G., Kaaks, R., Kühn, T., Boeing, H., Aleksandrova, K., Tjønneland, A., Olsen, A., Overvad, K., Larsen, S. C., Redondo Cornejo, M. L., Agudo, A., Sánchez Pérez, M. J., Altzibar, J. M., Navarro, C., … Riboli, E. (2017). Coffee Drinking and Mortality in 10 European Countries. *Annals of Internal Medicine*, *167*(4), 236–247. https://doi.org/10.7326/M16-2945

Page 143. Double-blind, placebo-controlled.

978. Scalbert, A., Manach, C., Morand, C., Rémésy, C., & Jiménez, L. (2005). Dietary Polyphenols and the Prevention of Diseases. *Critical Reviews in Food Science and Nutrition*, *45*(4), 287–306. https://doi.org/10.1080/1040869059096

979. Tajik, N., Tajik, M., Mack, I., & Enck, P. (2017). The potential effects of chlorogenic acid, the main phenolic components in coffee, on health: a comprehensive review of the literature. *European Journal of Nutrition*, *56*(7), 2215–2244. https://doi.org/10.1007/s00394-017-1379-1

980. Zhao, Y., Wang, J., Ballevre, O., Luo, H., & Zhang, W. (2012). Antihypertensive effects and mechanisms of chlorogenic acids. *Hypertension Research*, *35*(4), 370–374. https://doi.org/10.1038/hr.2011.195

Page 144. *Beyond the potential*.

981. Ross, G. W., Abbott, R. D., Petrovitch, H., Morens, D. M., Grandinetti, A., Tung, K. H., Tanner, C. M., Masaki, K. H., Blanchette, P. L., Curb, J. D., Popper, J. S., & White, L. R. (2000). Association of coffee and caffeine intake with the risk of

Parkinson disease. *JAMA*, *283*(20), 2674–2679. https://doi.org/10.1001/jama.283.20.2674

982. Costa, J., Lunet, N., Santos, C., Santos, J., & Vaz-Carneiro, A. (2010). Caffeine exposure and the risk of Parkinson's disease: a systematic review and meta-analysis of observational studiess. *J. Alzheimers. Dis.*, *20*(s1), S221–S238. https://content.iospress.com/articles/journal-of-alzheimers-disease/jad091525

Page 144. *Similarly, a large observational*.

983. Zhang, Y., Yang, H., Li, S., Li, W.-D., & Wang, Y. (2021). Consumption of coffee and tea and risk of developing stroke, dementia, and poststroke dementia: A cohort study in the UK Biobank. *PLoS Med.*, *18*(11), e1003830. https://doi.org/10.1371/journal.pmed.1003830

Page 144. *One candidate is a serotonin*.

984. Yan, R., Zhang, J., Park, H.-J., Park, E. S., Oh, S., Zheng, H., Junn, E., Voronkov, M., Stock, J. B., & Mouradian, M. M. (2018). Synergistic neuroprotection by coffee components eicosanoyl-5-hydroxytryptamide and caffeine in models of Parkinson's disease and DLB. *Proc. Natl. Acad. Sci. U. S. A.*, *115*(51), E12053–E12062. https://doi.org/10.1073/pnas.1813365115

Page 144. *The chemical can slow*.

985. Basurto-Islas, G., Blanchard, J., Tung, Y. C., Fernandez, J. R., Voronkov, M., Stock, M., Zhang, S., Stock, J. B., & Iqbal, K. (2014). Therapeutic benefits of a component of coffee in a rat model of Alzheimer's disease. *Neurobiol. Aging*, *35*(12), 2701–2712. https://doi.org/10.1016/j.neurobiolaging.2014.06.012

Page 144. *The two main species cultivated*.

986. Cheney, R. H. (1925). *Coffee: a monograph of the economic species of the genus Coffea L.* New York University Press.

987. Meyer, F. G. (1965). Notes on wild coffea arabica from southwestern ethiopia, with some historical considerations. *Economic Botany*, *19*(2), 136–151. https://doi.org/10.1007/BF02862825

988. Davis, A. P., Govaerts, R., Bridson, D. M., & Stoffelen, P. (2006). An annotated taxonomic conspectus of the genus Coffea (Rubiaceae). *Botanical*

Journal of the Linnean Society, *152*(4), 465–512. https://doi.org/10.1111/j.1095-8339.2006.00584.x

Page 144. *It was there that I*. Applies to quote that follows in next sentence as well.

989. Banesio, F. N. (1945). Discurso sôbre a salubérrima bebida chamada Cahue ou Café. *Revista do café português, vol. 7, nº27*, Lisboa. See https://digital.bbm.usp.br/bitstream/bbm/3911/1/022456_COMPLETO.pdf

Page 145. *We don't know for sure*. Citation referred to in the rest of the paragraph as well.

990. Clifford, M. N. (Ed.). (2012). *Coffee: botany, biochemistry and production of beans and beverage*. Springer Science & Business Media.

Page 145. *The root of the word*.

991. Kaye, A. S. (1986). The Etymology of "Coffee": The Dark Brew. *Journal of the American Oriental Society*, *106*(3), 557–558. https://doi.org/10.2307/602112

Page 145. *On October 7, 1984*.

992. CAFFEINE IS NATURAL INSECTICIDE, SCIENTIST SAYS. (1984, October 7). *The New York Times*, 36. https://www.nytimes.com/1984/10/07/us/caffeine-is-natural-insecticide-scientist-says.html

Page 145 and 146. *Nathanson discovered this by*. The rest of the paragraph and the next three paragraphs rely on this reference as well, including the quotations.

993. Nathanson, J. A. (1984). Caffeine and Related Methylxanthines: Possible Naturally Occurring Pesticides. *Science*, *226*(4671), 184–187. https://doi.org/10.1126/science.6207592

Page 146. *A similar effect was found*.

994. Hollingsworth, R. G., Armstrong, J. W., & Campbell, E. (2002). Caffeine as a repellent for slugs and snails. *Nature*, *417*(6892), 915–916. https://doi.org/10.1038/417915a

Page 146. *Biologists did just that*. In addition this reference also applies to the next paragraph.

995. Uefuji, H., Tatsumi, Y., Morimoto, M., Kaothien-Nakayama, P., Ogita, S., & Sano, H. (2005). Caffeine production in tobacco plants by simultaneous expression of three coffee N-methyltrasferases and its potential as a pest repellant. *Plant Mol. Biol.*, *59*(2), 221–227. https://doi.org/10.1007/s11103-005-8520-x

Page 147. *In naturally occurring caffeine-bearing*.

996. Huang, R., O'Donnell, A. J., Barboline, J. J., & Barkman, T. J. (2016). Convergent evolution of caffeine in plants by co-option of exapted ancestral enzymes. *Proceedings of the National Academy of Sciences*, *113*(38), 10613–10618. https://doi.org/10.1073/pnas.1602575113

Page 147. *Under this model*.

997. Kim, Y.-S., & Sano, H. (2008). Pathogen resistance of transgenic tobacco plants producing caffeine. *Phytochemistry*, *69*(4), 882–888. https://doi.org/10.1016/j.phytochem.2007.10.021

Page 147. *The most trouble-some*.

998. Damon, A. (2000). A review of the biology and control of the coffee berry borer, *Hypothenemus hampei* (Coleoptera: Scolytidae). *Bulletin of Entomological Research*, *90*(6), 453–465. https://doi.org/10.1017/S0007485300000584

Page 147. *The coffee berry borer*.

999. Cure, J. R., Rodríguez, D., Gutierrez, A. P., & Ponti, L. (2020). The coffee agroecosystem: bio-economic analysis of coffee berry borer control (Hypothenemus hampei). *Scientific Reports*, *10*(1), 12262. https://doi.org/10.1038/s41598-020-68989-x

Page 147. *The beetle itself*.

1000. Ceja-Navarro, J. A., Vega, F. E., Karaoz, U., Hao, Z., Jenkins, S., Lim, H. C., Kosina, P., Infante, F., Northen, T. R., & Brodie, E. L. (2015). Gut microbiota mediate caffeine detoxification in the primary insect pest of coffee. *Nature Communications*, *6*(1), 7618. https://doi.org/10.1038/ncomms8618

1001. Saarni, M. (2015). Coffee berry borer's gut microbes detoxify caffeine. *Earth and Environmental Sciences Area* https://eesa.lbl.gov/coffee-berry-borers-gut-microbes-detoxify-caffeine/

Page 147 and 148. *The amount of caffeine*. These references apply to the next two paragraphs as well.

1002. Cunningham, I. (2018). Tributes flow for Lachlan Foote, who touched the hearts of many. *Blue Mountains Gazette* https://www.bluemountainsgazette.com.au/story/5162424/tributes-flow-for-lachlan-foote-who-touched-the-hearts-of-many/?cs=1432

1003. Molloy, S. (2019). Man's freak caffeine death sparks plea. *news.com.au* https://www.news.com.au/lifestyle/health/health-problems/mans-freak-death-from-caffeine-toxicity-sparks-urgent-warning-from-his-devastated-family/news-story/9d96f2d0f7c1e13d7d0cdaa1f46795bd

1004. A Current Affair Staff. (2019).' He was cold': Heartbreaking loss prompts family's caffeine warning. *9News.* https://www.9news.com.au/national/caffeine-powder-death-blue-mountains-man-lachlan-foote-parents-speak-with-a-current-affair/f989db49-8788-48db-b411-cb07a4e39841

1005. Molloy, S. (2019). Caffeine powder victim's final hours. *news.com.au* https://www.news.com.au/lifestyle/health/health-problems/the-father-of-a-young-man-who-died-of-caffeine-toxicity-speaks-about-his-sons-final-hours/news-story/f6698b821c9228722c4c49efce3e2c67

1006. Australian Government Department of Health. (2019). Government acts to ban pure and highly concentrated caffeine products. Australian Government Department of Health https://www.health.gov.au/ministers/senator-the-hon-richard-colbeck/media/government-acts-to-ban-pure-and-highly-concentrated-caffeine-products

Page 148. *The dog ate*.

1007. Easton, D. (2015). Caffeine. *American College of Veterinary Pharmacists*. https://vetmeds.org/pet-poison-control-list/caffeine/

Page 149. *Caffeinated coffee was associated*.

1008. Grosso, G., Micek, A., Castellano, S., Pajak, A., & Galvano, F. (2016). Coffee, tea, caffeine and risk of depression: A systematic review and dose-response meta-analysis of observational studies. *Mol. Nutr. Food Res.*, *60*(1), 223–234. https://doi.org/10.1002/mnfr.201500620

1009. Lucas, M. (2011). Coffee, Caffeine, and Risk of Depression Among Women. *Archives of Internal Medicine*, *171*(17), 1571. https://doi.org/10.1001/archinternmed.2011.393

Page 149. *Drinking two or three cups*.

1010. Lucas, M., O'Reilly, E. J., Pan, A., Mirzaei, F., Willett, W. C., Okereke, O. I., & Ascherio, A. (2014). Coffee, caffeine, and risk of completed suicide: results from three prospective cohorts of American adults. *World J. Biol. Psychiatry*, *15*(5), 377–386. https://doi.org/10.3109/15622975.2013.795243

Page 149. *Although coffee has a reputation*.

1011. Kim, E., Hoffmann, T. J., Nah, G., Vittinghoff, E., Delling, F., & Marcus, G. M. (2021). Coffee Consumption and Incident Tachyarrhythmias. *JAMA Internal Medicine*, *181*(9), 1185. https://doi.org/10.1001/jamainternmed.2021.3616

1012. Chieng, D., Canovas, R., Segan, L., Sugumar, H., Voskoboinik, A., Prabhu, S., Ling, L.-H., Lee, G., Morton, J. B., Kaye, D. M., Kalman, J. M., & Kistler, P. M. (2022). The impact of coffee subtypes on incident cardiovascular disease, arrhythmias, and mortality: long-term outcomes from the UK Biobank. *European Journal of Preventive Cardiology*, *29*(17), 2240–2249. https://doi.org/10.1093/eurjpc/zwac189

Page 149. *However, a more recent study*.

1013. Marcus, G. M., Rosenthal, D. G., Nah, G., Vittinghoff, E., Fang, C., Ogomori, K., Joyce, S., Yilmaz, D., Yang, V., Kessedjian, T., Wilson, E., Yang, M., Chang, K., Wall, G., & Olgin, J. E. (2023). Acute Effects of Coffee Consumption on Health among Ambulatory Adults. *The New England Journal of Medicine*, *388*(12), 1092–1100. https://doi.org/10.1056/NEJMoa2204737

Page 149. *Caffeine poses clear downsides*.

1014. Winston, A. P., Hardwick, E., & Jaberi, N. (2005). Neuropsychiatric effects of caffeine. *Advances in Psychiatric Treatment*, *11*(6), 432–439. https://doi.org/10.1192/apt.11.6.432

1015. Nardi, A. E., Lopes, F. L., Valença, A. M., Freire, R. C., Veras, A. B., de-Melo-Neto, V. L., Nascimento, I., King, A. L., Mezzasalma, M. A., Soares-Filho, G. L., & Zin, W. A. (2007). Caffeine challenge test in panic disorder and depression with panic attacks. *Compr. Psychiatry*, *48*(3), 257–263. https://doi.org/10.1016/j.comppsych.2006.12.001

1016. Juliano, L. M., & Griffiths, R. R. (2004). A critical review of caffeine withdrawal: empirical validation of symptoms and signs, incidence, severity, and associated features. *Psychopharmacology*, *176*(1), 1–29. https://doi.org/10.1007/s00213-004-2000-x

Page 150. *In studies involving female twins.*

1017. Kendler, K. S., & Prescott, C. A. (1999). Caffeine intake, tolerance, and withdrawal in women: a population-based twin study. *Am. J. Psychiatry*, *156*(2), 223–228. https://doi.org/10.1176/ajp.156.2.223

1018. Yang, A., Palmer, A. A., & de Wit, H. (2010). Genetics of caffeine consumption and responses to caffeine. *Psychopharmacology*, *211*(3), 245–257. https://doi.org/10.1007/s00213-010-1900-1

Page 150. *Caffeine is perceived as bitter.*

1019. Cornelis, M. C., Tordoff, M. G., El-Sohemy, A., & van Dam, R. M. (2017). Recalled taste intensity, liking and habitual intake of commonly consumed foods. *Appetite*, *109*, 182–189. https://doi.org/10.1016/j.appet.2016.11.036

1020. Chandrashekar, J., Mueller, K. L., Hoon, M. A., Adler, E., Feng, L., Guo, W., Zuker, C. S., & Ryba, N. J. P. (2000). T2Rs Function as Bitter Taste Receptors. *Cell*, *100*(6), 703–711. https://doi.org/10.1016/S0092-8674(00)80706-0

1021. Chandrashekar, J., Hoon, M. A., Ryba, N. J. P., & Zuker, C. S. (2006). The receptors and cells for mammalian taste. *Nature*, *444*(7117), 288–294. https://doi.org/10.1038/nature05401

1022. Brockhoff, A., Behrens, M., Roudnitzky, N., Appendino, G., Avonto, C., & Meyerhof, W. (2011). Receptor agonism and antagonism of dietary bitter compounds. *J. Neurosci.*, *31*(41), 14775–14782. https://doi.org/10.1523/JNEUROSCI.2923-11.2011

Page 151. *Why the difference?*

1023. Bufe, B., Breslin, P. A. S., Kuhn, C., Reed, D. R., Tharp, C. D., Slack, J. P., Kim, U.-K., Drayna, D., & Meyerhof, W. (2005). The Molecular Basis of Individual Differences in Phenylthiocarbamide and Propylthiouracil Bitterness

Perception. *Current Biology*, *15*(4), 322–327. https://doi.org/10.1016/j.cub.2005.01.047

1024. Reed, D. R., Zhu, G., Breslin, P. A. S., Duke, F. F., Henders, A. K., Campbell, M. J., Montgomery, G. W., Medland, S. E., Martin, N. G., & Wright, M. J. (2010). The perception of quinine taste intensity is associated with common genetic variants in a bitter receptor cluster on chromosome 12. *Hum. Mol. Genet.*, *19*(21), 4278–4285. https://doi.org/10.1093/hmg/ddq324

1025. Ledda, M., Kutalik, Z., Souza Destito, M. C., Souza, M. M., Cirillo, C. A., Zamboni, A., Martin, N., Morya, E., Sameshima, K., Beckmann, J. S., le Coutre, J., Bergmann, S., & Genick, U. K. (2014). GWAS of human bitter taste perception identifies new loci and reveals additional complexity of bitter taste genetics. *Hum. Mol. Genet.*, *23*(1), 259–267. https://doi.org/10.1093/hmg/ddt404

1026. Knaapila, A., Hwang, L.-D., Lysenko, A., Duke, F. F., Fesi, B., Khoshnevisan, A., James, R. S., Wysocki, C. J., Rhyu, M., Tordoff, M. G., Bachmanov, A. A., Mura, E., Nagai, H., & Reed, D. R. (2012). Genetic analysis of chemosensory traits in human twins. *Chem. Senses*, *37*(9), 869–881. https://doi.org/10.1093/chemse/bjs070

1027. Hwang, L.-D., Breslin, P. A. S., Reed, D. R., Zhu, G., Martin, N. G., & Wright, M. J. (2016). Is the Association Between Sweet and Bitter Perception due to Genetic Variation? *Chemical Senses*, *41*(9), 737–744. https://doi.org/10.1093/chemse/bjw083

Page 151. *To figure out what is really going on*.

1028. Ong, J.-S., Hwang, L.-D., Zhong, V. W., An, J., Gharahkhani, P., Breslin, P. A. S., Wright, M. J., Lawlor, D. A., Whitfield, J., MacGregor, S., Martin, N. G., & Cornelis, M. C. (2018). Understanding the role of bitter taste perception in coffee, tea and alcohol consumption through Mendelian randomization. *Sci. Rep.*, *8*(1), 16414. https://doi.org/10.1038/s41598-018-34713-z

Page 151. *One of the ways*.

1029. Porkka-Heiskanen, T., Strecker, R. E., Thakkar, M., Bjørkum, A. A., Greene, R. W., & McCarley, R. W. (1997). Adenosine: A Mediator of the Sleep-Inducing Effects of Prolonged Wakefulness. *Science*. https://doi.org/10.1126/science.276.5316.1265

Page 151. *Caffeine is a molecular mimic*.

1030. Huang, Z.-L., Qu, W.-M., Eguchi, N., Chen, J.-F., Schwarzschild, M. A., Fredholm, B. B., Urade, Y., & Hayaishi, O. (2005). Adenosine A2A, but not A1, receptors mediate the arousal effect of caffeine. *Nature Neuroscience*, *8*(7), 858–859. https://doi.org/10.1038/nn1491

Page 151. *Some of us carry*.

1031. Cornelis, M. C., El-Sohemy, A., & Campos, H. (2007). Genetic polymorphism of the adenosine A2A receptor is associated with habitual caffeine consumption. *Am. J. Clin. Nutr.*, *86*(1), 240–244. https://doi.org/10.1093/ajcn/86.1.240

1032. Rétey, J. v, Adam, M., Khatami, R., Luhmann, U. F. O., Jung, H. H., Berger, W., & Landolt, H.-P. (2007). A genetic variation in the adenosine A2A receptor gene (ADORA2A) contributes to individual sensitivity to caffeine effects on sleep. *Clin. Pharmacol. Ther.*, *81*(5), 692–698. https://doi.org/10.1038/sj.clpt.6100102

1033. Rogers, P. J., Hohoff, C., Heatherley, S. v, Mullings, E. L., Maxfield, P. J., Evershed, R. P., Deckert, J., & Nutt, D. J. (2010). Association of the anxiogenic and alerting effects of caffeine with ADORA2A and ADORA1 polymorphisms and habitual level of caffeine consumption. *Neuropsychopharmacology*, *35*(9), 1973–1983. https://doi.org/10.1038/npp.2010.71

Page 151. *One of these adenosine*.

1034. Cornelis, M. C., & van Dam, R. M. (2021). Genetic determinants of liking and intake of coffee and other bitter foods and beverages. *Sci. Rep.*, *11*(1), 23845. https://doi.org/10.1038/s41598-021-03153-7

Page 152. *One CYP1A2 variant is*.

1035. Masi, C., Dinnella, C., Pirastu, N., Prescott, J., & Monteleone, E. (2016). Caffeine metabolism rate influences coffee perception, preferences and intake. *Food Qual. Prefer.*, *53*, 97–104. https://doi.org/10.1016/j.foodqual.2016.06.002

Page 152. *Even more intriguing*.

1036. Lipchock, S. v, Spielman, A. I., Mennella, J. A., Mansfield, C. J., Hwang, L.-D., Douglas, J. E., & Reed, D. R. (2017). Caffeine Bitterness is Related to Daily

Caffeine Intake and Bitter Receptor mRNA Abundance in Human Taste Tissue. *Perception*, *46*(3–4), 245–256. https://doi.org/10.1177/0301006616686098

Page 152 and 153. *Besides caffeine, dark chocolate*.

1037. di Tomaso, E., Beltramo, M., & Piomelli, D. (1996). Brain cannabinoids in chocolate. *Nature*, *382*(6593), 677–678. https://doi.org/10.1038/382677a0

1038. di Marzo, V., Sepe, N., de Petrocellis, L., Berger, A., Crozier, G., Fride, E., & Mechoulam, R. (1998). Trick or treat from food endocannabinoids? *Nature*, *396*(6712), 636–636. https://doi.org/10.1038/25267

1039. Gobbi, G., Bambico, F. R., Mangieri, R., Bortolato, M., Campolongo, P., Solinas, M., Cassano, T., Morgese, M. G., Debonnel, G., Duranti, A., Tontini, A., Tarzia, G., Mor, M., Trezza, V., Goldberg, S. R., Cuomo, V., & Piomelli, D. (2005). Antidepressant-like activity and modulation of brain monoaminergic transmission by blockade of anandamide hydrolysis. *Proceedings of the National Academy of Sciences*, *102*(51), 18620–18625. https://doi.org/10.1073/pnas.0509591102

Page 153. *In 2013, researchers discovered*.

1040. Wright, G. A., Baker, D. D., Palmer, M. J., Stabler, D., Mustard, J. A., Power, E. F., Borland, A. M., & Stevenson, P. C. (2013). Caffeine in floral nectar enhances a pollinator's memory of reward. *Science*, *339*(6124), 1202–1204. https://doi.org/10.1126/science.1228806

Page 154. *Neuroethologist Karl von Frisch*

1041. Karl von Frisch – Facts. *NobelPrize.org. Nobel Prize Outreach AB.* https://www.nobelprize.org/prizes/medicine/1973/frisch/facts/

1042. von Frisch, K., & Lindauer, M. (1956). The "Language" and Orientation of the Honey Bee. *Annual Review of Entomology*, *1*(1), 45–58. https://doi.org/10.1146/annurev.en.01.010156.000401

1043. Munz, T. (2016). *The dancing bees: Karl von Frisch and the discovery of the honeybee language*. University of Chicago Press.

Page 154. *As noted earlier*.

1044. Baker, H. G., & Baker, I. (1975). Studies of nectar-constitution and pollinator-plant coevolution. In *Coevolution of Animals and Plants* (pp. 100–140). University of Texas Press. https://doi.org/10.7560/710313-007

Page 154. *When researchers placed sugar*.

1045. Couvillon, M. J., al Toufailia, H., Butterfield, T. M., Schrell, F., Ratnieks, F. L. W., & Schürch, R. (2015). Caffeinated forage tricks honeybees into increasing foraging and recruitment behaviors. *Curr. Biol.*, *25*(21), 2815–2818. https://doi.org/10.1016/j.cub.2015.08.052

Page 155. *The first study on its use*.

1046. McIndoo, N. E. (1916). Effects of nicotine as an insecticide. *Journal of Agricultural Research*, *7*(3), 89.

Page 155. *So potent is its use*.

1047. McBride, J. S., Altman, D. G., Klein, M., & White, W. (1998). Green tobacco sickness. *Tobacco Control*, *7*(3), 294–298. https://doi.org/10.1136/tc.7.3.294

1048. Gehlbach, S. H., Williams, W. A., Perry, L. D., Freeman, J. I., Langone, J. J., Peta, L. V., & Van Vunakis, H. (1975). Nicotine absorption by workers harvesting green tobacco. *The Lancet*, *305*(7905), 478-480. https://doi.org/10.1016/S0140-6736(75)92829-9

Page 155. *More recently*.

1049. Crall, J. D., Switzer, C. M., Oppenheimer, R. L., Ford Versypt, A. N., Dey, B., Brown, A., Eyster, M., Guérin, C., Pierce, N. E., Combes, S. A., & de Bivort, B. L. (2018). Neonicotinoid exposure disrupts bumblebee nest behavior, social networks, and thermoregulation. *Science*, *362*(6415), 683–686. https://doi.org/10.1126/science.aat1598

1050. Tsvetkov, N., Samson-Robert, O., Sood, K., Patel, H. S., Malena, D. A., Gajiwala, P. H., Maciukiewicz, P., Fournier, V., & Zayed, A. (2017). Chronic exposure to neonicotinoids reduces honey bee health near corn crops. *Science*, *356*(6345), 1395–1397. https://doi.org/10.1126/science.aam7470

1051. Schulz, R., Bub, S., Petschick, L. L., Stehle, S., & Wolfram, J. (2021). Applied pesticide toxicity shifts toward plants and invertebrates, even in GM crops. *Science*, *372*(6537), 81–84. https://doi.org/10.1126/science.abe1148

1052. Yamamuro, M., Komuro, T., Kamiya, H., Kato, T., Hasegawa, H., & Kameda, Y. (2019). Neonicotinoids disrupt aquatic food webs and decrease fishery yields. *Science*, *366*(6465), 620–623. https://doi.org/10.1126/science.aax3442

Page 156. *Among the most familiar*.

1053. Yamamoto, R. T., & Fraenkel, G. S. (1960). The Specificity of the Tobacco Hornworm, *Protoparce sexta*, to Solanaceous Plants. *Annals of the Entomological Society of America*, *53*(4), 503–507. https://doi.org/10.1093/aesa/53.4.503

1054. Baldwin, I. T. (2001). An Ecologically Motivated Analysis of Plant-Herbivore Interactions in Native Tobacco. *Plant Physiology*, *127*(4), 1449–1458. https://doi.org/10.1104/pp.010762

1055. Mechaber, W. L., & Hildebrand, J. G. (2000). Novel, Non-Solanaceous Hostplant Record for *Manduca sexta* (Lepidoptera: Sphingidae) in the Southwestern United States. *Annals of the Entomological Society of America*, *93*(3), 447–451. https://doi.org/10.1603/0013-8746(2000)093[0447:NNSHRF]2.0.CO;2

Page 156. *Not only has the tobacco*.

1056. Kumar, P., Pandit, S. S., Steppuhn, A., & Baldwin, I. T. (2014). Natural history-driven, plant-mediated RNAi-based study reveals *CYP6B46*'s role in a nicotine-mediated antipredator herbivore defense. *Proceedings of the National Academy of Sciences*, *111*(4), 1245–1252. https://doi.org/10.1073/pnas.1314848111

Page 156. *If this weren't enough*.

1057. Thurston, R., & Fox, P. M. (1972). Inhibition by Nicotine of Emergence of Apanteles congregatus1 from Its Host, the Tobacco Hornworm2.3. *Annals of the Entomological Society of America*, *65*(3), 547–550. https://doi.org/10.1093/aesa/65.3.547

1058. Barbosa, P., Saunders, J. A., Kemper, J., Trumbule, R., Olechno, J., & Martinat, P. (1986). Plant allelochemicals and insect parasitoids effects of nicotine onCotesia congregata (say) (Hymenoptera: Braconidae) andHyposoter annulipes

(Cresson) (Hymenoptera: Ichneumonidae). *Journal of Chemical Ecology*, *12*(6), 1319–1328. https://doi.org/10.1007/BF01012351

1059. Barbosa, P., Gross, P., & Kemper, J. (1991). Influence of Plant Allelochemicals on the Tobacco Hornworm and its Parasitoid, Cotesia Congregata. *Ecology*, *72*(5), 1567–1575. https://doi.org/10.2307/1940956

1060. Garvey, M., Bredlau, J., Kester, K., Creighton, C., & Kaplan, I. (2021). Toxin or medication? Immunotherapeutic effects of nicotine on a specialist caterpillar. *Functional Ecology*, *35*(3), 614–626. https://doi.org/10.1111/1365-2435.13743

Page 156. *Human evidence of tobacco.*

1061. Duke, D., Wohlgemuth, E., Adams, K. R., Armstrong-Ingram, A., Rice, S. K., & Young, D. C. (2021). Earliest evidence for human use of tobacco in the Pleistocene Americas. *Nature Human Behaviour*, *6*(2), 183–192. https://doi.org/10.1038/s41562-021-01202-9

Page 156. *Previously, the oldest evidence.*

1062. Carmody, S., Davis, J., Tadi, S., Sharp, J. S., Hunt, R. K., & Russ, J. (2018). Evidence of tobacco from a Late Archaic smoking tube recovered from the Flint River site in southeastern North America. *Journal of Archaeological Science: Reports*, *21*, 904–910. https://doi.org/10.1016/j.jasrep.2018.05.013

Page 156. *Tartar from both.*

1063. Eerkens, J. W., Tushingham, S., Brownstein, K. J., Garibay, R., Perez, K., Murga, E., Kaijankoski, P., Rosenthal, J. S., & Gang, D. R. (2018). Dental calculus as a source of ancient alkaloids: Detection of nicotine by LC-MS in calculus samples from the Americas. *Journal of Archaeological Science: Reports*, *18*, 509–515. https://doi.org/10.1016/j.jasrep.2018.02.004

Page 156 and 157. *The hair of a baby.*

1064. Niemeyer, H. M., de Souza, P., Camilo, C., & Echeverría, J. (2018). Chemical evidence of prehistoric passive tobacco consumption by a human perinate (early Formative Period, South-Central Andes). *Journal of Archaeological Science*, *100*, 130–138. https://doi.org/10.1016/j.jas.2018.10.010

Page 157 and 158. *Independently, tobacco in the form of pituri*. The next three paragraphs are based on the references below.

1065. Langley, J. N., & Dickinson, W. L. (1890). Pituri and Nicotin. *The Journal of Physiology*, *11*(4–5), 265–306. https://doi.org/10.1113/jphysiol.1890.sp000332

1066. Johnston, T. H., & Cleland, J. B. (1933). The History of the Aboriginal Narcotic, Pituri. *Oceania*, *4*(2), 201–223. http://www.jstor.org/stable/40327460

1067. Watson, P. L., Luanratana, O., & Griffin, W. J. (1983). The ethnopharmacology of pituri. *Journal of Ethnopharmacology*, *8*(3), 303–311. https://doi.org/10.1016/0378-8741(83)90067-3

1068. Ratsch, A., Steadman, K. J., & Bogossian, F. (2010). The pituri story: a review of the historical literature surrounding traditional Australian Aboriginal use of nicotine in Central Australia. *Journal of Ethnobiology and Ethnomedicine*, *6*(1), 26. https://doi.org/10.1186/1746-4269-6-26

1069. Keogh, L. (2011). Duboisia Pituri: A Natural History. *Historical Records of Australian Science*, *22*(2), 199. https://doi.org/10.1071/HR11008

1070. Moghbel, N., Ryu, B., Ratsch, A., & Steadman, K. J. (2017). Nicotine alkaloid levels, and nicotine to nornicotine conversion, in Australian Nicotiana species used as chewing tobacco. *Heliyon*, *3*(11), e00469. https://doi.org/10.1016/j.heliyon.2017.e00469

Page 158. *There is even*. The quote by Spencer and Gillen is mentioned by Ratsch et al.

1071. Ratsch, A., Steadman, K. J., & Bogossian, F. (2010). The pituri story: a review of the historical literature surrounding traditional Australian Aboriginal use of nicotine in Central Australia. *Journal of Ethnobiology and Ethnomedicine*, *6*(1), 26. https://doi.org/10.1186/1746-4269-6-26

1072. Spencer, B., & Gillen, F. J. (1898). *The native tribes of Central Australia*. Macmillan and Company, limited.

Page 158. *In the United States*.

1073. National Institute on Drug Abuse. (2022). Overdose death rates. National Institute on Drug Abuse. https://nida.nih.gov/drug-topics/trends-statistics/overdose-death-rates

Page 158 and 159. *Although alcohol is typically*.

1074. CDC. (2021). Deaths from excessive alcohol use in the United States. Centers for Disease Control and Prevention https://www.cdc.gov/alcohol/features/excessive-alcohol-deaths.html

Page 159. *However, these numbers pale*.

1075. CDCTobaccoFree. (2021). Fast facts and fact sheets. Centers for Disease Control and Prevention https://www.cdc.gov/tobacco/data_statistics/fact_sheets/index.htm

Page 159. *Zooming out*. This reference supports the next paragraph as well.

1076. Reitsma, M. B., Kendrick, P. J., Ababneh, E., Abbafati, C., Abbasi-Kangevari, M., Abdoli, A., Abedi, A., Abhilash, E. S., Abila, D. B., Aboyans, V., Abu-Rmeileh, N. M. E., Adebayo, O. M., Advani, S. M., Aghaali, M., Ahinkorah, B. O., Ahmad, S., Ahmadi, K., Ahmed, H., Aji, B., … Gakidou, E. (2021). Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990–2019: a systematic analysis from the Global Burden of Disease Study 2019. *Lancet*, *397*(10292), 2337–2360. https://doi.org/10.1016/S0140-6736(21)01169-7

Page 160. *I smoked just one a day*.

1077. Obama, B. (2020). *A promised land*. Crown, Penguin Random House.

Page 160. *Once the coughing subsided*.

1078. Pomerleau, C. S., & Pomerleau, O. F. (1992). Euphoriant effects of nicotine in smokers. *Psychopharmacology*, *108*(4), 460–465. https://doi.org/10.1007/BF02247422

Page 160. *Of course, I knew*.

1079. Hackshaw, A., Morris, J. K., Boniface, S., Tang, J.-L., & Milenković, D. (2018). Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. *BMJ*, j5855. https://doi.org/10.1136/bmj.j5855

1080. Moylan, S., Jacka, F. N., Pasco, J. A., & Berk, M. (2013). How cigarette smoking may increase the risk of anxiety symptoms and anxiety disorders: a critical review of biological pathways. *Brain and Behavior*, *3*(3), 302–326. https://doi.org/10.1002/brb3.137

Page 160. *A major difference*.

1081. Csordas, A., & Bernhard, D. (2013). The biology behind the atherothrombotic effects of cigarette smoke. *Nature Reviews Cardiology*, *10*(4), 219–230. https://doi.org/10.1038/nrcardio.2013.8

Page 160. *Does this mean nicotine*.

1082. Glantz, S. A., & Bareham, D. W. (2018). E-Cigarettes: Use, Effects on Smoking, Risks, and Policy Implications. *Annu. Rev. Public Health*, *39*, 215–235. https://doi.org/10.1146/annurev-publhealth-040617-013757

Page 161. *The evidence that does exist*.

1083. Benowitz, N. L., & Burbank, A. D. (2016). Cardiovascular toxicity of nicotine: Implications for electronic cigarette use. *Trends Cardiovasc. Med.*, *26*(6), 515–523. https://doi.org/10.1016/j.tcm.2016.03.001

1084. Lee, H.-W., Park, S.-H., Weng, M.-W., Wang, H.-T., Huang, W. C., Lepor, H., Wu, X.-R., Chen, L.-C., & Tang, M.-S. (2018). E-cigarette smoke damages DNA and reduces repair activity in mouse lung, heart, and bladder as well as in human lung and bladder cells. *Proc. Natl. Acad. Sci. U. S. A.*, *115*(7), E1560–E1569. https://doi.org/10.1073/pnas.1718185115

Page 161. *E-cigarette use*.

1085. Xie, W., Kathuria, H., Galiatsatos, P., Blaha, M. J., Hamburg, N. M., Robertson, R. M., Bhatnagar, A., Benjamin, E. J., & Stokes, A. C. (2020). Association of Electronic Cigarette Use With Incident Respiratory Conditions Among US Adults From 2013 to 2018. *JAMA Netw Open*, *3*(11), e2020816. https://doi.org/10.1001/jamanetworkopen.2020.20816

1086. Young, R. P., & Scott, R. J. (2020). Inhaled nicotine and lung cancer: Potential role of the nicotinic acetylcholine receptor. *Proc. Natl. Acad. Sci. U. S. A.*, *117*(9), 4460–4461. https://doi.org/10.1073/pnas.1921567117

1087. Garcia-Arcos, I., Geraghty, P., Baumlin, N., Campos, M., Dabo, A. J., Jundi, B., Cummins, N., Eden, E., Grosche, A., Salathe, M., & Foronjy, R. (2016). Chronic electronic cigarette exposure in mice induces features of COPD in a nicotine-dependent manner. *Thorax*, *71*(12), 1119–1129. https://doi.org/10.1136/thoraxjnl-2015-208039

Page 161. *The longer-term effects*.

1088. National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Population Health and Public Health Practice, and Committee on the Review of the Health Effects of Electronic Nicotine Delivery Systems. (2018). *Public Health Consequences of E-Cigarettes*. National Academies Press.

1089. CDC's Office on Smoking, and Health. (2021). Smoking and Tobacco Use; Electronic Cigarettes. From: https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html

Page 162. *We know little*.

1090. Grando, S. A. (2014). Connections of nicotine to cancer. *Nat. Rev. Cancer*, *14*(6), 419–429. https://doi.org/10.1038/nrc3725

Page 162. *One of the more*. This reference supports the next paragraph as well.

1091. Tang, M.-S., Wu, X.-R., Lee, H.-W., Xia, Y., Deng, F.-M., Moreira, A. L., Chen, L.-C., Huang, W. C., & Lepor, H. (2019). Electronic-cigarette smoke induces lung adenocarcinoma and bladder urothelial hyperplasia in mice. *Proc. Natl. Acad. Sci. U. S. A.*, *116*(43), 21727–21731. https://doi.org/10.1073/pnas.1911321116

Page 162. *Mutations in the DNA*.

1092. Gerstung, M., Jolly, C., Leshchiner, I., Dentro, S. C., Gonzalez, S., Rosebrock, D., Mitchell, T. J., Rubanova, Y., Anur, P., Yu, K., Tarabichi, M., Deshwar, A., Wintersinger, J., Kleinheinz, K., Vázquez-García, I., Haase, K., Jerman, L., Sengupta, S., Macintyre, G., … Consortium, P. (2020). The evolutionary history of 2,658 cancers. *Nature*, *578*(7793), 122–128. https://doi.org/10.1038/s41586-019-1907-7

1093. Lee, H.-W., Park, S.-H., Weng, M.-W., Wang, H.-T., Huang, W. C., Lepor, H., Wu, X.-R., Chen, L.-C., & Tang, M.-S. (2018). E-cigarette smoke damages DNA and reduces repair activity in mouse lung, heart, and bladder as well as in human lung and bladder cells. *Proc. Natl. Acad. Sci. U. S. A.*, *115*(7), E1560–E1569. https://doi.org/10.1073/pnas.1718185115

1094. Shahab, L., Goniewicz, M. L., Blount, B. C., Brown, J., McNeill, A., Alwis, K. U., Feng, J., Wang, L., & West, R. (2017). Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users: A Cross-sectional Study. *Ann. Intern. Med.*, *166*(6), 390–400. https://doi.org/10.7326/M16-1107

Page 162. *Because other studies.*

1095. Haussmann, H.-J., & Fariss, M. W. (2016). Comprehensive review of epidemiological and animal studies on the potential carcinogenic effects of nicotine per se. *Crit. Rev. Toxicol.*, *46*(8), 701–734. https://doi.org/10.1080/10408444.2016.1182116

Page 162. *Despite the negatives.*

1096. Godwin-Austen, R. B., Lee, P. N., Marmot, M. G., & Stern, G. M. (1982). Smoking and Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *45*(7), 577–581. https://doi.org/10.1136/jnnp.45.7.577

1097. Quik, M., & Jeyarasasingam, G. (2000). Nicotinic receptors and Parkinson's disease. *European Journal of Pharmacology*, *393*(1–3), 223–230. https://doi.org/10.1016/S0014-2999(99)00888-2

1098. Li, X., Li, W., Liu, G., Shen, X., & Tang, Y. (2015). Association between cigarette smoking and Parkinson's disease: A meta-analysis. *Archives of Gerontology and Geriatrics*, *61*(3), 510–516. https://doi.org/10.1016/j.archger.2015.08.004

1099. Mappin-Kasirer, B., Pan, H., Lewington, S., Kizza, J., Gray, R., Clarke, R., & Peto, R. (2020). Tobacco smoking and the risk of Parkinson disease. *Neurology*, *94*(20), e2132–e2138. https://doi.org/10.1212/WNL.0000000000009437

PAGE 162 AND 163. *A small clinical study.*

1100. Oertel, W. H., Müller, H.-H., Unger, M. M., Schade-Brittinger, C., Balthasar, K., Articus, K., Brinkman, M., Venuto, C. S., Tracik, F., Eberling, J., Eggert, K. M., Kamp, C., Kieburtz, K., & Boyd, J. T. (2023). Transdermal Nicotine Treatment and Progression of Early Parkinson's Disease. *NEJM Evidence*, *2*(9). https://doi.org/10.1056/EVIDoa2200311

Page 163. *Remarkably, increased consumption*.

1101. Nielsen, S. S., Franklin, G. M., Longstreth, W. T., Swanson, P. D., & Checkoway, H. (2013). Nicotine from edible *Solanaceae* and risk of Parkinson disease. *Annals of Neurology*, *74*(3), 472–477. https://doi.org/10.1002/ana.23884

1102. Domino, E. F., Hornbach, E., & Demana, T. (1993). The Nicotine Content of Common Vegetables. *New England Journal of Medicine*, *329*(6), 437–437. https://doi.org/10.1056/NEJM199308053290619

Page 163. *It isn't just the human*.

1103. Baracchi, D., Marples, A., Jenkins, A. J., Leitch, A. R., & Chittka, L. (2017). Nicotine in floral nectar pharmacologically influences bumblebee learning of floral features. *Scientific Reports*, *7*(1), 1951. https://doi.org/10.1038/s41598-017-01980-1

Page 163. *Significantly, some of these genetic variants*.

1104. Amos, C. I., Wu, X., Broderick, P., Gorlov, I. P., Gu, J., Eisen, T., Dong, Q., Zhang, Q., Gu, X., Vijayakrishnan, J., Sullivan, K., Matakidou, A., Wang, Y., Mills, G., Doheny, K., Tsai, Y.-Y., Chen, W. V., Shete, S., Spitz, M. R., & Houlston, R. S. (2008). Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. *Nature Genetics*, *40*(5), 616–622. https://doi.org/10.1038/ng.109

Page 163. *This study was repeated in Denmark*.

1105. Kaur-Knudsen, D., Bojesen, S. E., Tybjærg-Hansen, A., & Nordestgaard, B. G. (2011). Nicotinic Acetylcholine Receptor Polymorphism, Smoking Behavior, and Tobacco-Related Cancer and Lung and Cardiovascular Diseases: A Cohort Study. *Journal of Clinical Oncology*, *29*(21), 2875–2882. https://doi.org/10.1200/JCO.2010.32.9870

Page 163. *The mutation in the rarer*.

1106. Bierut, L. J., Stitzel, J. A., Wang, J. C., Hinrichs, A. L., Grucza, R. A., Xuei, X., Saccone, N. L., Saccone, S. F., Bertelsen, S., Fox, L., Horton, W. J., Breslau, N., Budde, J., Cloninger, C. R., Dick, D. M., Foroud, T., Hatsukami, D., Hesselbrock, V., Johnson, E. O., … Goate, A. M. (2008). Variants in nicotinic receptors and risk for nicotine dependence. *Am. J. Psychiatry*, *165*(9), 1163–1171. https://doi.org/10.1176/appi.ajp.2008.07111711

Page 163. *A study of thousands*. These references supports the next paragraph as well.

1107. Loukola, A., Buchwald, J., Gupta, R., Palviainen, T., Hällfors, J., Tikkanen, E., Korhonen, T., Ollikainen, M., Sarin, A.-P., Ripatti, S., Lehtimäki, T., Raitakari, O., Salomaa, V., Rose, R. J., Tyndale, R. F., & Kaprio, J. (2015). A Genome-Wide Association Study of a Biomarker of Nicotine Metabolism. *PLOS Genetics*, *11*(9), e1005498. https://doi.org/10.1371/journal.pgen.1005498

1108. Sofuoglu, M., Herman, A. I., Nadim, H., & Jatlow, P. (2012). Rapid nicotine clearance is associated with greater reward and heart rate increases from intravenous nicotine. *Neuropsychopharmacology*, *37*(6), 1509–1516. https://doi.org/10.1038/npp.2011.336

Page 164. *Fast nicotine metabolizers*. This reference applies to the next paragraph as well.

1109. Lerman, C., Schnoll, R. A., Hawk Jr, L. W., Cinciripini, P., George, T. P., Wileyto, E. P., Swan, G. E., Benowitz, N. L., Heitjan, D. F., Tyndale, R. F., & Group, P.-P. R. (2015). Use of the nicotine metabolite ratio as a genetically informed biomarker of response to nicotine patch or varenicline for smoking cessation: a randomised, double-blind placebo-controlled trial. *Lancet Respir Med*, *3*(2), 131–138. https://doi.org/10.1016/S2213-2600(14)70294-2

Chapter 8. Devil's Breath and Silent Death

Page 166. Quote from William Shakespeare's *Antony and Cleopatra*, Act 1. Scene 5.

1110. Folger Shakespeare Library. (n.d.) *Shakespeare's Plays, Sonnets and Poems from The Folger Shakespeare*. Retrieved from https://folger.edu/explore/shakespeares-works/all-works.

Page 166 and 167. *We've all been there*.

1111. Bockmann, T., Sanches, M. (2022). Love Addiction. In: Pontes, H.M. (eds) *Behavioral Addictions. Studies in Neuroscience, Psychology and Behavioral Economics.* Springer, Cham. https://doi.org/10.1007/978-3-031-04772-5_6

1112. Fisher, H. (2005). *Why we love: The nature and chemistry of romantic love.* Macmillan.

Page 167. *In medieval Europe*.

1113. Dafni, A., Blanché, C., Khatib, S. A., Petanidou, T., Aytaç, B., Pacini, E., Kohazurova, E., Geva-Kleinberger, A., Shahvar, S., Dajic, Z., Klug, H. W., & Benítez, G. (2021). In search of traces of the mandrake myth: the historical, and ethnobotanical roots of its vernacular names. *Journal of Ethnobiology and Ethnomedicine*, *17*(1), 68. https://doi.org/10.1186/s13002-021-00494-5

1114. Chidiac, E. J., Kaddoum, R. N., & Fuleihan, S. F. (2012). Mandragora: anesthetic of the ancients. *Anesthesia & Analgesia*, *115*(6), 1437–1441. https://doi.org/10.1213/ANE.0b013e318259ee4d

1115. Fatur, K. (2020). “Hexing Herbs” in Ethnobotanical Perspective: A Historical Review of the Uses of Anticholinergic Solanaceae Plants in Europe. *Economic Botany*, *74*(2), 140–158. https://doi.org/10.1007/s12231-020-09498-w

Page 167. *Scopolamine produces*. Quote from reference below.

1116. Geis, G. (1959). In scopolamine veritas. *J. Crim. L. & Criminology*, *50*, 347. https://scholarlycommons.law.northwestern.edu/jclc/vol50/iss4/4

Page 168. *The alkaloid is one of the most potent*.

1117. Logan, J. C. (1905). The Use of Scopolamine in Anæsthesia. *The American Journal of Nursing*, *6*(3), 166. https://doi.org/10.2307/3403145

1118. Soban, D., Ruprecht, J., Keys, T. E., & Schneck, H. J. (1989). [The history of scopolamine--with special reference to its use in anesthesia]. *Anaesthesiologie Und Reanimation*, *14*(1), 43–54.

1119. Scholtz, S., MacMorris, L., Krogmann, F., & Auffarth, G. U. (2019). Poisons, Drugs and Medicine: On the Use of Atropine and Scopolamine in Medicine and Ophthalmology: An Historical Review of their Applications. (2019). *Journal of Eye Study and Treatment*, *2019*(01). https://doi.org/10.33513/JEST/1901-13

1120. Duffy, R. (2007, July 22). *Colombian Devil’s Breath*. Vice. https://www.vice.com/en/article/kw3kam/colombian-devil-s-breath-1-of-2

1121. Ullrich, S. F., Hagels, H., & Kayser, O. (2017). Scopolamine: a journey from the field to clinics. *Phytochemistry Reviews*, *16*(2), 333–353. https://doi.org/10.1007/s11101-016-9477-x

1122. World Health Organization. (2021). World Health Organization model list of essential medicines: 22nd list (2021). World Health Organization. https://iris.who.int/handle/10665/345533

Page 167. *Scopolamine is an anticolinergic drug*.

1123. Spinks, A., & Wasiak, J. (2011). Scopolamine (hyoscine) for preventing and treating motion sickness. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD002851.pub4

Page 167. *People around the world*.

1124. Benítez, G., March-Salas, M., Villa-Kamel, A., Cháves-Jiménez, U., Hernández, J., Montes-Osuna, N., Moreno-Chocano, J., & Cariñanos, P. (2018). The genus Datura L. (Solanaceae) in Mexico and Spain – Ethnobotanical perspective at the interface of medical and illicit uses. *Journal of Ethnopharmacology*, *219*, 133–151. https://doi.org/10.1016/j.jep.2018.03.007

1125. Griffin, W. J., & Lin, G. D. (2000). Chemotaxonomy and geographical distribution of tropane alkaloids. *Phytochemistry*, *53*(6), 623–637. https://doi.org/10.1016/S0031-9422(99)00475-6

1126. Bussmann, R. W., & Sharon, D. (2006). Traditional medicinal plant use in Northern Peru: tracking two thousand years of healing culture. *Journal of Ethnobiology and Ethnomedicine*, *2*(1), 47. https://doi.org/10.1186/1746-4269-2-47

1127. Bennett, B. C. (1992). Hallucinogenic Plants of the Shuar and Related Indigenous Groups in Amazonian Ecuador and Peru. *Brittonia*, *44*(4), 483. https://doi.org/10.2307/2807199

1128. Schultes, R. E., & Plowman, T. (1979). The ethnobotany of Brugmansia. *Journal of Ethnopharmacology*, *1*(2), 147–164. https://doi.org/10.1016/0378-8741(79)90004-7

1129. Litzinger, W. J. (1981). Ceramic evidence for prehistoric datura use in North America. *Journal of Ethnopharmacology*, *4*(1), 57–74. https://doi.org/10.1016/0378-8741(81)90020-9

Page 167. *Georgia O'Keefe's paintings*.

1130. O'Keefe, G. (1932). *Jimson Weed/White Flower No. 1*. https://www.sothebys.com/en/auctions/ecatalogue/2014/american-art-n09229/lot.11.html

Page 168. *Another important source*.

1131. Evans, W. C., & Than, M. P. (1962). The Alkaloids of the Genus *Datura* , Section Brugmansia: Part I. *D. Cornigera* Hook. *Journal of Pharmacy and Pharmacology*, *14*(1), 147–156. https://doi.org/https://doi.org/10.1111/j.2042-7158.1962.tb11070.x

1132. Alves, M. N., Sartoratto, A., & Trigo, J. R. (2007). Scopolamine in *Brugmansia Suaveolens* (Solanaceae): Defense, Allocation, Costs, and Induced Response. *Journal of Chemical Ecology*, *33*(2), 297–309. https://doi.org/10.1007/s10886-006-9214-9

1133. Algradi, A. M., Liu, Y., Yang, B.-Y., & Kuang, H.-X. (2021). Review on the genus Brugmansia: Traditional usage, phytochemistry, pharmacology, and toxicity. *Journal of Ethnopharmacology*, *279*, 113910. https://doi.org/10.1016/j.jep.2021.113910

1134. Pinto, C. F., Salinas, S., Flores-Prado, L., Echeverría, J., & Niemeyer, H. M. (2016). Sequestration of tropane alkaloids from Brugmansia suaveolens (Solanaceae) by the treehopper Alchisme grossa (Hemiptera: Membracidae). *Biochemical Systematics and Ecology*, *66*, 161–165. https://doi.org/10.1016/j.bse.2016.03.015

Page 168. *Some species of Duboisia*.

1135. Kohnen, K. L., Sezgin, S., Spiteller, M., Hagels, H., & Kayser, O. (2018). Localization and Organization of Scopolamine Biosynthesis in Duboisia myoporoides R. Br. *Plant and Cell Physiology*, *59*(1), 107–118. https://doi.org/10.1093/pcp/pcx165

Page 169. *Most species of Brugsmansia*.

1136. Dupin, J., & Smith, S. D. (2019). Integrating historical biogeography and environmental niche evolution to understand the geographic distribution of Datureae. *American Journal of Botany*, *106*(5), 667–678. https://doi.org/10.1002/ajb2.1281

Page 169. *The huge white.*

1137. Soteras, F., Moré, M., Ibañez, A. C., Iglesias, M. del R., & Cocucci, A. A. (2018). Range overlap between the sword-billed hummingbird and its guild of long-flowered species: An approach to the study of a coevolutionary mosaic. *PLOS ONE*, *13*(12), e0209742. https://doi.org/10.1371/journal.pone.0209742

1138. Kite, G. C., & Leon, C. (1995). Volatile compounds emitted from flowers and leaves of *Brugmansia* × *candida* (Solanaceae). *Phytochemistry*, *40*(4), 1093–1095. https://doi.org/10.1016/0031-9422(95)00485-P

1139. Alves, M. N., Sartoratto, A., & Trigo, J. R. (2007). Scopolamine in *Brugmansia Suaveolens* (Solanaceae): Defense, Allocation, Costs, and Induced Response. *Journal of Chemical Ecology*, *33*(2), 297–309. https://doi.org/10.1007/s10886-006-9214-9

Page 169. *The Zuni Pueblo.*

1140. Doelle, W. H. (2009). *Zuni origins: toward a new synthesis of Southwestern archaeology*. University of Arizona Press.

1141. Kintigh, K. W., Glowacki, D. M., & Huntley, D. L. (2004). Long-Term Settlement History and the Emergence of Towns in the Zuni Area. *American Antiquity*, *69*(3), 432–456. https://doi.org/10.2307/4128401

1142. Pueblo of Zuni. (n.d.). *ashwi.org*. Retrieved October 13, 2023, from https://www.ashiwi.org/index.html

Page 169. *Historically, Zuni rain.*

1143. Stevenson, M. C. (1915). *Ethnobotany of the Zuni Indians* (Vol. 30). US Government Printing Office.

Page 169. *Such use presaged.*

1144. Störck, A. (1762). *Libellus, quo demonstratur: stramonium, hyosciamum, aconitum*. typis Joannis Thomae Trattner.

Page 169. *The use of Hyoscyamus.*

1145. Ullrich, S. F., Hagels, H., & Kayser, O. (2017). Scopolamine: a journey from the field to clinics. *Phytochemistry Reviews*, *16*(2), 333–353. https://doi.org/10.1007/s11101-016-9477-x

Page 169. *Scopolamine got its name.*

1146. Geis, G. (1959). In scopolamine veritas. *J. Crim. L. & Criminology*, *50*, 347. https://scholarlycommons.law.northwestern.edu/jclc/vol50/iss4/4

1147. Schneiderlin, Ein neue Narkose. (1900). *54 Aerztliche Mitteilungen aus und für Baden*

1148. Schneiderlin, Die Skopolamine (Hyossin) Morphium Narkose. (1903). *50 Münchener Medizinische WochenSchrift 374*

1149. Goerig, M. (2014). The Development of Anaesthesiology in German-Speaking Countries. In *The Wondrous Story of Anesthesia* (pp. 371–389). Springer New York. https://doi.org/10.1007/978-1-4614-8441-7_29

Page 170. *By 1902, Austrian physician.*

1150. Steinbuchel, V. (1902). Vorlaufige Mittheilung uber die Anwendung von Skopolamin-Morphium-Injectionem in der Geburtshilfe. *Zentralbl F Gynak*, *26*, 1304.

Page 170. *Eventually, two German physicians.*

1151. Gauss, C. J. (1906). Anwendung des Skopolamin-Morphium Dammerschlafes in der Geburtshilfe. *Med Klin*, *2*, 136-138.

1152. Krönig, P. (1908). Scopolamine-Morphine Narcosis In Labour. *The British Medical Journal*, *2*(2490), 805–808. http://www.jstor.org/stable/25279080

1153. Twilight Sleep: the Dammerschlaf of the Germans. (1915). *Canadian Medical Association journal*, *5*(9), 805–808.

1154. Haultain, F. W., & Swift, B. H. (1916). THE MORPHINE-HYOSCINE METHOD OF PAINLESS CHILDBIRTH: OR SO-CALLED “TWILIGHT SLEEP.”. *British Medical Journal*, *2*(2911), 513–515. https://doi.org/10.1136/bmj.2.2911.513

Page 170. *Given that there was generally no safe.*

1155. Daniel, M. F. (1914). What Do You Know about Twilight Sleep?. *Texas Medical Journal*, *30*(3), 123.

1156. Geis, G. (1959). In scopolamine veritas. *J. Crim. L. & Criminology*, *50*, 347. https://scholarlycommons.law.northwestern.edu/jclc/vol50/iss4/4

1157. Leavitt, J. W. (1980). Birthing and Anesthesia: The Debate over Twilight Sleep. *Signs*, *6*(1), 147–164. http://www.jstor.org/stable/3173972

1158. Johnson, B., & Quinlan, M. M. (2015). Technical Versus Public Spheres: A Feminist Analysis of Women's Rhetoric in the Twilight Sleep Debates of 1914–1916. *Health Communication*, *30*(11), 1076–1088. https://doi.org/10.1080/10410236.2014.921269

1159. Tracy, M., & Leupp, C. (1914). *Painless childbirth*. McClure Publications, Incorporated.

Page 170. *Initially, twilight sleep*.

1160. Leavitt, J. W. (1980). Birthing and Anesthesia: The Debate over Twilight Sleep. *Signs*, *6*(1), 147–164. http://www.jstor.org/stable/3173972

Page 170. *Scopolamine even moonlighted*.

1161. House, R. E. (1931). The Use of Scopolamine in Criminology. *The American Journal of Police Science*, *2*(4), 328. https://doi.org/10.2307/1147361

1162. Geis, G. (1959). In scopolamine veritas. *J. Crim. L. & Criminology*, *50*, 347. https://scholarlycommons.law.northwestern.edu/jclc/vol50/iss4/4

1163. Moenssens, A. A. (1961). Narcoanalysis in Law Enforcement. *The Journal of Criminal Law, Criminology, and Police Science*, *52*(4), 453-458. https://scholarlycommons.law.northwestern.edu/jclc/vol52/iss4/10

1164. Bimmerle, G. (1993). Truth Drugs in Interrogation. *CIA Historical Review Program*.

1165. Winter, A. (2005). The Making of "Truth Serum." *Bulletin of the History of Medicine*, *79*(3), 500–533. http://www.jstor.org/stable/44448255

1166. Lakstygal, A. M., Kolesnikova, T. O., Khatsko, S. L., Zabegalov, K. N., Volgin, A. D., Demin, K. A., Shevyrin, V. A., Wappler-Guzzetta, E. A., & Kalueff,

A. v. (2019). DARK Classics in Chemical Neuroscience: Atropine, Scopolamine, and Other Anticholinergic Deliriant Hallucinogens. *ACS Chemical Neuroscience*, *10*(5), 2144–2159. https://doi.org/10.1021/acschemneuro.8b00615

1167. Passie, T., & Benzenhöfer, U. (2018). MDA, MDMA, and other "mescaline-like" substances in the US military's search for a truth drug (1940s to 1960s). *Drug Testing and Analysis*, *10*(1), 72–80. https://doi.org/10.1002/dta.2292

1168. Widacki, J. (2021). The use of narcoanalysis by Polish counterintelligence in the 1930s. *European Polygraph*, *15*(1), 39–52. https://doi.org/10.2478/ep-2021-0003

Page 170 and 171. *Scopolamine derived from Brugmansia*.

1169. Lusthof, K. J., Bosman, I. J., Kubat, B., & Vincenten-van Maanen, M. J. (2017). Toxicological results in a fatal and two non-fatal cases of scopolamine-facilitated robberies. *Forensic Science International*, *274*, 79–82. https://doi.org/10.1016/j.forsciint.2017.01.024

1170. Alonso, C. F., Casado, E. D., Jorge, O. Q., Morales, C. M., Serrano, B. B., & Santiago-Sáez, A. (2022). Drug facilitated crimes by "burundanga" or scopolamine. *Spanish Journal of Legal Medicine*, *48*(2), 74–77. https://doi.org/10.1016/j.remle.2022.01.003

1171. Diaz, G. (2015). Toxicosis by Plant Alkaloids in Humans and Animals in Colombia. *Toxins*, *7*(12), 5408–5416. https://doi.org/10.3390/toxins7124892

1172. Reichert, S., Lin, C., Ong, W., Him, C. C., & Hameed, S. (2017). Million dollar ride: Crime committed during involuntary scopolamine intoxication. *Canadian Family Physician Medecin de Famille Canadien*, *63*(5), 369–370.

1173. U.S. Embassy Quito. (2014). Security Message for U.S. Citizens: Quito (Ecuador), Drugged Robberies. https://www.osac.gov/Content/Report/d4c5b6fd-e20c-4a6a-90ab-15f4ad745f2a

1174. U.S. Embassy Bogota. (2011). Emergency Message for U.S. Citizens: Colombia (Bogoto), Increase in Robberies Around Chapinero District. https://www.osac.gov/Content/Report/2efa4937-0dd0-43ae-98ca-15f4ad0fe28f

Page 171. *However, there is little evidence*.

1175. *Scopolamine: Myths and realities*. (2018, August 16). The Bogota Post. https://thebogotapost.com/scopolamine-myths-and-realities/31604/

1176. Saner, E. (2015). "Devil's breath" aka scopolamine: can it really zombify you? *The Guardian*. https://www.theguardian.com/society/shortcuts/2015/sep/02/devils-breath-aka-scopolamine-can-it-really-zombify-you

Page 171. *The rare toxicology analyses*.

1177. Uribe-Granja, M. G., Moreno-López, C. L., Zamora-Suárez, A., & Acosta, P. J. (2005). Perfil epidemiológico de la intoxicación con burundanga en la clínica Uribe Cualla SA de Bogotá, DC. *Acta Neurológica Colombiana*, *21*(3), 197-201.

Page 171. *A different urban legend*.

1178. Matthiolus, P. (1565). *Commentarii pedacii Dioscoridis anazerbi de Materia Medica*. Venetiis: Valgarisiana 1074.

1179. Kraemer, H. (1894). *Belladonna: A Study of Its History, Action and Uses in Medicine*. Johnson & Johnson.

1180. Campbell, E. A. (2007). Don't Say It with Nightshades: Sentimental Botany and the Natural History of "Atropa Belladonna." *Victorian Literature and Culture*, *35*(2), 607–615. http://www.jstor.org/stable/40347177

1181. Lee, M. R. (2007). Solanaceae IV: *Atropa belladonna*, deadly nightshade. *The Journal of the Royal College of Physicians of Edinburgh*, *37*(1), 77–84.

1182. Maurya, V. K., Kumar, S., Kabir, R., Shrivastava, G., Shanker, K., Nayak, D., Khurana, A., Manchanda, R. K., Gadugu, S., Kar, S. K., Verma, A. K., & Saxena, S. K. (2020). Dark Classics in Chemical Neuroscience: An Evidence-Based Systematic Review of Belladonna. *ACS Chemical Neuroscience*, *11*(23), 3937–3954. https://doi.org/10.1021/acschemneuro.0c00413

1183. Forbes, T. R. (1977). Why is it called "beautiful lady"? A note on belladonna. *Bulletin of the New York Academy of Medicine*, *53*(4), 403–406.

1184. Feinsod, M. (2000). The blind beautiful eye. *Journal of neuro-ophthalmology*, *20*(1), 22-24.

1185. The U.S. Forest Service. (n.d.). The Powerful Solanaceae: Belladonna. https://www.fs.usda.gov/wildflowers/ethnobotany/Mind_and_Spirit/belladonna.shtml

Page 171. *Atropine is now used.*

1186. Pineles, S. L., Kraker, R. T., VanderVeen, D. K., Hutchinson, A. K., Galvin, J. A., Wilson, L. B., & Lambert, S. R. (2017). Atropine for the Prevention of Myopia Progression in Children. *Ophthalmology*, *124*(12), 1857–1866. https://doi.org/10.1016/j.ophtha.2017.05.032

Page 172. *Cocaine is produced.*

1187. White, D. M., Huang, J.-P., Jara-Muñoz, O. A., MadriñáN, S., Ree, R. H., & Mason-Gamer, R. J. (2021). The Origins of Coca: Museum Genomics Reveals Multiple Independent Domestications from Progenitor *Erythroxylum gracilipes*. *Systematic Biology*, *70*(1), 1–13. https://doi.org/10.1093/sysbio/syaa074

Page 172. *The question is why coca plants.*

1188. Nathanson, J. A., Hunnicutt, E. J., Kantham, L., & Scavone, C. (1993). Cocaine as a naturally occurring insecticide. *Proceedings of the National Academy of Sciences*, *90*(20), 9645–9648. https://doi.org/10.1073/pnas.90.20.9645

Page 173. *More recent studies.*

1189. Blum, M. S., Rivier, L., & Plowman, T. (1981). Fate of cocaine in the lymantriid *Eloria noyesi*, a predator of *Erythroxylum coca*. *Phytochemistry*, *20*(11), 2499–2500. https://doi.org/10.1016/0031-9422(81)83080-4

1190. Kanno, M., Hiramatsu, S., Kondo, S., Tanimoto, H., & Ichinose, T. (2021). Voluntary intake of psychoactive substances is regulated by the dopamine receptor Dop1R1 in Drosophila. *Scientific Reports*, *11*(1), 3432. https://doi.org/10.1038/s41598-021-82813-0

Page 173. *Not surprisingly.*

1191. Collenette, C. L. (1950). LXXIX.— *A revision of the genus* Eloria *Walker* (Heterocera, Lymantriidæ). *Annals and Magazine of Natural History*, *3*(34), 813–865. https://doi.org/10.1080/00222935008654717

1192. Blum, M. S., Rivier, L., & Plowman, T. (1981). Fate of cocaine in the lymantriid *Eloria noyesi*, a predator of *Erythroxylum coca*. *Phytochemistry*, *20*(11), 2499–2500. https://doi.org/10.1016/0031-9422(81)83080-4

1193. Plowman, T., & Rivier, L. (1983). Cocaine and Cinnamoylcocaine Content of Erythroxylum Species. *Annals of Botany*, *51*(5), 641–659. https://doi.org/10.1093/oxfordjournals.aob.a086511

1194. Boucher, D. H. (1991). Cocaine and the Coca Plant. *BioScience*, *41*(2), 72–76. https://doi.org/10.2307/1311558

1195. Chen, R., Wu, X., Wei, H., Han, D. D., & Gu, H. H. (2006). Molecular cloning and functional characterization of the dopamine transporter from *Eloria noyesi*, a caterpillar pest of cocaine-rich coca plants. *Gene*, *366*(1), 152–160. https://doi.org/10.1016/j.gene.2005.09.018

Page 173. *This tiny moth has even*.

1196. Berenbaum, M. (1991). Just Say "Notodontid?" *American Entomologist*, *37*(4), 196–197. https://doi.org/10.1093/ae/37.4.196

1197. Bolivia, Peru Reject Use of Bugs in Cocaine Fight: War on Drugs: Latin nations want to switch to legal crops, not to caterpillars or worms to eat coca leaves. (1990, February 22). *Los Angeles Times*. https://www.latimes.com/archives/la-xpm-1990-02-22-mn-1722-story.html

1198. Plan to Eradicate Coca Would Use Caterpillars. (1990, February 20). *The New York Times*. https://www.nytimes.com/1990/02/20/us/plan-to-eradicate-coca-would-use-caterpillars.html

1199. Kornheiser, T. (1990, February 21). THE CATERPILLAR THAT ATE COLOMBIA. *The Washington Post*. https://www.washingtonpost.com/archive/lifestyle/1990/02/21/the-caterpillar-that-ate-colombia/a3f91fe9-5900-4df2-b2b1-ea33c4a1fb9f/

Page 173. *This same idea*.

1200. Glass, H. (2015, May 14). These caterpillars could destroy Colombia's massive cocaine production. *Insider*. https://www.businessinsider.com/these-caterpillars-could-destroy-colombias-massive-cocaine-production-2015-5

1201. Council on Hemispheric Affairs. (2015, June 5). *Eloria Noyesi: Colombia's Potential Solution to Eradicating Illicit Coca*. COHA. https://coha.org/eloria-noyesi-colombias-potential-solution-to-eradicating-illicit-coca/

1202. Rogers, K. (2015, May 14). The Moths that Could Destroy Colombia's Cocaine Trade. *Vice*. https://www.vice.com/en/article/ae38xj/the-moths-that-could-destroy-colombias-cocaine-trade

1203. Emblin, R. (2015, June 29). Colombia: Butterflies on the front line of the coca wars. *The City Paper*. https://thecitypaperbogota.com/features/butterflies-for-the-frontline-alberto-gomez-colombia/

Page 173. *Cocaine is different*. References below apply to the paragraphs through page 174, up to the paragraph that begins with "Cocaine exerts…"

1204. Kilty, J. E., Lorang, D., & Amara, S. G. (1991). Cloning and Expression of a Cocaine-Sensitive Rat Dopamine Transporter. *Science*, *254*(5031), 578–579. https://doi.org/10.1126/science.1948035

1205. Amara, S. G., & Sonders, M. S. (1998). Neurotransmitter transporters as molecular targets for addictive drugs. *Drug and Alcohol Dependence*, *51*(1–2), 87–96. https://doi.org/10.1016/S0376-8716(98)00068-4

1206. Rothman, R. B., Baumann, M. H., Dersch, C. M., Romero, D. v, Rice, K. C., Carroll, F. I., & Partilla, J. S. (2001). Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse*, *39*(1), 32–41. https://doi.org/https://doi.org/10.1002/1098-2396(20010101)39:1<32::AID-SYN5>3.0.CO;2-3

1207. NIDA. 2020, June 11. How does cocaine produce its effects?. Retrieved from https://nida.nih.gov/publications/research-reports/cocaine/how-does-cocaine-produce-its-effects

Page 174. *Cocaine exerts its strongest*

1208. Kelz, M. B., Chen, J., Carlezon, W. A., Whisler, K., Gilden, L., Beckmann, A. M., Steffen, C., Zhang, Y.-J., Marotti, L., Self, D. W., Tkatch, T., Baranauskas, G., Surmeier, D. J., Neve, R. L., Duman, R. S., Picciotto, M. R., & Nestler, E. J. (1999). Expression of the transcription factor ΔFosB in the brain controls sensitivity to cocaine. *Nature*, *401*(6750), 272–276. https://doi.org/10.1038/45790

Page 174. *The situation is the opposite in insects*. Note that studies in honeybees do show responses similar to those in humans because cocaine impacts biogenic amine reuptake, which also impacts reward circuits. The hypothesis proposed by Barron et al. referenced below is that "Ecologically, cocaine is an effective plant defence compound *via* disruption of herbivore motor control but, because the neurochemical systems targeted by cocaine also modulate reward processing, the reinforcing properties of cocaine occur as a `side effect'."

1209. Nathanson, J. A., Hunnicutt, E. J., Kantham, L., & Scavone, C. (1993). Cocaine as a naturally occurring insecticide. *Proceedings of the National Academy of Sciences*, *90*(20), 9645–9648. https://doi.org/10.1073/pnas.90.20.9645

1210. Roeder, T. (1999). Octopamine in invertebrates. *Progress in Neurobiology*, *59*(5), 533–561. https://doi.org/10.1016/S0301-0082(99)00016-7

1211. Roeder, T., Seifert, M., Kähler, C., & Gewecke, M. (2003). Tyramine and octopamine: Antagonistic modulators of behavior and metabolism. *Archives of Insect Biochemistry and Physiology*, *54*(1), 1–13. https://doi.org/10.1002/arch.10102

1212. Barron, A. B., Maleszka, R., Helliwell, P. G., & Robinson, G. E. (2009). Effects of cocaine on honey bee dance behaviour. *Journal of Experimental Biology*, *212*(2), 163–168. https://doi.org/10.1242/jeb.025361

Page 174. *The oldest evidence.*

1213. Dillehay, T. D., Rossen, J., Ugent, D., Karathanasis, A., Vásquez, V., & Netherly, P. J. (2010). Early Holocene coca chewing in northern Peru. *Antiquity*, *84*(326), 939–953. https://doi.org/10.1017/S0003598X00067004

Page 174. *Aymara and Quecha people.*

1214. Dillehay, T. D., Rossen, J., Ugent, D., Karathanasis, A., Vásquez, V., & Netherly, P. J. (2010). Early Holocene coca chewing in northern Peru. *Antiquity*, *84*(326), 939–953. https://doi.org/10.1017/S0003598X00067004

1215. Hanna, J. M. (1974). Coca Leaf Use in Southern Peru: Some Biosocial Aspects. *American Anthropologist*, *76*(2), 281–296. http://www.jstor.org/stable/674183

1216. Plowman, T. (1984). The Ethnobotany of Coca (Erythroxylum spp., Erythroxylaceae). *Advances in Economic Botany*, *1*, 62–111. http://www.jstor.org/stable/43931370

1217. Grisaffi, T. (2010). We Are Originarios... "We Just Aren't from Here": Coca leaf and Identity Politics in the Chapare, Bolivia. *Bulletin of Latin American Research*, *29*(4), 425–439. http://www.jstor.org/stable/25741493

1218. Toyne, M. (2023). Transformation of Coca to Cocaine: An Overview of Traditional Drug Use and Modern Drug Abuse. *The University of Western Ontario Journal of Anthropology*, *25*(1), 94–115. https://doi.org/10.5206/uwoja.v25i1.16031

Page 175. *Either methods of preparation*.

1219. Holmstedt, B., Lindgren, J.-E., Rivier, L., & Plowman, T. (1979). Cocaine in blood of coca chewers. *Journal of Ethnopharmacology*, *1*(1), 69–78. https://doi.org/10.1016/0378-8741(79)90017-5

Page 175. *Today there are roughly*.

1220. Gootenberg, P. (2008). *Andean Cocaine: The Making of a Global Drug*. University of North Carolina Press. http://www.jstor.org/stable/10.5149/9780807887790_gootenberg

Page 175. *The Incans built*.

1221. Valdez, L. M., Taboada, J., & Valdez, J. E. (2015). Ancient Use of Coca Leaves in the Peruvian Central Highlands. *J. Anthropol. Res.*, *71*(2), 231–258. https://doi.org/10.3998/jar.0521004.0071.204

Page 175. *Early in the Spanish*.

1222. Biondich, A. S., & Joslin, J. D. (2016). Coca: The History and Medical Significance of an Ancient Andean Tradition. *Emerg. Med. Int.*, *2016*, 4048764. https://doi.org/10.1155/2016/4048764

Page 175 and 176. *Cocaine as a drug was therefore*.

1223. Markel, H. (2012). *An Anatomy of Addiction: Sigmund Freud, William Halsted, and the Miracle Drug Cocaine.* Vintage.

Page 176. *The initial recipe*.

1224. How Coca-Cola Obtains Its Coca. (1988, July 1). *The New York Times*. https://www.nytimes.com/1988/07/01/business/how-coca-cola-obtains-its-coca.html.

Page 176. *The product went on sale.*

1225. Hale, G. E. (2013). When Jim Crow Drank Coke. *The New York Times*, 28, 89–91. https://www.nytimes.com/2013/01/29/opinion/when-jim-crow-drank-coke.html

Page 176. *In response to a public.*

1226. Marietjie, B. (2012). Coca-Cola : definitely a taste for life! : intellectual property. *Without Prejudice*, *12*(6), 35–37. https://doi.org/10.10520/EJC124417\

Page 176. *Nevertheless, some news articles.*

1227. Gootenberg, P. (2004). Secret Ingredients: The Politics of Coca in US–Peruvian Relations, 1915–65. *Journal of Latin American Studies*, *36*(2), 233–265. https://doi.org/10.1017/S0022216X04007424

1228. May, C. D. (1988). *How Coca-Cola obtains its Coca. The New York Times, July 1.* https://timesmachine.nytimes.com/timesmachine/1988/07/01/248188.html?pageNumber=81

1229. Edwards, J. (2013, May 5). See The New Jersey Factory Where Cocaine Is Removed From The Ingredients Of Coca-Cola. *Insider*. https://www.businessinsider.com/stepan-and-cocaine-in-coca-cola-2013-3

1230. Geib, C. (2023, May 2). *The Weird (and Wired) Truth Behind What's Really in Coca-Cola*. Eater. https://www.eater.com/23620802/cocaine-in-coca-cola-coke-recipe-gastropod

Page 176. *Nonetheless, methyl salicylate.*

1231. Novák, M., & Salemink, C. (1987). The Essential Oil of *Erythroxylum coca*. *Planta Medica*, *53*(01), 113–113. https://doi.org/10.1055/s-2006-962643

Page 176. *At least until the twentieth.*

1232. https://timesmachine.nytimes.com/timesmachine/1988/07/01/248188.html?pageNumber=81

1233. Edwards, J. (2013, May 5). See The New Jersey Factory Where Cocaine Is Removed From The Ingredients Of Coca-Cola. *Insider*. https://www.businessinsider.com/stepan-and-cocaine-in-coca-cola-2013-3

1234. Geib, C. (2023, May 2). *The Weird (and Wired) Truth Behind What's Really in Coca-Cola*. Eater. https://www.eater.com/23620802/cocaine-in-coca-cola-coke-recipe-gastropod

1235. Cocaine Hydrochloride USP CII. (n.d.). Mallinckrodt Pharmaceuticals. https://www.mallinckrodt.com/products/generics/compounding-powders/cocaine-hydrochloride-usp-cii/

Page 177. *Incidentally, Mallinckrodt*.

1236. Office of Public Affairs. (2017). Mallinckrodt Agrees to Pay Record $35 Million Settlement for Failure to Report Suspicious Orders of Pharmaceutical Drugs and for Recordkeeping Violations. U. S. Department of Justice. https://www.justice.gov/opa/pr/mallinckrodt-agrees-pay-record-35-million-settlement-failure-report-suspicious-orders

1237. Bernstein, L., & Higham, S. (2017, April 2). The government's struggle to hold opioid manufacturers accountable. *The Washington Post*. https://www.washingtonpost.com/graphics/investigations/dea-mallinckrodt/

Page 177. *In Über Coca*.

1238. Freud, S. (1885). *Über coca*. M. Perles. Quoted in: Shaffer, H. (1984). Uber coca: Freud's cocaine discoveries. *Journal of Substance Abuse Treatment*, *1*(3), 205–217. https://doi.org/10.1016/0740-5472(84)90023-0

Page 178. *Freud used cocaine*.

1239. Markel, H. (2012). *An anatomy of addiction: Sigmund Freud, William Halsted, and the miracle drug, cocaine*. Vintage.

Page 177. *The same year that*.

1240. Goerig, M., Bacon, D., & van Zundert, A. (2012). Carl Koller, Cocaine, and Local Anesthesia. *Regional Anesthesia and Pain Medicine*, *37*(3), 318–324. https://doi.org/10.1097/AAP.0b013e31825051f3

Page 177. *Cocaine's use as a local*.

1241. Einhorn, A., Fiedler, K., Ladisch, C., & Uhlfelder, E. (1909). Ueber p-Aminobenzoësäurealkaminester. *Justus Liebig's Annalen Der Chemie*, *371*(2), 142–161. https://doi.org/10.1002/jlac.19093710204

1242. Löfgren Nils. (1948). *Studies on local anesthetics : xylocaine a new synthetic drug*. Ivar HŒggströms. Retrieved October 15 2023 from http://catalog.hathitrust.org/api/volumes/oclc/3699457.html.

Page 177. *Before physicians*.

1243. Griffith, H. R., & Johnson, G. E. (1942). The use of curare in general anesthesia. The Journal of The *American Society of Anesthesiologists*, 3(4), 418-420. https://doi.org/10.1097/00000542-194207000-00006

1244. Dillane, D., Chartrand, D., & Maltby, R. (2017). Harold Griffith's legacy: a tribute on the 75th anniversary of the introduction of curare into anesthetic practice. *Canadian Journal of Anesthesia/Journal Canadien d'anesthésie*, *64*(6), 559–568. https://doi.org/10.1007/s12630-017-0864-6

1245. Bennett, A. E. (1968). The history of the introduction of curare into medicine. *Anesthesia and Analgesia*, *47*(5), 484–492.

1246. O'Hara, M. (2022). The Shadows of Curare. *History of Pharmacy and Pharmaceuticals*, *63*(2), 247–269. https://doi.org/10.3368/hopp.63.2.247

Page 177. *If there ever was a toxin*.

1247. Lee, M. R. (2005). Curare: the South American arrow poison. *The Journal of the Royal College of Physicians of Edinburgh*, *35*(1), 83–92.

1248. Bisset, N. G. (1992). Curare. In *Alkaloids: Chemical and Biological Perspectives* (pp. 1–150). Springer New York. https://doi.org/10.1007/978-1-4612-2908-7_1

1249. Roberts, M. F. (Ed.). (2013). *Alkaloids: biochemistry, ecology, and medicinal applications*. Springer Science & Business Media.

Page 177. *The term curare*.

1250. Harper, D. (n.d.(. Etymology of curare. Online Etymology Dictionary. From https://www.etymonline.com/word/curare

Page 178. *This use explains*.

1251. Gill, R. (2018). The flying death comes to America. *New Scientist*, *237*(3161), 40–41. https://doi.org/10.1016/S0262-4079(18)30132-5

Page 178. *In 1800*. Quote from reference below.

1252. von Humboldt, A., & Bonpland, A. (1852). *Personal narrative of travels to the equinoctial regions of America, during the years 1799-1804* (Vol. 2). Henry G. Bohn.

Page 178. *After reading that passage*.

1253. The Flying Death and Other Adventures in Anesthesia. (2019). *Brought to Light*. From https://broughttolight.ucsf.edu/2016/10/31/the-flying-death-and-other-adventures-in-anesthesia/

1254. Gill, R. C. (1940). *White water and black magic*, Henry Holt.

1255. Humble, R. M. (1982). The Gill-Merrill Expedition. *Anesthesiology*, *57*(6), 519–526. https://doi.org/10.1097/00000542-198212000-00014

1256. Bisset, N. G. (1992). War and hunting poisons of the New World. Part 1. Notes on the early history of curare. *Journal of Ethnopharmacology*, *36*(1), 1–26. https://doi.org/10.1016/0378-8741(92)90056-W

Page 179. *Like cobratoxin*.

1257. Lester, H. A. (1972). Vulnerability of desensitized or curare-treated acetylcholine receptors to irreversible blockade by cobra toxin. *Molecular Pharmacology*, *8*(6), 632–644.

Page 179 and 180. *In 1935.* References below apply to the next three paragraphs.

1258. King, H. (1935). 330. Curare alkaloids. Part I. Tubocurarine. *Journal of the Chemical Society (Resumed)*, 1381. https://doi.org/10.1039/jr9350001381

1259. Gill, R. C. (1940). *White water and black magic*, Henry Holt.

1260. King, H. (1946). Botanical Origin of Tube-Curare. *Nature*, *158*(4015), 515–516. https://doi.org/10.1038/158515b0

1261. Wintersteiner, O., & Dutcher, J. D. (1943). Curare Alkaloids from *Chondodendron tomentosum*. *Science*, *97*(2525), 467–470. https://doi.org/10.1126/science.97.2525.467

1262. Humble, R. M. (1982). The Gill-Merrill Expedition. *Anesthesiology*, *57*(6), 519–526. https://doi.org/10.1097/00000542-198212000-00014

Page 180. *By 1941*.

1263. Gray, T. C., & Halton, J. (1946). Curarine with Balanced Anaesthesia. *BMJ*, *2*(4469), 293–295. https://doi.org/10.1136/bmj.2.4469.293

1264. Griffith, H.R., & Johnson, G. E. (1942). The use of curare in general anesthesia. *Anesthesiology*, *3*(4), 418–420. https://doi.org/10.1097/00000542-194207000-00006

Page 180. *In 1946 and 1947*.

1265. Smith, S. M., Brown, H. O., Toman, J. E., & Goodman, L. S. (1947). The lack of cerebral effects of d-tubocuarine. *Anesthesiology*, *8*(1), 1–14. https://doi.org/10.1097/00000542-194701000-00001

1266. Plenk, H. P. (1992). *Medicine in the Beehive State 1940-1990*. Utah Medical Association, 540 East 500 South, Salt Lake City, UT 84102.

1267. Anderson, R. (2010). A TORTURED PATH: Curare's Journey from Poison Darts to Paralysis by Design. *Molecular Interventions*, *10*(5), 252–258. https://doi.org/10.1124/mi.10.5.1

Page 180. *It also sparked.*

1268. Bevan, D. R. (1992). Curare 1942–1992. *Canadian Journal of Anaesthesia*, *39*(1), 4–5. https://doi.org/10.1007/BF03008664

Page 180 and 181. *The connection between*.

1269. Allen, G. W. (1953). Black widow spider (Latrodectus mactans) poisoning treated with d-tubocurarine chloride. *Annals of Internal Medicine*, *39*(3), 624–625. https://doi.org/10.7326/0003-4819-39-3-624

Page 181. *The Indigenous people who discovered*.

1270. Gomes, M. F., & Sampaio, J. A. L. (2019). [Biopiracy and Traditional Knowledge: Faces of Biocolonialism and its Regulation]. *Veredas Do Direito: Direito Ambiental e Desenvolvimento Sustentável*, *16*(34), 91–121. https://doi.org/10.18623/rvd.v16i34.1274

1271. Bruch, K., Stelzer, J., & Hasse, G. (2021). Institutionalizing Biopiracy: Analysis of the Benefit-Sharing Rules in the Brazilian Biodiversity Law. *The Journal of Environment & Development*, *17*.

1272. Bil, G., & Virdi, J. (2022). Special Issue Introduction: Colonial Histories of Plant-Based Pharmaceuticals. *History of Pharmacy and Pharmaceuticals*, *63*(2), 134–148. https://doi.org/10.3368/hopp.63.2.134

1273. Yano, L. I. (1993). Protection of the Ethnobiological Knowledge of Indigenous Peoples. *UCLA L. Rev.*, *41*, 443.

1274. O'Hara, M. (2022). The Shadows of Curare. *History of Pharmacy and Pharmaceuticals*, *63*(2), 247–269. https://doi.org/10.3368/hopp.63.2.247

1275. Bouchard, S. M. (2009). South American Indigenous Knowledge of Psychotropics. In *Psychiatrists and Traditional Healers* (pp. 37–51). https://doi.org/https://doi.org/10.1002/9780470741054.ch4

1276. Pedrollo, C. T., & Kinupp, V. F. (2015). Sustainability or Colonialism? Legislative obstacles to research and development of natural products and patents on traditional knowledge in Brazil. *Acta Botanica Brasilica*, *29*(3), 452–456. https://doi.org/10.1590/0102-33062015abb0101

Chapter 9. Opioid Overlords

Page 182. *On and on they walked*. Quote from reference below.

1277. Baum, L. F., & Denslow, W. W. (1900). *The Wonderful Wizard of Oz* by L. Frank Baum with Pictures by W. W. Denslow. George M. Hill Company.

Page 182. *During fieldwork in the Galápagos*.

1278. Weeks, A., & Tye, A. (2009). Phylogeography of palo santo trees (*Bursera graveolens* and *Bursera malacophylla* ; Burseraceae) in the Galápagos archipelago. *Botanical Journal of the Linnean Society*, *161*(4), 396–410. https://doi.org/10.1111/j.1095-8339.2009.01008.x

Page 182 and 183. *The aromatic resins*.

1279. Tucker, A. O. (1986). Frankincense and myrrh. *Economic Botany*, *40*(4), 425–433. https://doi.org/10.1007/BF02859654

1280. van Beek, G. W. (1960). Frankincense and Myrrh. *The Biblical Archaeologist*, *23*(3), 70–95. https://doi.org/10.2307/3209285

1281. Zviely, M., & Boix-Camps, A. (2015). Sesquiterpenoides-the holy fragrance ingredients. *Isr. Chem. Eng.*, *1*, 27-31.

1282. De Feo, V. (1992). Medicinal and magical plants in the northern Peruvian Andes. *FITOTERAPIA-MILANO-*, *63*, 417-417.

1283. Dohling, C. (2008). *Boswellia serrata* (Frankincense)-from traditional Indian medicine (Ayurveda) to evidence-based medicine. *Phytomedicine: International Journal of Phytotherapy & Phytopharmacology*, *15*(6-7), 540-541.

1284. Bradley, S. (2018). Myrrh: Medical Knowledge from Arabia into Chinese Materia Medica. *Medicina nei secoli: Journal of history of medicine and medical humanities*, *30*(3), 881-906.

1285. Thulin, M., & Per Claeson. (1991). The Botanical Origin of Scented Myrrh (Bissabol or Habak Hadi). *Economic Botany*, *45*(4), 487–494. http://www.jstor.org/stable/4255391

Page 183. *The Gospel of St. Mark*. Called "vinum murratum" (see reference below by Dolara et al.).

1286. Dolara, P., Luceri, C., Ghelardini, C., Monserrat, C., Aiolli, S., Luceri, F., Lodovici, M., Menichetti, S., & Romanelli, M. N. (1996). Analgesic effects of myrrh. *Nature*, *379*(6560), 29–29. https://doi.org/10.1038/379029a0

Page 183. *Extracts from frankincense.*

1287. Menon, M., & Kar, A. (1971). Analgesic and psychopharmacological effects of the gum resin of *Boswellia serrata*. *Planta Medica*, *19*(02), 333–341. https://doi.org/10.1055/s-0028-1099651

Page 183. *One of the principal terpenoids*.

1288. Moussaieff, A., Rimmerman, N., Bregman, T., Straiker, A., Felder, C. C., Shoham, S., Kashman, Y., Huang, S. M., Lee, H., Shohami, E., Mackie, K., Caterina, M. J., Walker, J. M., Fride, E., & Mechoulam, R. (2008). Incensole acetate, an incense component, elicits psychoactivity by activating TRPV3 channels in the brain. *The FASEB Journal*, *22*(8), 3024–3034. https://doi.org/10.1096/fj.07-101865

Page 183. *For example carvacrol.*

1289. Vogt-Eisele, A. K., Weber, K., Sherkheli, M. A., Vielhaber, G., Panten, J., Gisselmann, G., & Hatt, H. (2007). Monoterpenoid agonists of TRPV3. *British Journal of Pharmacology*, *151*(4), 530–540. https://doi.org/10.1038/sj.bjp.0707245

1290. Xu, H., Delling, M., Jun, J. C., & Clapham, D. E. (2006). Oregano, thyme and clove-derived flavors and skin sensitizers activate specific TRP channels. *Nature Neuroscience*, *9*(5), 628–635. https://doi.org/10.1038/nn1692

Page 184. *Myrrh is even more remarkable*.

1291. Dolara, P., Luceri, C., Ghelardini, C., Monserrat, C., Aiolli, S., Luceri, F., Lodovici, M., Menichetti, S., & Romanelli, M. N. (1996). Analgesic effects of myrrh. *Nature*, *379*(6560), 29–29. https://doi.org/10.1038/379029a0

Page 184. *The usual, and incorrect*.

1292. Brownstein, M. J. (1993). A brief history of opiates, opioid peptides, and opioid receptors. *Proc. Natl. Acad. Sci. U. S. A.*, *90*(12), 5391–5393. https://doi.org/10.1073/pnas.90.12.5391

1293. Neligan, A. R. (1927). *The Opium Question: With Special Reference to Persia*. John Bale, sons & Danielsson, Limited.

Page 184. *However, the ancient Assyrian*.

1294. Thompson, R. C. (1924). *The Assyrian herbal*. Luzac and Company.

Page 184. *Other evidence offered*. See Krikorian (1975) for details, including the quote from Erica Reiner "No word either…" that he wrote was from a letter that she sent to him.

1295. Terry, C. E., Pellens, M., & Others. (1928). *The Opium Problem.* https://www.cabdirect.org/cabdirect/abstract/19292700929

1296. Krikorian, A. D. (1975). Were the opium poppy and opium known in the ancient Near East? *J. Hist. Biol.*, *8*(1), 96–114. https://www.ncbi.nlm.nih.gov/pubmed/11609871

Page 184. *As for the depictions*.

1297. Krikorian, A. D. (1975). Were the opium poppy and opium known in the ancient Near East? *J. Hist. Biol.*, *8*(1), 96–114. https://www.ncbi.nlm.nih.gov/pubmed/11609871

Page 184 and 185. *The first people to cultivate*. These references support this paragraph and the next paragraph.

1298. Hammer, K., & Fritsch, R. (1977). The question of ancestral species of cultivated poppy (*Papaver somniferum* L.). *Die Kulturpflanze*, 25, 113–124.

1299. Salavert, A., Zazzo, A., Martin, L., Antolín, F., Gauthier, C., Thil, F., Tombret, O., Bouby, L., Manen, C., Mineo, M., Mueller-Bieniek, A., Piqué, R., Rottoli, M., Rovira, N., Toulemonde, F., & Vostrovská, I. (2020). Direct dating reveals the early history of opium poppy in western Europe. *Sci. Rep.*, *10*(1), 20263. https://doi.org/10.1038/s41598-020-76924-3

1300. Jesus, A., Bonhomme, V., Evin, A., Ivorra, S., Soteras, R., Salavert, A., Antolín, F., & Bouby, L. (2021). A morphometric approach to track opium poppy domestication. *Sci. Rep.*, *11*(1), 9778. https://doi.org/10.1038/s41598-021-88964-4

Page 186. *For example, a remarkable kitchen*

1301. Peyronel, L., Vacca, A., & Wachter-Sarkady, C. (2014). Food and Drink preparation at Ebla, Syria. New data from the Royal Palace G (*c.* 2450-2300 BC). *Food and History*, *12*(3), 3–38. https://doi.org/10.1484/J.FOOD.5.110584

1302. Lawler, A. (2018). Cannabis, opium use part of ancient Near Eastern cultures. *Science*, *360*(6386), 249–250. https://doi.org/10.1126/science.360.6386.249

Page 186. *Base-ring juglets*.

1303. Merrillees, R. S. (1962). Opium Trade in the Bronze Age Levant. *Antiquity*, *36*(144), 287–292. https://doi.org/10.1017/S0003598X00036814

Page 186. *In 2018, scientists had the technology*.

1304. Smith, R. K., Stacey, R. J., Bergström, E., & Thomas-Oates, J. (2018). Detection of opium alkaloids in a Cypriot base-ring juglet. *The Analyst*, *143*(21), 5127–5136. https://doi.org/10.1039/C8AN01040D

Page 186. *When opium poppy supplies were running low*. Quotation "in all instances…" is from Emboden (1981), referenced below.

1305. Emboden, W. A. (1981). Transcultural use of narcotic water lilies in ancient Egyptian and Maya drug ritual. *J. Ethnopharmacol.*, *3*(1), 39–83. https://doi.org/10.1016/0378-8741(81)90013-1

Page 186 and 187. *Blue water lilies*. The quote "water chaos" is from Emboden (1981). This reference applies to the next paragraph as well.

1306. Emboden, W. A. (1981). Transcultural use of narcotic water lilies in ancient Egyptian and Maya drug ritual. *J. Ethnopharmacol.*, *3*(1), 39–83. https://doi.org/10.1016/0378-8741(81)90013-1

Page 187. *In chapter 81*.

1307. Budge, A.E.W. (1975). *The Book of the Dead* (The Papyrus of Ani) (pp. 310-311). Crown Publications reprint of the 1920 imprint of the Medici Society.

Page 187. *Tutankhamun was depicted*.

1308. Turner, M. (2000). Attribution and iconography. *Mediterranean Archaeology*, *13*, 55–66. http://www.jstor.org/stable/24651831

Page 187. *A related water lily*.

1309. de Rios, M. D., Alger, N., Crumrine, N. R., Furst, P. T., Harman, R. C., Hellmuth, N. M., Hopkins, N. A., King, W. C., Koss, J. D., La Barre, W., Landar, H. J., Long, J. K., Proskouriakoff, T., Rubel, A. J., Samaranch, F., J. Eric S. Thompson, & Wescott, R. W. (1974). The Influence of Psychotropic Flora and Fauna on Maya Religion [and Comments and Reply]. *Current Anthropology*, *15*(2), 147–164. http://www.jstor.org/stable/2740991

Page 187. *In both civilizations*.

1310. Emboden, W. A. (1981). Transcultural use of narcotic water lilies in ancient Egyptian and Maya drug ritual. *J. Ethnopharmacol.*, *3*(1), 39–83. https://doi.org/10.1016/0378-8741(81)90013-1

Page 187. *So similar were the*. Quote is from Emboden (1981) below.

1311. Emboden, W. A. (1981). Transcultural use of narcotic water lilies in ancient Egyptian and Maya drug ritual. *J. Ethnopharmacol.*, *3*(1), 39–83. https://doi.org/10.1016/0378-8741(81)90013-1

Page 188. *We now know*.

1312. Diaz, J. L. (1977). Ethnopharmacology of Sacred Psychoactive Plants Used by the Indians of Mexico. *Annual Review of Pharmacology and Toxicology*, *17*(1), 647–675. https://doi.org/10.1146/annurev.pa.17.040177.003243

1313. Emboden, W. A. (1981). Transcultural use of narcotic water lilies in ancient Egyptian and Maya drug ritual. *J. Ethnopharmacol.*, *3*(1), 39–83. https://doi.org/10.1016/0378-8741(81)90013-1

1314. Emboden, W. A. (1983). The ethnobotany of the Dresden Codex with especial reference to the narcotic *Nymphaea ampla*. *Botanical Museum Leaflets, Harvard University.*, *29*(2), 87–132. http://www.jstor.org/stable/41762844

Page 188. *Today, apomorphine is sold*.

1315. Chaudhuri, K. R., & Clough, C. (1998). Subcutaneous apomorphine in Parkinson's disease. *BMJ*, *316*(7132), 641–641. https://doi.org/10.1136/bmj.316.7132.641

1316. Dula, E., Bukofzer, S., Perdok, R., & George, M. (2001). Double-Blind, Crossover Comparison of 3 mg Apomorphine SL with Placebo and with 4 mg Apomorphine SL in Male Erectile Dysfunction. *European Urology*, *39*(5), 558–564. https://doi.org/10.1159/000052503

Page 188. *Another water lily alkaloid*.

1317. Bhattacharya, S. K., Bose, R., Ghosh, P., Tripathi, V. J., Ray, A. B., & Dasgupta, B. (1978). Psychopharmacological studies on (--)-nuciferine and its Hofmann degradation product atherosperminine. *Psychopharmacology*, *59*(1), 29–33. https://doi.org/10.1007/BF00428026

Page 188. *Given the opposing effects*.

1318. Emboden, W. A. (1981). Transcultural use of narcotic water lilies in ancient Egyptian and Maya drug ritual. *J. Ethnopharmacol.*, *3*(1), 39–83. https://doi.org/10.1016/0378-8741(81)90013-1

1319. Bertol, E., Fineschi, V., Karch, S. B., Mari, F., & Riezzo, I. (2004). Nymphaea cults in ancient Egypt and the New World: a lesson in empirical pharmacology. *JRSM*, *97*(2), 84–85. https://doi.org/10.1258/jrsm.97.2.84

Page 188. Jaguar and lotus image based on Fig. 4a in:

1320. McDonald, J. A., & Stross, B. (2012). Water lily and cosmic serpent: equivalent conduits of the Maya spirit realm. *Journal of Ethnobiology*, *32*(1), 74-107.

Page 188. Ancient Egyptian person and lotus image based on

1321. *Mesu smelling a lotus*. from the Metropolitan Museum of Art, New York (accession number 50.194): https://www.metmuseum.org/art/collection/search/546032.

Page 189. *Europe was the site of domestication*.

1322. Schmitz, R. (1985). Friedrich Wilhelm Sertürner and the discovery of morphine. *Pharmacy in History*, *27*(2), 61–74. https://www.ncbi.nlm.nih.gov/pubmed/11611724

1323. Huxtable, R. J., & Schwarz, S. K. (2001). The isolation of morphine--first principles in science and ethics. *Molecular Interventions*, *1*(4), 189–191.

Page 189. *After building in water*. Quote "none older than…" and "the outcome…" from Huxtable and Schwarz (2001) referenced below.

1324. Sertuerner. (1817). Ueber das Morphium, eine neue salzfähige Grundlage, und die Mekonsäure, als Hauptbestandtheile des Opiums. *Annalen der Physik*, *55*(1), 56-89.

1325. Huxtable, R. J., & Schwarz, S. K. (2001). The isolation of morphine--first principles in science and ethics. *Molecular Interventions*, *1*(4), 189–191.

Page 189. *Morphine is still*.

1326. Kane S. P. (2022). *Morphine*, ClinCalc DrugStats Database, Version 2022.08. ClinCalc: https://clincalc.com/DrugStats/Drugs/Morphine.

Page 189. *The alkaloid thebaine*.

1327. Li, X., Krysiak-Baltyn, K., Richards, L., Jarrold, A., Stevens, G. W., Bowser, T., Speight, R. E., & Gras, S. L. (2020). High-Efficiency Biocatalytic Conversion of Thebaine to Codeine. *ACS Omega*, *5*(16), 9339–9347. https://doi.org/10.1021/acsomega.0c00282

1328. Aceto, M. D., Harris, L. S., Abood, M. E., & Rice, K. C. (1999). Stereoselective μ- and δ-opioid receptor-related antinociception and binding with (+)-thebaine. *European Journal of Pharmacology*, *365*(2–3), 143–147. https://doi.org/10.1016/S0014-2999(98)00862-0

Page 190. *The modern method of harvesting*.

1329. Kabay, J. (1930). Die Erzeugung des Morphins nach ungarischen Verfahren. *Pharmazeutische Monatshefte*, *11*, 73

Page 190. *In 2004, scientists.*

1330. Millgate, A. G., Pogson, B. J., Wilson, I. W., Kutchan, T. M., Zenk, M. H., Gerlach, W. L., Fist, A. J., & Larkin, P. J. (2004). Morphine-pathway block in top1 poppies. *Nature*, *431*(7007), 413–414. https://doi.org/10.1038/431413a

Page 191. *I had somewhat expected this*.

1331. Kiechl, S., Willeit, J., Rungger, G., Egger, G., Oberhollenzer, F., & Bonora, E. (1998). Alcohol consumption and atherosclerosis: what is the relation? Prospective results from the Bruneck Study. *Stroke*, *29*(5), 900–907. https://doi.org/10.1161/01.str.29.5.900

1332. Whitman, I. R., Agarwal, V., Nah, G., Dukes, J. W., Vittinghoff, E., Dewland, T. A., & Marcus, G. M. (2017). Alcohol Abuse and Cardiac Disease. *Journal of the American College of Cardiology*, *69*(1), 13–24. https://doi.org/10.1016/j.jacc.2016.10.048

1333. Texas Department of Transportation. (n.d.). *Impaired driving and penalties - DUI/DWI*. From: https://www.txdot.gov/safety/driving-laws/impaired-driving.html

Page 191. *On June 3, 2018*.

1334. Letter from Hon. Mike McAuliffe, Justice of the Peace, Taylor County, Texas. Attachment included the Autopsy Report for William Kurt Whiteman conducted by the Office of Chief Medical Examiner, Tarrant County Medical Examiner's District, Tarrant County, Texas, case number 1720245.

Page 191. *My initially*.

1335. Engvall, E., & Perlmann, P. (1971). Enzyme-linked immunosorbent assay (ELISA) quantitative assay of immunoglobulin G. *Immunochemistry*, *8*(9), 871–874. https://doi.org/10.1016/0019-2791(71)90454-X

Page 192. *Black peppercorns are produced*.

1336. Hu, L., Xu, Z., Wang, M., Fan, R., Yuan, D., Wu, B., Wu, H., Qin, X., Yan, L., Tan, L., Sim, S., Li, W., Saski, C. A., Daniell, H., Wendel, J. F., Lindsey, K., Zhang, X., Hao, C., & Jin, S. (2019). The chromosome-scale reference genome of black pepper provides insight into piperine biosynthesis. *Nature Communications*, *10*(1), 4702. https://doi.org/10.1038/s41467-019-12607-6

Page 192. *Piperine binds to.*

1337. McNamara, F. N., Randall, A., & Gunthorpe, M. J. (2005). Effects of piperine, the pungent component of black pepper, at the human vanilloid receptor (TRPV1). *British Journal of Pharmacology*, *144*(6), 781–790. https://doi.org/10.1038/sj.bjp.0706040

Page 192. *Overuse of these spices.*

1338. Tobaldini, G., Sardi, N. F., Guilhen, V. A., & Fischer, L. (2019). Pain Inhibits Pain: an Ascending-Descending Pain Modulation Pathway Linking Mesolimbic and Classical Descending Mechanisms. *Molecular Neurobiology*, *56*(2), 1000–1013. https://doi.org/10.1007/s12035-018-1116-7

1339. Choy, M., el Fassi, S., & Treur, J. (2021). An adaptive network model for pain and pleasure through spicy food and its desensitization. *Cognitive Systems Research*, *66*, 211–220. https://doi.org/10.1016/j.cogsys.2020.10.006

Page 192. *As you might have guessed.*

1340. Scott, W. P., & McKibben, G. H. (1978). Toxicity of Black Pepper Extract to Boll Extract to Boll Weevils. *Journal of Economic Entomology*, *71*(2), 343–344. https://doi.org/10.1093/jee/71.2.343

1341. Samuel, M., Oliver, S. v., Coetzee, M., & Brooke, B. D. (2016). The larvicidal effects of black pepper (Piper nigrum L.) and piperine against insecticide resistant and susceptible strains of Anopheles malaria vector mosquitoes. *Parasites & Vectors*, *9*(1), 238. https://doi.org/10.1186/s13071-016-1521-6

1342. Hussain, A., Rizwan-ul-Haq, M., Al-Ayedh, H., & Aljabr, A. M. (2017). Toxicity and Detoxification Mechanism of Black Pepper and Its Major Constituent in Controlling Rhynchophorus ferrugineus Olivier (Curculionidae: Coleoptera). *Neotropical Entomology*, *46*(6), 685–693. https://doi.org/10.1007/s13744-017-0501-7

1343. Devasahayam, S. (2000). Insect pests of black pepper. In *Black pepper* (pp. 336–362). CRC Press.

Page 192. *Piperidine forms the backbone.*

1344. Anderson, T. (1850). Vorläufiger Bericht über die Wirkung der Salpetersäure auf Organische Alkalien. *Annalen Der Chemie Und Pharmacie*, *75*(1), 80–83. https://doi.org/10.1002/jlac.18500750110

1345. Cahours, A. (1852). Recherches sur un nouvel alcali dérivé de la pipérine. *Comptes rendus*, *34*, 481-4.

Page 192. *In this way*.

1346. Otto, E. (1939). *U.S. Patent No. 2,167,351*. Washington, DC: U.S. Patent and Trademark Office.

1347. Latta, K. S., Ginsberg, B., & Barkin, R. L. (2002). Meperidine: A Critical Review. *American Journal of Therapeutics*, *9*(1), 53–68. https://doi.org/10.1097/00045391-200201000-00010

Page 193. *Still, pethidine's structure*. These references apply to the next paragraph as well.

1348. Janssen, P. A. J. (1982). Potent, New Analgesics, Tailor-Made for Different Purposes. *Acta Anaesthesiologica Scandinavica*, *26*(3), 262–268. https://doi.org/10.1111/j.1399-6576.1982.tb01765.x

1349. Stanley, T. H. (1992). The history and development of the fentanyl series. *Journal of Pain and Symptom Management*, *7*(3), S3–S7. https://doi.org/10.1016/0885-3924(92)90047-L

1350. Stanley, T. H. (2014). The Fentanyl Story. *The Journal of Pain*, *15*(12), 1215–1226. https://doi.org/10.1016/j.jpain.2014.08.010

1351. Stanley, T. H., Egan, T. D., & van Aken, H. (2008). A Tribute to Dr. Paul A. J. Janssen: Entrepreneur Extraordinaire, Innovative Scientist, and Significant Contributor to Anesthesiology. *Anesthesia & Analgesia*, *106*(2), 451–462. https://doi.org/10.1213/ane.0b013e3181605add

Page 193. *In the United States*.

1352. Kane S. P. (2022). *Fentanyl*, ClinCalc DrugStats Database, Version 2022.08. ClinCalc: https://clincalc.com/DrugStats/Drugs/Fentanyl.

Page 193. *In 2017, the year*.

1353. Centers for Disease Control and Prevention, & National Center for Injury Prevention and Control. (n.d.). *U.S. County Opioid Dispensing Rates, 2017*. https://www.cdc.gov/drugoverdose/rxrate-maps/county2017.html

Page 193. *And carfentanil*.

1354. Drug Enforcement Administration. (2017). *Carfentanil: a dangerous new factor in the US opioid crisis*. From: https://www.justice.gov/usao-edky/file/898991/download

Page 193 and 194. *There have been*.

1355. Alexander, M. J., Kiang, M. v., & Barbieri, M. (2018). Trends in Black and White Opioid Mortality in the United States, 1979–2015. *Epidemiology*, *29*(5), 707–715. https://doi.org/10.1097/EDE.0000000000000858

1356. Ciccarone, D. (2019). The triple wave epidemic: Supply and demand drivers of the US opioid overdose crisis. *International Journal of Drug Policy*, *71*, 183–188. https://doi.org/10.1016/j.drugpo.2019.01.010

1357. Jenkins, R. A. (2021). The fourth wave of the US opioid epidemic and its implications for the rural US: A federal perspective. *Preventive Medicine*, *152*, 106541. https://doi.org/10.1016/j.ypmed.2021.106541

Page 194. *There were 80,926.*

1358. Steenhuysen, J., & Trotta, D. (2021, July 14). U.S. drug overdose deaths rise 30% to record during pandemic. *Reuters*. https://reuters.com/world/us/us-drug-overdose-deaths-rise-30-record-during-pandemic-2021-07-14/

Page 194. *One in three*.

1359. American Psychiatry Association. (2018). Nearly one in three people know someone addicted to opioids; More than half of millennials believe it is easy to get illegal opioids. From: https://www.psychiatry.org/newsroom/news-releases/nearly-one-in-three-people-know-someone-addicted-to-opioids-more-than-half-of-millennials-believe-it-is-easy-to-get-illegal-opioids

Page 194. *The LCMS*.

1360. Verplaetse, R., & Henion, J. (2016). Quantitative determination of opioids in whole blood using fully automated dried blood spot desorption coupled to on-line SPE-LC-MS/MS. *Drug Testing and Analysis*, *8*(1), 30–38. https://doi.org/10.1002/dta.1927

Page 196. *Some years before*.

1361. Goldstein, A., Barrett, R. W., James, I. F., Lowney, L. I., Weitz, C. J., Knipmeyer, L. L., & Rapoport, H. (1985). Morphine and other opiates from beef brain and adrenal. *Proceedings of the National Academy of Sciences*, *82*(15), 5203–5207. https://doi.org/10.1073/pnas.82.15.5203

Page 196. *That same year*.

1362. Oka, K., Kantrowitz, J. D., & Spector, S. (1985). Isolation of morphine from toad skin. *Proceedings of the National Academy of Sciences*, *82*(6), 1852–1854. https://doi.org/10.1073/pnas.82.6.1852

Page 196. *Shortly thereafter*.

1363. Weitz, C. J., Lowney, L. I., Faull, K. F., Feistner, G., & Goldstein, A. (1986). Morphine and codeine from mammalian brain. *Proceedings of the National Academy of Sciences*, *83*(24), 9784–9788. https://doi.org/10.1073/pnas.83.24.9784

1364. Kodaira, H., Lisek, C. A., Jardine, I., Arimura, A., & Spector, S. (1989). Identification of the convulsant opiate thebaine in mammalian brain. *Proceedings of the National Academy of Sciences*, *86*(2), 716–719. https://doi.org/10.1073/pnas.86.2.716

Page 196. *Then researchers*.

1365. Weitz, C. J., Faull, K. F., & Goldstein, A. (1987). Synthesis of the skeleton of the morphine molecule by mammalian liver. *Nature*, *330*(6149), 674–677. https://doi.org/10.1038/330674a0

Page 196. *Major controversy*.

1366. Hazum, E., Sabatka, J. J., Chang, K.-J., Brent, D. A., Findlay, J. W. A., & Cuatrecasas, P. (1981). Morphine in Cow and Human Milk: Could Dietary Morphine Constitute a Ligand for Specific Morphine (μ) Receptors? *Science*, *213*(4511), 1010–1012. https://doi.org/10.1126/science.6267691

1367. Rowell, F. J., Spark, P., & Rich, C. G. (1982). Non-peptide morphine-like compounds in vertebrate brain tissue and food. *Brit J Pharmacol*, *77*, 461P.

Page 196. *If mammals did*. The rationale for this statement is that mammals are ~300 million years old as a lineage. If we assume that the mammalian crown group synthesized morphinan alkaloids, this would imply that the age is far older than the origin of the angiosperms, which includes the opium poppy, by at ~150 million years.

1368. Kemp, T. S. (2005). *The origin and evolution of mammals*. Oxford University Press, USA.

1369. Ziegler, J., Facchini, P. J., Geißler, R., Schmidt, J., Ammer, C., Kramell, R., Voigtländer, S., Gesell, A., Pienkny, S., & Brandt, W. (2009). Evolution of morphine biosynthesis in opium poppy. *Phytochemistry*, *70*(15–16), 1696–1707. https://doi.org/10.1016/j.phytochem.2009.07.006

1370. Winzer, T., Kern, M., King, A. J., Larson, T. R., Teodor, R. I., Donninger, S. L., Li, Y., Dowle, A. A., Cartwright, J., Bates, R., Ashford, D., Thomas, J., Walker, C., Bowser, T. A., & Graham, I. A. (2015). Morphinan biosynthesis in opium poppy requires a P450-oxidoreductase fusion protein. *Science*, *349*(6245), 309–312. https://doi.org/10.1126/science.aab1852

1371. Guo, L., Winzer, T., Yang, X., Li, Y., Ning, Z., He, Z., Teodor, R., Lu, Y., Bowser, T. A., Graham, I. A., & Ye, K. (2018). The opium poppy genome and morphinan production. *Science*, *362*(6412), 343–347. https://doi.org/10.1126/science.aat4096

1372. Li, Y., Winzer, T., He, Z., & Graham, I. A. (2020). Over 100 Million Years of Enzyme Evolution Underpinning the Production of Morphine in the Papaveraceae Family of Flowering Plants. *Plant Communications*, *1*(2), 100029. https://doi.org/10.1016/j.xplc.2020.100029

1373. Yang, X., Gao, S., Guo, L., Wang, B., Jia, Y., Zhou, J., Che, Y., Jia, P., Lin, J., Xu, T., Sun, J., & Ye, K. (2021). Three chromosome-scale Papaver genomes reveal punctuated patchwork evolution of the morphinan and noscapine biosynthesis pathway. *Nature Communications*, *12*(1), 6030. https://doi.org/10.1038/s41467-021-26330-8

1374. Catania, T., Li, Y., Winzer, T., Harvey, D., Meade, F., Caridi, A., Leech, A., Larson, T. R., Ning, Z., Chang, J., van de Peer, Y., & Graham, I. A. (2022). A functionally conserved STORR gene fusion in Papaver species that diverged 16.8

million years ago. *Nature Communications*, *13*(1), 3150. https://doi.org/10.1038/s41467-022-30856-w

Page 196. *In 2004.*

1375. Poeaknapo, C., Schmidt, J., Brandsch, M., Dräger, B., & Zenk, M. H. (2004). Endogenous formation of morphine in human cells. *Proceedings of the National Academy of Sciences*, *101*(39), 14091–14096. https://doi.org/10.1073/pnas.0405430101

Page 196. *Six years later*.

1376. Grobe, N., Lamshöft, M., Orth, R. G., Dräger, B., Kutchan, T. M., Zenk, M. H., & Spiteller, M. (2010). Urinary excretion of morphine and biosynthetic precursors in mice. *Proceedings of the National Academy of Sciences*, *107*(18), 8147–8152. https://doi.org/10.1073/pnas.1003423107

Page 196. *Zenk's research.*

1377. Goumon, Y., Laux, A., Muller, A., & Aunis, D. (2009). Central and peripheral endogenous morphine. *An R Acad Nac Farm*, *75*(3), 389-418.

1378. Laux, A., Muller, A. H., Miehe, M., Dirrig-Grosch, S., Deloulme, J. C., Delalande, F., Stuber, D., Sage, D., van Dorsselaer, A., Poisbeau, P., Aunis, D., & Goumon, Y. (2011). Mapping of endogenous morphine-like compounds in the adult mouse brain: Evidence of their localization in astrocytes and GABAergic cells. *Journal of Comparative Neurology*, *519*(12), 2390–2416. https://doi.org/10.1002/cne.22633

Page 197. *In 1973.*

1379. Allan, C. (2007). Awakenings. *BMJ*, *334*(7604), 1169.2-1169. https://doi.org/10.1136/bmj.39227.715370.59

1380. Sandler, M., Carter, S. B., Hunter, K. R., & Stern, G. M. (1973). Tetrahydroisoquinoline Alkaloids: in vivo Metabolites of L-Dopa in Man. *Nature*, *241*(5390), 439–443. https://doi.org/10.1038/241439a0

1381. Nagatsu, T., & Yoshida, M. (1988). An endogenous substance of the brain, tetrahydroisoquinoline, produces parkinsonism in primates with decreased dopamine, tyrosine hydroxylase and biopterin in the nigrostriatal regions.

Neuroscience Letters, *87*(1–2), 178–182. https://doi.org/10.1016/0304-3940(88)90166-8

1382. Surh, Y.-J., & Kim, H.-J. (2010). Neurotoxic Effects of Tetrahydroisoquinolines and Underlying Mechanisms. *Experimental Neurobiology*, *19*(2), 63–70. https://doi.org/10.5607/en.2010.19.2.63

1383. Charron, G., Doudnikoff, E., Laux, A., Berthet, A., Porras, G., Canron, M.-H., Barroso-Chinea, P., Li, Q., Qin, C., Nosten-Bertrand, M., Giros, B., Delalande, F., van Dorsselaer, A., Vital, A., Goumon, Y., & Bezard, E. (2011). Endogenous morphine-like compound immunoreactivity increases in parkinsonism. *Brain*, *134*(8), 2321–2338. https://doi.org/10.1093/brain/awr166

Page 198. *THP levels are elevated*.

1384. Myers, R. D., McCaleb, M. L., & Ruwe, W. D. (1982). Alcohol drinking induced in the monkey by Tetrahydropapaveroline (THP) infused into the cerebral ventricle. *Pharmacology Biochemistry and Behavior*, *16*(6), 995–1000. https://doi.org/10.1016/0091-3057(82)90059-4

1385. Haber, H., Roske, I., Rottmann, M., Georgi, M., & Melzig, M. F. (1996). Alcohol induces formation of morphine precursors in the striatum of rats. *Life Sciences*, *60*(2), 79–89. https://doi.org/10.1016/S0024-3205(96)00597-8

1386. McCoy, J. G., Strawbridge, C., McMurtrey, K. D., Kane, V. B., & Ward, C. P. (2003). A re-evaluation of the role of tetrahydropapaveroline in ethanol consumption in rats. *Brain Research Bulletin*, *60*(1–2), 59–65. https://doi.org/10.1016/S0361-9230(03)00018-2

1387. Sango, K., Maruyama, W., Matsubara, K., Dostert, P., Minami, C., Kawai, M., & Naoi, M. (2000). Enantio-selective occurrence of (S)-tetrahydropapaveroline in human brain. *Neuroscience Letters*, *283*(3), 224–226. https://doi.org/10.1016/S0304-3940(00)00963-0

Page 199. *Owing to its bitter*.

1388. Claghorn, J. L., Ordy, J. M., & Nagy, A. (1965). Spontaneous Opiate Addiction in Rhesus Monkeys. *Science*, *149*(3682), 440–441. https://doi.org/10.1126/science.149.3682.440

1389. Kumar, R., Mumford, L., & Teixeira, A. R. (1977). Influencing morphine self-administration in dependent rats [proceedings]. *British Journal of Pharmacology*, *60*(2), 276P.

1390. Glendinning, J. I. (1994). Is the bitter rejection response always adaptive? *Physiology & Behavior*, *56*(6), 1217–1227. https://doi.org/10.1016/0031-9384(94)90369-7

Page 199. *This molecule forms cross-linkages*.

1391. Morimoto, S., Suemori, K., Moriwaki, J., Taura, F., Tanaka, H., Aso, M., Tanaka, M., Suemune, H., Shimohigashi, Y., & Shoyama, Y. (2001). Morphine Metabolism in the Opium Poppy and Its Possible Physiological Function. *Journal of Biological Chemistry*, *276*(41), 38179–38184. https://doi.org/10.1074/jbc.M107105200

Page 199. *In laboratory experiments, fruit flies*.

1392. Kanno, M., Hiramatsu, S., Kondo, S., Tanimoto, H., & Ichinose, T. (2021). Voluntary intake of psychoactive substances is regulated by the dopamine receptor Dop1R1 in Drosophila. *Scientific Reports*, *11*(1), 3432. https://doi.org/10.1038/s41598-021-82813-0

Page 199 and 200. *Rats preferred food*.

1393. Stolerman, I. P., & Kumar, R. (1970). Preferences for morphine in rats: Validation of an experimental model of dependence. *Psychopharmacologia*, *17*(2), 137–150. https://doi.org/10.1007/BF00402704

Page 200. *And just like in humans*.

1394. Alexander, B. K., Coambs, R. B., & Hadaway, P. F. (1978). The effect of housing and gender on morphine self-administration in rats. *Psychopharmacology*, *58*(2), 175–179. https://doi.org/10.1007/BF00426903

1395. Raz, S., & Berger, B. D. (2010). Social isolation increases morphine intake: behavioral and psychopharmacological aspects. *Behavioural Pharmacology*, *21*(1), 39–46. https://doi.org/10.1097/FBP.0b013e32833470bd

1396. Heilig, M., Epstein, D. H., Nader, M. A., & Shaham, Y. (2016). Time to connect: bringing social context into addiction neuroscience. *Nature Reviews Neuroscience*, *17*(9), 592–599. https://doi.org/10.1038/nrn.2016.67

1397. Gage, S. H., & Sumnall, H. R. (2019). Rat Park: How a rat paradise changed the narrative of addiction. *Addiction*, *114*(5), 917–922. https://doi.org/10.1111/add.14481

1398. Christie, N. C. (2021). The role of social isolation in opioid addiction. *Social Cognitive and Affective Neuroscience*, *16*(7), 645–656. https://doi.org/10.1093/scan/nsab029

Page 200. *This initial aversion*. Sullivan et al. (2008) below coined the term "paradox of drug reward."

1399. Sullivan, R. J., Hagen, E. H., & Hammerstein, P. (2008). Revealing the paradox of drug reward in human evolution. *Proceedings of the Royal Society B: Biological Sciences*, *275*(1640), 1231–1241. https://doi.org/10.1098/rspb.2007.1673

Page 200. *But when carpenter ants*.

1400. Entler, B. v., Cannon, J. T., & Seid, M. A. (2016). Morphine addiction in ants: a new model for self-administration and neurochemical analysis. *Journal of Experimental Biology*, *219*(18), 2865–2869. https://doi.org/10.1242/jeb.140616

Page 200. *Another hint came*.

1401. Zabala, N. A., Miralto, A., Maldonado, H., Nuñez, J. A., Jaffe, K., & de C. Calderon, L. (1984). Opiate receptor in praying mantis: Effect of morphine and naloxone. *Pharmacology Biochemistry and Behavior*, *20*(5), 683–687. https://doi.org/10.1016/0091-3057(84)90185-0

1402. Zabala, N. A., & Gómez, M. A. (1991). Morphine analgesia, tolerance and addiction in the cricket Pteronemobius sp. (Orthoptera, Insecta). *Pharmacology, Biochemistry, and Behavior*, *40*(4), 887–891. https://doi.org/10.1016/0091-3057(91)90102-8

1403. Gritsai, O. B., Dubynin, V. A., Pilipenko, V. E., & Petrov, O. P. (2004). Effects of Peptide and Non-Peptide Opioids on Protective Reaction of the Cockroach Periplaneta americana in the "Hot Camera." *Journal of Evolutionary Biochemistry and Physiology*, *40*(2), 153–160. https://doi.org/10.1023/B:JOEY.0000033806.85565.3e

1404. Gavra, T., & Libersat, F. (2011). Involvement of the opioid system in the hypokinetic state induced in cockroaches by a parasitoid wasp. *Journal of Comparative Physiology A*, *197*(3), 279–291. https://doi.org/10.1007/s00359-010-0610-9

Page 201. *For monarch butterflies.*

1405. Zalucki, M. P., Brower, L. P., & Alonso-M, A. (2001). Detrimental effects of latex and cardiac glycosides on survival and growth of first-instar monarch butterfly larvae *Danaus plexippus* feeding on the sandhill milkweed *Asclepias humistrata*. *Ecological Entomology*, *26*(2), 212–224. https://doi.org/10.1046/j.1365-2311.2001.00313.x

Page 202. *For humans.*

1406. Maté, G. (2008). *In the realm of hungry ghosts: Close encounters with addiction*. Random House Digital, Inc.

Page 203. *Drug use disorders.*

1407. Sullivan, R. J., Hagen, E. H., & Hammerstein, P. (2008). Revealing the paradox of drug reward in human evolution. *Proceedings of the Royal Society B: Biological Sciences*, *275*(1640), 1231–1241. https://doi.org/10.1098/rspb.2007.1673

1408. Hagen, E. H., Sullivan, R. J., Schmidt, R., Morris, G., Kempter, R., & Hammerstein, P. (2009). Ecology and neurobiology of toxin avoidance and the paradox of drug reward. *Neuroscience*, *160*(1), 69–84. https://doi.org/10.1016/j.neuroscience.2009.01.077

Chapter 10. The Herbivore's Dilemma

Page 203. *Quote beginning with "Tell me what you…" is from Brillat-Savarin's 1825 book referenced below.*

1409. Brillat-Savarin, J. A. (2009). *The Physiology of Taste: or Meditations on Transcendental Gastronomy; Introduction by Bill Buford*. Everyman's Library.

Page 203. *Our choices.*

1410. Nabhan, G. P. (2013). *Food, genes, and culture: eating right for your origins*. Washington, DC: Island Press.

Page 203 and 204. *Anthropologist Fatimah Jackson*.

1411. Jackson, L. C., Oseguera, M., Medrano, S., & Kim, Y. L. (1988). Carbamylation of hemoglobin in vivo with chronic sublethal dietary cyanide: Implications for hemoglobin S. *Biochemical Medicine and Metabolic Biology*, *39*(1), 64–68. https://doi.org/10.1016/0885-4505(88)90059-X

1412. Jackson, F. L. C. (1990). Two evolutionary models for the interactions of dietary organic cyanogens, hemoglobins, and falciparum malaria. *American Journal of Human Biology*, *2*(5), 521–532. https://doi.org/10.1002/ajhb.1310020508

1413. Jackson, F. L. C. (1991). Secondary Compounds in Plants (Allelochemicals) as Promoters of Human Biological Variability. *Annual Review of Anthropology*, *20*(1), 505–544. https://doi.org/10.1146/annurev.an.20.100191.002445

1414. Linda, F., & Jackson, C. (1991). Influence of chronic sublethal cyanide on body weight in neonatal swine: Implications for humans consuming cassava (Manihot esculenta). *American Journal of Human Biology*, *3*(4), 339–345. https://doi.org/10.1002/ajhb.1310030405

1415. Jackson, F. L. (1994). The bioanthropological impact of chronic exposure to sublethal cyanogens from cassava in Africa. *Acta Horticulturae*, *375*, 295–310. https://doi.org/10.17660/ActaHortic.1994.375.30

1416. Jackson, F. (1996). The coevolutionary relationship of humans and domesticated plants. *American Journal of Physical Anthropology*, *101*(S23), 161–176. https://onlinelibrary.wiley.com/doi/10.1002/(SICI)1096-8644(1996)23+%3C161::AID-AJPA6%3E3.0.CO;2-8

1417. Hardin, J. A., & Jackson, F. L. (2009). Applications of natural products in the control of mosquito-transmitted diseases. *African Journal of Biotechnology*, *8*(25).

1418. Jackson, F., & Mulla, S. (2020). In conversation with Fatimah Jackson: The life and career of an African American Muslim biological anthropologist. *Feminist Anthropology*, *1*(2), 155-164.

1419. Niba, L. L., Bokanga, M. M., Jackson, F. L., Schlimme, D. S., & Li, B. W. (2002). Physicochemical Properties and Starch Granular Characteristics of Flour from Various Manihot Esculenta (Cassava) Genotypes. *Journal of Food Science*, *67*(5), 1701–1705. https://doi.org/10.1111/j.1365-2621.2002.tb08709.x

Page 204 and 205. *In 2020, around 600,000*.

1420. WHO. (2021.) World malaria report 2021. https://reliefweb.int/report/world/world-malaria-report-2021

Page 205. *Sickle cell disease*. These references apply to the next five paragraphs as well.

1421. Herrick, J. B.. (1910). Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia. *Archives of Internal Medicine*, *VI*(5), 517–521. https://doi.org/10.1001/archinte.1910.00050330050003

1422. Allison, A. C. (1954). Protection Afforded by Sickle-cell Trait Against Subtertian Malarial Infection. *BMJ*, *1*(4857), 290–294. https://doi.org/10.1136/bmj.1.4857.290

1423. Allison, A. C. (1956). Sickle cells and evolution. *Scientific American*, *195*(2), 87–95. http://www.jstor.org/stable/24943942

1424. Aidoo, M., Terlouw, D. J., Kolczak, M. S., McElroy, P. D., ter Kuile, F. O., Kariuki, S., Nahlen, B. L., Lal, A. A., & Udhayakumar, V. (2002). Protective effects of the sickle cell gene against malaria morbidity and mortality. *The Lancet*, *359*(9314), 1311–1312. https://doi.org/10.1016/S0140-6736(02)08273-9

1425. Allison, A. C. (2009). Genetic control of resistance to human malaria. *Current Opinion in Immunology*, *21*(5), 499–505. https://doi.org/10.1016/j.coi.2009.04.001

1426. Serjeant, G. R. (2010). One hundred years of sickle cell disease. *British Journal of Haematology*, *151*(5), 425–429. https://doi.org/10.1111/j.1365-2141.2010.08419.x

1427. Elguero, E., Délicat-Loembet, L. M., Rougeron, V., Arnathau, C., Roche, B., Becquart, P., Gonzalez, J.-P., Nkoghe, D., Sica, L., Leroy, E. M., Durand, P., Ayala, F. J., Ollomo, B., Renaud, F., & Prugnolle, F. (2015). Malaria continues to select for sickle cell trait in Central Africa. *Proceedings of the National Academy of Sciences*, *112*(22), 7051–7054. https://doi.org/10.1073/pnas.1505665112

Page 205. *Enter the cassava.*

1428. Jones, D. A. (1998). Why are so many food plants cyanogenic? *Phytochemistry*, *47*(2), 155–162. https://doi.org/10.1016/S0031-9422(97)00425-1

1429. Teles, F. F. F. (2002). Chronic poisoning by hydrogen cyanide in cassava and its prevention in Africa and Latin America. *Food and Nutrition Bulletin*, *23*(4), 407–412. https://doi.org/10.1177/156482650202300418

1430. Nzwalo, H., & Cliff, J. (2011). Konzo: From Poverty, Cassava, and Cyanogen Intake to Toxico-Nutritional Neurological Disease. *PLoS Neglected Tropical Diseases*, *5*(6), e1051. https://doi.org/10.1371/journal.pntd.0001051

1431. Wang, W., Feng, B., Xiao, J., Xia, Z., Zhou, X., Li, P., Zhang, W., Wang, Y., Møller, B. L., Zhang, P., Luo, M.-C., Xiao, G., Liu, J., Yang, J., Chen, S., Rabinowicz, P. D., Chen, X., Zhang, H.-B., Ceballos, H., … Peng, M. (2014). Cassava genome from a wild ancestor to cultivated varieties. *Nature Communications*, *5*(1), 5110. https://doi.org/10.1038/ncomms6110

1432. Pinto-Zevallos, D. M., Pareja, M., & Ambrogi, B. G. (2016). Current knowledge and future research perspectives on cassava (Manihot esculenta Crantz) chemical defenses: An agroecological view. *Phytochemistry*, *130*, 10–21. https://doi.org/10.1016/j.phytochem.2016.05.013

1433. Newton, C. R. (2017). Cassava, konzo, and neurotoxicity. *The Lancet Global Health*, *5*(9), e853–e854. https://doi.org/10.1016/S2214-109X(17)30306-6

Page 205. *Cassava was introduced.*

1434. Iwuagwu, O. (2012). The spread of cassava (manioc) in Igboland, south-east Nigeria: a reappraisal of the evidence. *The Agricultural History Review*, *60*(1), 60–76. http://www.jstor.org/stable/23317131

1435. Jackson, F. L. C., Jackson, R. T., Delumen, B. O., Sio, F. K., Dinkins, L., & Muhammad, A. F. H. (1992). Cassava (*Manihot esculent a)* in Liberia: History, geography, traditional processing and cyanogenic glycoside levels. *Ecology of Food and Nutrition*, *28*(3), 227–242. https://doi.org/10.1080/03670244.1992.9991274

Page 205. *Fatiman Jackson found that.*

1436. Jackson, F. L. C. (1990). Two evolutionary models for the interactions of dietary organic cyanogens, hemoglobins, and falciparum malaria. *American Journal of Human Biology*, *2*(5), 521–532. https://doi.org/10.1002/ajhb.1310020508

Page 205. *Two activities*.

1437. Deykin, D., Balko, C., & Cerami, A. (1972). Cyanate as an Inhibitor of Red-Cell Sickling. *New England Journal of Medicine*, *287*(16), 807–812. https://doi.org/10.1056/NEJM197210192871606

1438. de Furia, F. G., Miller, D. R., Cerami, A., & Manning, J. M. (1972). The Effects of Cyanate In Vitro on Red Blood Cell Metabolism and Function in Sickle Cell Anemia. *Journal of Clinical Investigation*, *51*(3), 566–574. https://doi.org/10.1172/JCI106845

1439. May, A., Bellingham, A. J., Huehns, E. R., & Beaven, G. H. (1972). Effect of cyanate on sickling. *The Lancet*, *299*(7752), 658–661. https://doi.org/10.1016/S0140-6736(72)90462-X

1440. Nagel, R. L., Raventos, C., Tanowitz, H. B., & Wittner, M. (1980). Effect of sodium cyanate on *Plasmodium falciparum* in vitro. *The Journal of Parasitology*, *66*(3), 483–487.

1441. Jackson, L. C., Oseguera, M., Medrano, S., & Kim, Y. L. (1988). Carbamylation of hemoglobin in vivo with chronic sublethal dietary cyanide: Implications for hemoglobin S. *Biochemical Medicine and Metabolic Biology*, *39*(1), 64–68. https://doi.org/10.1016/0885-4505(88)90059-X

1442. Jackson, F. L. C. (1990). Two evolutionary models for the interactions of dietary organic cyanogens, hemoglobins, and falciparum malaria. *American Journal of Human Biology*, *2*(5), 521–532. https://doi.org/10.1002/ajhb.1310020508

Page 206. *Putting two and two*. This reference supports the next two paragraphs as well.

1443. Jackson, F. L. C. (1990). Two evolutionary models for the interactions of dietary organic cyanogens, hemoglobins, and falciparum malaria. *American Journal of Human Biology*, *2*(5), 521–532. https://doi.org/10.1002/ajhb.1310020508

Page 206. *Indeed, cyanates can cross*. From Jackson (1990): “newborns in many high cyanogen consuming indigenous groups are ritually given small amounts of specific cassava-based foods as reaffirmations of their membership in that ethnic group or clan. Thus, an indigenous Liberian’s postnatal exposure to dietary cyanogens may begin very early.”

1444. Tewe, O. O., Maner, J. H., & Gomez, G. (1977). Influence of cassava diets on placental thiocyanate transfer, tissue rhodanese activity and performance of rats during gestation. *Journal of the Science of Food and Agriculture*, *28*(8), 750–756. https://doi.org/10.1002/jsfa.2740280814

1445. Meberg, A., Sande, H., Foss, O. P., & Stenwig, J. T. (1979). Smoking during pregnancy—Effects on the fetus and on thiocyanate levels in mother and baby. *Acta Paediatrica*, *68*(5), 547–552. https://doi.org/10.1111/j.1651-2227.1979.tb05053.x

1446. Dorea, J. G. (2004). Maternal Thiocyanate and Thyroid Status during Breast-Feeding. *Journal of the American College of Nutrition*, *23*(2), 97–101. https://doi.org/10.1080/07315724.2004.10719348

Page 206 and 207.

1447. Cliff, J., Nicala, D., Saute, F., Givragy, R., Azambuja, G., Taela, A., Chavane, L., & Howarth, J. (1997). Konzo associated with war in Mozambique. *Tropical Medicine and International Health*, *2*(11), 1068–1074. https://doi.org/10.1046/j.1365-3156.1997.d01-178.x

1448. Nzwalo, H., & Cliff, J. (2011). Konzo: From Poverty, Cassava, and Cyanogen Intake to Toxico-Nutritional Neurological Disease. *PLoS Neglected Tropical Diseases*, *5*(6), e1051. https://doi.org/10.1371/journal.pntd.0001051

1449. Maxmen, A. (2017, February 23). *Poverty Plus A Poisonous Plant Blamed For Paralysis In Rural Africa*. NPR. https://www.npr.org/sections/thesalt/2017/02/23/515819034/poverty-plus-a-poisonous-plant-blamed-for-paralysis-in-rural-africa

Page 207. *The Tucano people*.

1450. Wilson, W. M., & Dufour, D. L. (2002). Why "bitter" cassava? Productivity of "bitter" and "sweet" cassava in a Tukanoan Indian settlement in the northwest Amazon. *Economic Botany*, *56*(1), 49-57. http://www.jstor.org/stable/4256519

Page 208. *Malaria was introduced*. The date 1558 as the date for introduction of cassava is contentious and after the book had gone to press some new information came to light in a 2023 publication. According to many secondary sources (e.g., Silvestre and Arraudeau 1983), this is the date of its first appearance, attributed to the Portuguese, using Mauny's reference to 1558.

But according to Ankei, Mauny's reference to 1558 had nothing to do with the introduction to Africa question and was referring to a report by Thevet in 1558 from Brazil, where it is native. As for the malaria question, this was addressed earlier in the discussion of the use of quinine. However, some nuance is important here too–*Plasmodium falciparum* unquestionably was moved via the Colombian exchange and trans-Atlantic slave trade from humans in Europe and Africa. However, several lines of evidence indicates the possibility that other *Plasmodium* species (e.g. *P. vivax*) may have already been in the "New World" prior to European colonization but there remains significant skepticism given shortcomings of the approaches used to address the question and the results of the Dorp et al. (2020) study referenced below, and the fact that no known malaria-resistance alleles are segregating in Indigenous South American individuals.

1451. Thevet, A. (1558). *Les singularitez de la France Antarctique, autrement nommée Amérique: & de plusieurs terres et isles Découvertes de nostre temps.* Maurice de La Porte.

1452. Mauny, R. (1953). Notes historiques autour des principales plantes cultivées d'Afrique occidentale. *Bulletin d l'institut français d'afrique noire 15,* 684–730.

1453. Yalcindag, E., Elguero, E., Arnathau, C., Durand, P., Akiana, J., Anderson, T. J., Aubouy, A., Balloux, F., Besnard, P., Bogreau, H., Carnevale, P., D'Alessandro, U., Fontenille, D., Gamboa, D., Jombart, T., le Mire, J., Leroy, E., Maestre, A., Mayxay, M., … Prugnolle, F. (2012). Multiple independent introductions of *Plasmodium falciparum* in South America. *Proceedings of the National Academy of Sciences*, *109*(2), 511–516. https://doi.org/10.1073/pnas.1119058109

1454. Rodrigues, P. T., Valdivia, H. O., de Oliveira, T. C., Alves, J. M. P., Duarte, A. M. R. C., Cerutti-Junior, C., Buery, J. C., Brito, C. F. A., de Souza, J. C., Hirano, Z. M. B., Bueno, M. G., Catão-Dias, J. L., Malafronte, R. S., Ladeia-Andrade, S., Mita, T., Santamaria, A. M., Calzada, J. E., Tantular, I. S., Kawamoto, F., … Ferreira, M. U. (2018). Human migration and the spread of malaria parasites to the New World. *Scientific Reports*, *8*(1), 1993. https://doi.org/10.1038/s41598-018-19554-0

1455. Loy, D. E., Plenderleith, L. J., Sundararaman, S. A., Liu, W., Gruszczyk, J., Chen, Y.-J., Trimboli, S., Learn, G. H., MacLean, O. A., Morgan, A. L. K., Li, Y., Avitto, A. N., Giles, J., Calvignac-Spencer, S., Sachse, A., Leendertz, F. H., Speede, S., Ayouba, A., Peeters, M., … Hahn, B. H. (2018). Evolutionary history of human *Plasmodium vivax* revealed by genome-wide analyses of related ape parasites. *Proceedings of the National Academy of Sciences*, *115*(36). https://doi.org/10.1073/pnas.1810053115

1456. van Dorp, L., Gelabert, P., Rieux, A., de Manuel, M., de-Dios, T., Gopalakrishnan, S., Carøe, C., Sandoval-Velasco, M., Fregel, R., Olalde, I., Escosa, R., Aranda, C., Huijben, S., Mueller, I., Marquès-Bonet, T., Balloux, F., Gilbert, M. T. P., & Lalueza-Fox, C. (2020). Plasmodium vivax Malaria Viewed through the Lens of an Eradicated European Strain. *Molecular Biology and Evolution*, *37*(3), 773–785. https://doi.org/10.1093/molbev/msz264

1457. Ankei, T. (2023). Diffusion of Cassava Detoxification in Africa: A Reconsideration of its Biocultural History. *African Study Monographs. Supplementary Issue.*, *61*, 93-138. https://doi.org/10.14989/282792 See page 95.

Page 208. *Under this idea.*

1458. Dunn, F. L. (1965). On the antiquity of malaria in the western hemisphere. *Human Biology*, *37(4)* 385-393. http://www.jstor.org/stable/41448749

Page 208. *Jackon's idea is that*. Gene-culture coevolution is the framing of this statement.

1459. Jackson, F. (1996). The coevolutionary relationship of humans and domesticated plants. *American Journal of Physical Anthropology*, *101*(S23), 161–176. https://onlinelibrary.wiley.com/doi/10.1002/(SICI)1096-8644(1996)23+%3C161::AID-AJPA6%3E3.0.CO;2-8

1460. Cavalli-Sforza, L. L., & Feldman, M. W. (1981). *Cultural transmission and evolution: A quantitative approach* (No. 16). Princeton University Press.

1461. Etkin, N. L. (2003). The co-evolution of people, plants, and parasites: biological and cultural adaptations to malaria. *Proceedings of the Nutrition Society*, *62*(2), 311–317. https://doi.org/10.1079/pns2003244

1462. Nabhan, G. P. (2013). Finding a Bean for Your Genes and a Buffer Against Malaria. In *Food, Genes, and Culture* (pp. 63–91). Island Press/Center for Resource Economics. https://doi.org/10.5822/978-1-61091-493-2_4

Page 208. *Like so many.*

1463. Weld, E. D., Waitt, C., Barnes, K., & Garcia Bournissen, F. (2022). Twice neglected? Neglected diseases in neglected populations. *British Journal of Clinical Pharmacology*, *88*(2), 367–373. https://doi.org/10.1111/bcp.15148

Page 209. *The bacteria living*.

1464. Beijerinck, M. W. (1901). Uber oligonitrophile mikroben. *Zentralbl. Bakterol. Parasitenkd. Infektionskr. Hyg. Abt. II.*, *7*, 561-582.

1465. Multari, S., Stewart, D., & Russell, W. R. (2015). Potential of Fava Bean as Future Protein Supply to Partially Replace Meat Intake in the Human Diet. *Comprehensive Reviews in Food Science and Food Safety*, *14*(5), 511–522. https://doi.org/10.1111/1541-4337.12146

Page 209. *Incidentally, a similar hemoglobin*.

1466. Impossible Foods. *What is soy leghemoglobin or heme?*. https://faq.impossiblefoods.com/hc/en-us/articles/360019100553-What-is-soy-leghemoglobin-or-heme-

1467. Impossible Foods. *How do you make heme?*. https://faq.impossiblefoods.com/hc/en-us/articles/360034767354

Page 209. *I can see why*. Note that fava, faba, and broad bean all refer to *Vicia faba*.

1468. Jayakodi, M., Golicz, A. A., Kreplak, J., Fechete, L. I., Angra, D., Bednář, P., Bornhofen, E., Zhang, H., Boussageon, R., Kaur, S., Cheung, K., Čížková, J., Gundlach, H., Hallab, A., Imbert, B., Keeble-Gagnère, G., Koblížková, A., Kobrlová, L., Krejčí, P., … Andersen, S. U. (2023). The giant diploid faba genome unlocks variation in a global protein crop. *Nature*, *615*(7953), 652–659. https://doi.org/10.1038/s41586-023-05791-5

Page 209. *Luckily, neither Shane*.

1469. Carson, P. E., Flanagan, C. L., Ickes, C. E., & Alving, A. S. (1956). Enzymatic Deficiency in Primaquine-Sensitive Erythrocytes. *Science*, *124*(3220), 484–485. https://doi.org/10.1126/science.124.3220.484.b

Page 210. *Intriguingly*.

1470. Hutton, J. E. (1937). Favism: an unusually observed type of hemolytic anemia. *Journal of the American Medical Association*, *109*(20), 1618-1620. https://doi.org/10.1001/jama.1937.02780460028007

1471. ALLISON, A. C. (1960). Glucose-6-Phosphate Dehydrogenase Deficiency in Red Blood Cells of East Africans. *Nature*, *186*(4724), 531–532. https://doi.org/10.1038/186531a0

1472. Motulsky, A. (1961). Glucose-6-phosphate-dehydrogenase deficiency, haemolytic disease of the newborn, and malaria. *The Lancet*, *277*(7187), 1168-1169. https://doi.org/10.1016/S0140-6736(61)92095-5

1473. Roth, E. F., Raventos-Suarez, C., Rinaldi, A., & Nagel, R. L. (1983). Glucose-6-phosphate dehydrogenase deficiency inhibits in vitro growth of Plasmodium falciparum. *Proceedings of the National Academy of Sciences*, *80*(1), 298–299. https://doi.org/10.1073/pnas.80.1.298

1474. Tishkoff, S. A., Varkonyi, R., Cahinhinan, N., Abbes, S., Argyropoulos, G., Destro-Bisol, G., Drousiotou, A., Dangerfield, B., Lefranc, G., Loiselet, J., Piro, A., Stoneking, M., Tagarelli, A., Tagarelli, G., Touma, E. H., Williams, S. M., & Clark, A. G. (2001). Haplotype Diversity and Linkage Disequilibrium at Human *G6PD* : Recent Origin of Alleles That Confer Malarial Resistance. *Science*, *293*(5529), 455–462. https://doi.org/10.1126/science.1061573

Page 211. *One theory is that people*.

1475. Huheey, J. E., & Martin, D. L. (1975). Malaria, favism and glucose-6-phosphate dehydrogenase deficiency. *Experientia*, *31*(10), 1145-1147. https://doi.org/10.1007/bf02326760

1476. Golenser, J., Miller, J., Spira, D., Navok, T., & Chevion, M. (1983). Inhibitory effect of a fava bean component on the in vitro development of Plasmodium falciparum in normal and glucose-6-phosphate dehydrogenase deficient erythrocytes. *Blood*, *61*(3), 507–510. https://doi.org/10.1182/blood.V61.3.507.507

1477. Clark, I. A., Cowden, W. B., Hunt, N. H., Maxwell, L. E., & Mackie, E. J. (1984). Activity of divicine in Plasmodium vinckei-infected mice has implications for treatment of favism and epidemiology of G-6-PD deficiency. *British Journal of Haematology*, *57*(3), 479–487. https://doi.org/10.1111/j.1365-2141.1984.tb02922.x

1478. Katz, S. H. (1990). An evolutionary theory of cuisine. *Human Nature*, *1*(3), 233–259. https://doi.org/10.1007/BF02733985

1479. Ginsburg, H., Atamna, H., Shalmiev, G., Kanaani, J., & Krugliak, M. (1996). Resistance of glucose-6-phosphate dehydrogenase deficiency to malaria: effects of fava bean hydroxypyrimidine glucosides on *Plasmodium falciparum* growth in culture and on the phagocytosis of infected cells. *Parasitology*, *113*(1), 7–18. https://doi.org/10.1017/S0031182000066221

Page 210 and 211. *But the cost of this benefit*.

1480. Robinson, P. (1941). Favism in children. *American Journal of Diseases of Children*, *62*(4), 701-707. https://doi.org/10.1001/archpedi.1941.02000160002001

1481. Sallares, R., Bouwman, A., & Anderung, C. (2004). The Spread of Malaria to Southern Europe in Antiquity: New Approaches to Old Problems. *Medical History*, *48*(3), 311–328. https://doi.org/10.1017/S0025727300007651

Page 211. *In book 8*.

1482. Arie, T. H. D. (1961). Pythagoras and the Beans. *British Medical Journal*, *2*(5253), 709.

1483. Moynahan, E. J. (1961). Pythagoras and the Beans. *British Medical Journal*, *2*(5256), 897.

1484. Scarborough, J. (1982). Beans, Pythagoras, Taboos, and Ancient Dietetics. *The Classical World*, *75*(6), 355. https://doi.org/10.2307/4349404

1485. Hatfield, G. (2000). Plants of Life, Plants of Death. *Folklore*, *111*(2), 317-317.

1486. Meletis, J., & Konstantopoulos, K. (2004). Favism-from the “avoid fava beans” of Pythagoras to the present. *Haema*, *7*(1), 17-21.

1487. Laertius, D. (2020). *Lives of the Eminent Philosophers: Compact Edition*. Oxford University Press.

Page 211. *Malaria is most virulent*.

1488. Robinson, P. (1941). Favism in children. *American Journal of Diseases of Children*, *62*(4), 701-707. https://doi.org/10.1001/archpedi.1941.02000160002001

1489. Wharton, H. J., & Duesselmann, W. (1947). Favism: A short review and report of a case. *New England Journal of Medicine*, *236*(26), 974–977. https://doi.org/10.1056/NEJM194706262362604

1490. Belsey, M. A. (1973). The epidemiology of favism. *Bulletin of the World Health Organization*, *48*(1), 1–13.

1491. Beutler, E. (2008). Glucose-6-phosphate dehydrogenase deficiency: a historical perspective. *Blood*, *111*(1), 16–24. https://doi.org/10.1182/blood-2007-04-077412

Page 211 and 212. *As happens with*.

1492. Belsey, M. A. (1973). The epidemiology of favism. *Bulletin of the World Health Organization*, *48*(1), 1–13.

1493. Kaplan, M., Vreman, H. J., Hammerman, C., Schimmel, M. S., Abrahamov, A., & Stevenson, D. K. (1998). Favism by proxy in nursing glucose-6-phosphate dehydrogenase-deficient neonates. *Journal of Perinatology: Official Journal of the California Perinatal Association*, *18*(6 Pt 1), 477-479.

Page 212. *The bitterness came from the*.

1494. de Keukeleire, J., Ooms, G., Heyerick, A., Roldan-Ruiz, I., van Bockstaele, E., & de Keukeleire, D. (2003). Formation and Accumulation of α-Acids, β-Acids, Desmethylxanthohumol, and Xanthohumol during Flowering of Hops (*Humulus lupulus* L.). *Journal of Agricultural and Food Chemistry*, *51*(15), 4436–4441. https://doi.org/10.1021/jf034263z

Page 212. *Hops from the hop plant*.

1495. DeLyser, D. Y., & Kasper, W. J. (1994). Hopped Beer: The Case for Cultivation. *Economic Botany*, *48*(2), 166–170. http://www.jstor.org/stable/4255609

1496. Moir, M. (2000). Hops—A Millennium Review. *Journal of the American Society of Brewing Chemists*, *58*(4), 131–146. https://doi.org/10.1094/ASBCJ-58-0131

1497. Sakamoto, K., & Konings, W. N. (2003). Beer spoilage bacteria and hop resistance. *International Journal of Food Microbiology*, *89*(2–3), 105–124. https://doi.org/10.1016/S0168-1605(03)00153-3

1498. Patterson, M. W., & Hoalst-Pullen, N. (2014). Geographies of beer. In *The geography of beer: Regions, environment, and societies* (pp. 1-5). Dordrecht: Springer Netherlands. https://doi.org/10.1007/978-94-007-7787-3

Page 212. *Science demands a more general.*

1499. Sullivan, R. J., Hagen, E. H., & Hammerstein, P. (2008). Revealing the paradox of drug reward in human evolution. *Proceedings of the Royal Society B: Biological Sciences*, *275*(1640), 1231–1241. https://doi.org/10.1098/rspb.2007.1673

1500. Hagen, E. H., Sullivan, R. J., Schmidt, R., Morris, G., Kempter, R., & Hammerstein, P. (2009). Ecology and neurobiology of toxin avoidance and the paradox of drug reward. *Neuroscience*, *160*(1), 69–84. https://doi.org/10.1016/j.neuroscience.2009.01.077

Page 213. *A backup system.*

1501. Borison, H. L., Borison, R., & McCarthy, L. E. (1984). Role of the area postrema in vomiting and related functions. *Federation Proceedings*, *43*(15), 2955–2958.

1502. Glendinning, J. I. (2007). How Do Predators Cope With Chemically Defended Foods? *The Biological Bulletin*, *213*(3), 252–266. https://doi.org/10.2307/25066643

Page 213. *Our brain is protected.*

1503. Daneman, R., & Prat, A. (2015). The Blood–Brain Barrier. *Cold Spring Harbor Perspectives in Biology*, *7*(1), a020412. https://doi.org/10.1101/cshperspect.a020412

Pager 213. *We then avoid toxins.*

1504. Bernstein, I. L., & Webster, M. M. (1980). Learned taste aversions in humans. *Physiology & Behavior*, *25*(3), 363–366. https://doi.org/10.1016/0031-9384(80)90274-7

1505. Logue, A. W., Ophir, I., & Strauss, K. E. (1981). The acquisition of taste aversions in humans. *Behaviour Research and Therapy*, *19*(4), 319–333. https://doi.org/10.1016/0005-7967(81)90053-X

Page 213. *While nearly all toxins impart*.

1506. Glendinning, J. I. (1994). Is the bitter rejection response always adaptive? *Physiology & Behavior*, *56*(6), 1217–1227. https://doi.org/10.1016/0031-9384(94)90369-7

Page 214 and 215. *Physiologist John Glendinning*. These references support the next six paragraphs as well.

1507. Freeland, W. J., & Janzen, D. H. (1974). Strategies in Herbivory by Mammals: The Role of Plant Secondary Compounds. *The American Naturalist*, *108*(961), 269–289. https://doi.org/10.1086/282907

1508. Glendinning, J. I. (1994). Is the bitter rejection response always adaptive? *Physiology & Behavior*, *56*(6), 1217–1227. https://doi.org/10.1016/0031-9384(94)90369-7

Page 215 and 216.

1509. Jermy, T., Bernays, E. A., & Szentesi, A. (1982). The effect of repeated exposure to feeding deterrents on their acceptability to phytophagous insects. In *5th International Symposium on Insect-Plant Relationships (ed. by JH Visser & AK Minks)* (pp. 25-32).

1510. Skopec, M. M., Hagerman, A. E., & Karasov, W. H. (2004). Do Salivary Proline-Rich Proteins Counteract Dietary Hydrolyzable Tannin in Laboratory Rats? *Journal of Chemical Ecology*, *30*(9), 1679–1692. https://doi.org/10.1023/B:JOEC.0000042395.31307.be

Page 216. *And like oak gall wasps*.

1511. Athanasiadou, S., Kyriazakis, I., Jackson, F., & Coop, R. L. (2000). Effects of short-term exposure to condensed tannins on adult Trichostrongylus colubriformis. *Veterinary Record*, *146*(25), 728–732. https://doi.org/10.1136/vr.146.25.728

1512. Athanasiadou, S., Kyriazakis, I., Jackson, F., & Coop, R. L. (2001). Direct anthelmintic effects of condensed tannins towards different gastrointestinal nematodes of sheep: in vitro and in vivo studies. *Veterinary Parasitology*, *99*(3), 205–219. https://doi.org/10.1016/S0304-4017(01)00467-8

1513. Lisonbee, L. D., Villalba, J. J., Provenza, F. D., & Hall, J. O. (2009). Tannins and self-medication: Implications for sustainable parasite control in herbivores. *Behavioural Processes*, *82*(2), 184–189. https://doi.org/10.1016/j.beproc.2009.06.009

Page 216. *Carnivores tend to have.*

1514. Kim, S., Cho, Y. S., Kim, H.-M., Chung, O., Kim, H., Jho, S., Seomun, H., Kim, J., Bang, W. Y., Kim, C., An, J., Bae, C. H., Bhak, Y., Jeon, S., Yoon, H., Kim, Y., Jun, J., Lee, H., Cho, S., … Yeo, J.-H. (2016). Comparison of carnivore, omnivore, and herbivore mammalian genomes with a new leopard assembly. *Genome Biology*, *17*(1), 211. https://doi.org/10.1186/s13059-016-1071-4

1515. Hecker, N., Sharma, V., & Hiller, M. (2019). Convergent gene losses illuminate metabolic and physiological changes in herbivores and carnivores. *Proceedings of the National Academy of Sciences*, *116*(8), 3036–3041. https://doi.org/10.1073/pnas.1818504116

Page 216 and 217. *As any cat or dog owner knows.*

1516. ASPCA. (n.d.). *Toxic and Non-Toxic Plant List - Dogs*. Animal Poison Control. https://www.aspca.org/pet-care/animal-poison-control/dogs-plant-list

1517. ASPCA. (n.d.). *Toxic and Non-Toxic Plant List - Cats*. Animal Poison Control. https://www.aspca.org/pet-care/animal-poison-control/cats-plant-list

Page 217. *For example, grapes.*

1518. Wegenast, C. A., Meadows, I. D., Anderson, R. E., Southard, T., González Barrientos, C. R., & Wismer, T. A. (2022). Acute kidney injury in dogs following ingestion of cream of tartar and tamarinds and the connection to tartaric acid as the proposed toxic principle in grapes and raisins. *Journal of Veterinary Emergency and Critical Care*, *32*(6), 812–816. https://doi.org/10.1111/vec.13234

Page 217. *Another well-known.*

1519. Gruhzit, O. M. (1931). Anemia in dogs produced by feeding disulphide compounds. *Am. J. Med. Sci.*, *181*, 815-820.

1520. Hill, A. S., O'Neill, S., Rogers, Q. R., & Christopher, M. M. (2001). Antioxidant prevention of Heinz body formation and oxidative injury in cats.

American Journal of Veterinary Research, *62*(3), 370–374. https://doi.org/10.2460/ajvr.2001.62.370

1521. Tang, X., Xia, Z., & Yu, J. (2008). An experimental study of hemolysis induced by onion (*Allium cepa*) poisoning in dogs. *Journal of Veterinary Pharmacology and Therapeutics*, *31*(2), 143–149. https://doi.org/10.1111/j.1365-2885.2007.00930.x

Page 217. *Few children*.

1522. Repacholi, B. M., & Gopnik, A. (1997). Early reasoning about desires: Evidence from 14- and 18-month-olds. *Developmental Psychology*, *33*(1), 12–21. https://doi.org/10.1037/0012-1649.33.1.12

1523. Mennella, J. A., Pepino, M. Y., & Reed, D. R. (2005). Genetic and Environmental Determinants of Bitter Perception and Sweet Preferences. *Pediatrics*, *115*(2), e216–e222. https://doi.org/10.1542/peds.2004-1582

1524. Bell, K. I., & Tepper, B. J. (2006). Short-term vegetable intake by young children classified by 6- n-propylthoiuracil bitter-taste phenotypey. *The American Journal of Clinical Nutrition*, *84*(1), 245–251. https://doi.org/10.1093/ajcn/84.1.245

Page 217. *Omnivorous dogs like to eat*.

1525. Bradshaw, J. W. S. (2006). The Evolutionary Basis for the Feeding Behavior of Domestic Dogs (Canis familiaris) and Cats (Felis catus). *The Journal of Nutrition*, *136*(7), 1927S-1931S. https://doi.org/10.1093/jn/136.7.1927S

1526. Bosch, G., Hagen-Plantinga, E. A., & Hendriks, W. H. (2015). Dietary nutrient profiles of wild wolves: insights for optimal dog nutrition? *British Journal of Nutrition*, *113*(S1), S40–S54. https://doi.org/10.1017/S0007114514002311

Page 217. *Wolves in Minnesota*.

1527. Gable, T. D., Windels, S. K., & Bruggink, J. G. (2017). Estimating Biomass of Berries Consumed by Gray Wolves. *Wildlife Society Bulletin*, *41*(1), 129–131. https://www.jstor.org/stable/90003996

1528. Homkes, A. T., Gable, T. D., Windels, S. K., & Bump, J. K. (2020). Berry Important? Wolf Provisions Pups with Berries in Northern Minnesota. *Wildlife Society Bulletin*, *44*(1), 221–223. https://doi.org/10.1002/wsb.1065

Page 217 and 218. *As they began*.

1529. Perry, G. H., Dominy, N. J., Claw, K. G., Lee, A. S., Fiegler, H., Redon, R., Werner, J., Villanea, F. A., Mountain, J. L., Misra, R., Carter, N. P., Lee, C., & Stone, A. C. (2007). Diet and the evolution of human amylase gene copy number variation. *Nature Genetics*, *39*(10), 1256–1260. https://doi.org/10.1038/ng2123

1530. Axelsson, E., Ratnakumar, A., Arendt, M.-L., Maqbool, K., Webster, M. T., Perloski, M., Liberg, O., Arnemo, J. M., Hedhammar, Å., & Lindblad-Toh, K. (2013). The genomic signature of dog domestication reveals adaptation to a starch-rich diet. *Nature*, *495*(7441), 360–364. https://doi.org/10.1038/nature11837

Page 218. *Despite our shared*.

1531. ASPCA. (n.d.). *Toxic and Non-Toxic Plant List - Dogs*. Animal Poison Control. https://www.aspca.org/pet-care/animal-poison-control/dogs-plant-list

Page 218. *Dogs began to diverge*.

1532. Bergström, A., Stanton, D. W. G., Taron, U. H., Frantz, L., Sinding, M.-H. S., Ersmark, E., Pfrengle, S., Cassatt-Johnstone, M., Lebrasseur, O., Girdland-Flink, L., Fernandes, D. M., Ollivier, M., Speidel, L., Gopalakrishnan, S., Westbury, M. v., Ramos-Madrigal, J., Feuerborn, T. R., Reiter, E., Gretzinger, J., … Skoglund, P. (2022). Grey wolf genomic history reveals a dual ancestry of dogs. *Nature*, *607*(7918), 313–320. https://doi.org/10.1038/s41586-022-04824-9

Page 218. *Although our first*.

1533. Fleagle, J. G., Bown, T. M., Obradovich, J. D., & Simons, E. L. (1986). Age of the Earliest African Anthropoids. *Science*, *234*(4781), 1247–1249. https://doi.org/10.1126/science.234.4781.1247

1534. Dudley, R. (2004). Ethanol, Fruit Ripening, and the Historical Origins of Human Alcoholism in Primate Frugivory. *Integrative and Comparative Biology*, *44*(4), 315–323. https://doi.org/10.1093/icb/44.4.315

1535. Kay, R. F., Ross, C., & Williams, B. A. (1997). Anthropoid Origins. *Science*, *275*(5301), 797–804. https://doi.org/10.1126/science.275.5301.797

1536. Milton, K. (1999). A hypothesis to explain the role of meat-eating in human evolution. *Evolutionary Anthropology Issues News and Reviews*, *8*(1), 11-21. https://doi.org/10.1002/(SICI)1520-6505(1999)8:1<11::AID-EVAN6>3.0.CO;2-M

1537. Milton, K. (1999). Nutritional characteristics of wild primate foods: do the diets of our closest living relatives have lessons for us? *Nutrition*, *15*(6), 488–498. https://doi.org/10.1016/S0899-9007(99)00078-7

1538. Ni, X., Gebo, D. L., Dagosto, M., Meng, J., Tafforeau, P., Flynn, J. J., & Beard, K. C. (2013). The oldest known primate skeleton and early haplorhine evolution. *Nature*, *498*(7452), 60–64. https://doi.org/10.1038/nature12200

Page 218 and 219. *Then something remarkable.*

1539. Antón, S. C. (2003). Natural history of Homo erectus. *American Journal of Physical Anthropology*, *122(S37)*, 126–170. https://doi.org/10.1002/ajpa.10399

1540. White, T. D., Asfaw, B., Beyene, Y., Haile-Selassie, Y., Lovejoy, C. O., Suwa, G., & WoldeGabriel, G. (2009). *Ardipithecus ramidus* and the Paleobiology of Early Hominids. *Science*, *326*(5949), 64–86. https://doi.org/10.1126/science.1175802

1541. Suwa, G., Asfaw, B., Kono, R. T., Kubo, D., Lovejoy, C. O., & White, T. D. (2009). The *Ardipithecus ramidus* Skull and Its Implications for Hominid Origins. *Science*, *326*(5949), 68. https://doi.org/10.1126/science.1175825

1542. Hatala, K. G., Roach, N. T., Ostrofsky, K. R., Wunderlich, R. E., Dingwall, H. L., Villmoare, B. A., Green, D. J., Harris, J. W. K., Braun, D. R., & Richmond, B. G. (2016). Footprints reveal direct evidence of group behavior and locomotion in Homo erectus. *Scientific Reports*, *6*(1), 28766. https://doi.org/10.1038/srep28766

Page 219. *The brain size of H. erectus.*

1543. Erbsloh, F., Bernsmeier, A., & Hillesheim, H. (1958). [The glucose consumption of the brain & its dependence on the liver]. *Archiv fur Psychiatrie und Nervenkrankheiten, vereinigt mit Zeitschrift fur die gesamte Neurologie und Psychiatrie*, *196*(6), 611-626. https://doi.org/10.1007/bf00344388

1544. Fonseca-Azevedo, K., & Herculano-Houzel, S. (2012). Metabolic constraint imposes tradeoff between body size and number of brain neurons in human evolution. *Proceedings of the National Academy of Sciences*, *109*(45), 18571–18576. https://doi.org/10.1073/pnas.1206390109

1545. Rizal, Y., Westaway, K. E., Zaim, Y., van den Bergh, G. D., Bettis, E. A., Morwood, M. J., Huffman, O. F., Grün, R., Joannes-Boyau, R., Bailey, R. M., Sidarto, Westaway, M. C., Kurniawan, I., Moore, M. W., Storey, M., Aziz, F., Suminto, Zhao, J., Aswan, … Ciochon, R. L. (2020). Last appearance of Homo erectus at Ngandong, Java, 117,000–108,000 years ago. *Nature*, *577*(7790), 381–385. https://doi.org/10.1038/s41586-019-1863-2

Page 219. *There is some evidence*. These references also support the next paragraph.

1546. Aiello, L. C., & Wheeler, P. (1995). The Expensive-Tissue Hypothesis: The Brain and the Digestive System in Human and Primate Evolution. *Current Anthropology*, *36*(2), 199–221. https://doi.org/10.1086/204350

1547. Wrangham, R. W., Jones, J. H., Laden, G., Pilbeam, D., & Conklin-Brittain, N. (1999). The Raw and the Stolen. *Current Anthropology*, *40*(5), 567–594. https://doi.org/10.1086/300083

1548. Kaufman, J. A., Marcel Hladik, C., & Pasquet, P. (2003). On the Expensive-Tissue Hypothesis: Independent Support from Highly Encephalized Fish. *Current Anthropology*, *44*(5), 705–707. https://doi.org/10.1086/379258

1549. Wrangham, R., & Conklin-Brittain, N. (2003).'Cooking as a biological trait. *Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology*, *136*(1), 35–46. https://doi.org/10.1016/S1095-6433(03)00020-5

1550. Gorman, R. M. (2008). Cooking Up Bigger Brains. *Scientific American*, *298*(1), 102–105. https://doi.org/10.1038/scientificamerican0108-102

1551. Wobber, V., Hare, B., & Wrangham, R. (2008). Great apes prefer cooked food. *Journal of Human Evolution*, *55*(2), 340–348. https://doi.org/10.1016/j.jhevol.2008.03.003

1552. Wrangham, R. (2009). *Catching fire: how cooking made us human*. Basic books.

1553. Carmody, R. N., & Wrangham, R. W. (2009). The energetic significance of cooking. *Journal of Human Evolution*, *57*(4), 379–391. https://doi.org/10.1016/j.jhevol.2009.02.011

1554. Wrangham, R., & Carmody, R. (2010). Human adaptation to the control of fire. *Evolutionary Anthropology: Issues, News, and Reviews*, *19*(5), 187–199. https://doi.org/10.1002/evan.20275

1555. Carmody, R. N., Weintraub, G. S., & Wrangham, R. W. (2011). Energetic consequences of thermal and nonthermal food processing. *Proceedings of the National Academy of Sciences*, *108*(48), 19199–19203. https://doi.org/10.1073/pnas.1112128108

1556. Carmody, R. N., Weintraub, G. S., & Wrangham, R. W. (2012). Reply to Wollstonecroft et al.: Cooking increases the bioavailability of starch from diverse plant sources. *Proceedings of the National Academy of Sciences*, *109*(17). https://doi.org/10.1073/pnas.1202327109

1557. Gowlett, J. A. J., & Wrangham, R. W. (2013). Earliest fire in Africa: towards the convergence of archaeological evidence and the cooking hypothesis. *Azania: Archaeological Research in Africa*, *48*(1), 5–30. https://doi.org/10.1080/0067270X.2012.756754

1558. Tsuboi, M., Husby, A., Kotrschal, A., Hayward, A., Buechel, S. D., Zidar, J., Løvlie, H., & Kolm, N. (2015). Comparative support for the expensive tissue hypothesis: Big brains are correlated with smaller gut and greater parental investment in Lake Tanganyika cichlids. *Evolution*, *69*(1), 190–200. https://doi.org/10.1111/evo.12556

1559. Groopman, E. E., Carmody, R. N., & Wrangham, R. W. (2015). Cooking increases net energy gain from a lipid-rich food. *American Journal of Physical Anthropology*, *156*(1), 11–18. https://doi.org/10.1002/ajpa.22622

1560. Carmody, R. N., Dannemann, M., Briggs, A. W., Nickel, B., Groopman, E. E., Wrangham, R. W., & Kelso, J. (2016). Genetic Evidence of Human Adaptation to a Cooked Diet. *Genome Biology and Evolution*, *8*(4), 1091–1103. https://doi.org/10.1093/gbe/evw059

1561. Liao, W. B., Lou, S. L., Zeng, Y., & Kotrschal, A. (2016). Large Brains, Small Guts: The Expensive Tissue Hypothesis Supported within Anurans. *The American Naturalist*, *188*(6), 693–700. https://doi.org/10.1086/688894

Page 220. *More important for the purposes of this book*.

1562. Johns, T., & Duquette, M. (1991). Traditional detoxification of acorn bread with clay. *Ecology of Food and Nutrition*, *25*(3), 221–228. https://doi.org/10.1080/03670244.1991.9991170

Page 220. *Even though they are smaller*.

1563. Goyal, M. S., Hawrylycz, M., Miller, J. A., Snyder, A. Z., & Raichle, M. E. (2014). Aerobic Glycolysis in the Human Brain Is Associated with Development and Neotenous Gene Expression. *Cell Metabolism*, *19*(1), 49–57. https://doi.org/10.1016/j.cmet.2013.11.020

1564. Goyal, M. S., & Raichle, M. E. (2018). Glucose Requirements of the Developing Human Brain. *Journal of Pediatric Gastroenterology & Nutrition*, *66*(3), S46–S49. https://doi.org/10.1097/MPG.0000000000001875

Page 220. *Although people show much variation*.

1565. Thompson, D. A., Moskowitz, H. R., & Campbell, R. G. (1976). Effects of body weight and food intake on pleasantness ratings for a sweet stimulus. *Journal of Applied Physiology*, *41*(1), 77–83. https://doi.org/10.1152/jappl.1976.41.1.77

1566. Braun, T. D., Kunicki, Z. J., Blevins, C. E., Stein, M. D., Marsh, E., Feltus, S., Miranda, R., Thomas, J. G., & Abrantes, A. M. (2021). Prospective Associations between Attitudes toward Sweet Foods, Sugar Consumption, and Cravings for Alcohol and Sweets in Early Recovery from Alcohol Use Disorders. *Alcoholism Treatment Quarterly*, *39*(3), 269–281. https://doi.org/10.1080/07347324.2020.1868958

Page 221. *An underactive*. This reference applies to the next paragraph as well.

1567. Garbutt, J. C., Kampov-Polevoy, A. B., Kalka-Juhl, L. S., & Gallop, R. J. (2016). Association of the Sweet-Liking Phenotype and Craving for Alcohol With the Response to Naltrexone Treatment in Alcohol Dependence. *JAMA Psychiatry*, *73*(10), 1056. https://doi.org/10.1001/jamapsychiatry.2016.2157

1568. Bouhlal, S., Farokhnia, M., Lee, M. R., Akhlaghi, F., & Leggio, L. (2018). Identifying and Characterizing Subpopulations of Heavy Alcohol Drinkers Via a Sucrose Preference Test: A Sweet Road to a Better Phenotypic Characterization? *Alcohol and Alcoholism*, *53*(5), 560–569. https://doi.org/10.1093/alcalc/agy048

1569. Iatridi, V., Hayes, J. E., & Yeomans, M. R. (2019). Reconsidering the classification of sweet taste liker phenotypes: A methodological review. *Food Quality and Preference*, *72*, 56–76. https://doi.org/10.1016/j.foodqual.2018.09.001

1570. Braun, T. D., Kunicki, Z. J., Blevins, C. E., Stein, M. D., Marsh, E., Feltus, S., Miranda, R., Thomas, J. G., & Abrantes, A. M. (2021). Prospective Associations between Attitudes toward Sweet Foods, Sugar Consumption, and Cravings for Alcohol and Sweets in Early Recovery from Alcohol Use Disorders. *Alcoholism Treatment Quarterly*, *39*(3), 269–281. https://doi.org/10.1080/07347324.2020.1868958

Page 222. *In search of glucose*. The preferences or lack thereof for raw vs. cooked vegetables is highly nuanced. For example, in one study there was no significant difference between raw carrots vs. carrots that were boiled or oven-baked, there was a significant preference for raw tomatoes vs. cooked tomatoes, and there was a preference for cooked spinach over raw spinach (Donadini et al. 2012).

1571. Lawless, H. (1985). Sensory development in children: Research in taste and olfaction. *Journal of the American Dietetic Association*, *85*(5), 577–583. https://doi.org/10.1016/S0002-8223(21)03656-7

1572. Birch, L. L., McPhee, L., Steinberg, L., & Sullivan, S. (1990). Conditioned flavor preferences in young children. *Physiology & Behavior*, *47*(3), 501–505. https://doi.org/10.1016/0031-9384(90)90116-L

1573. Baxter, I. A., & Schroder, M. J. A. (1997). Vegetable consumption among Scottish children: a review of the determinants and proposed strategies to overcome low consumption. *British Food Journal*, *99*(10), 380–387. https://doi.org/10.1108/00070709710195167

1574. Nicklaus, S., Boggio, V., Chabanet, C., & Issanchou, S. (2004). A prospective study of food preferences in childhood. *Food Quality and Preference*, *15*(7–8), 805–818. https://doi.org/10.1016/j.foodqual.2004.02.010

1575. Cooke, L. J., & Wardle, J. (2005). Age and gender differences in children's food preferences. *British Journal of Nutrition*, *93*(5), 741–746. https://doi.org/10.1079/BJN20051389\

1576. Donadini, G., Fumi, M. D., & Porretta, S. (2012). Influence of preparation method on the hedonic response of preschoolers to raw, boiled or oven-baked vegetables. *LWT - Food Science and Technology*, *49*(2), 282–292. https://doi.org/10.1016/j.lwt.2012.07.019

1577. Poelman, A. A. M., Delahunty, C. M., & de Graaf, C. (2013). Cooking time but not cooking method affects children's acceptance of Brassica vegetables. *Food Quality and Preference*, *28*(2), 441–448. https://doi.org/10.1016/j.foodqual.2012.12.003

Page 222. *Like most other people*.

1578. Bell, K. I., & Tepper, B. J. (2006). Short-term vegetable intake by young children classified by 6- n-propylthoiuracil bitter-taste phenotypey. *The American Journal of Clinical Nutrition*, *84*(1), 245–251. https://doi.org/10.1093/ajcn/84.1.245

1579. Anzman-Frasca, S., Savage, J. S., Marini, M. E., Fisher, J. O., & Birch, L. L. (2012). Repeated exposure and associative conditioning promote preschool children's liking of vegetables. *Appetite*, *58*(2), 543–553. https://doi.org/10.1016/j.appet.2011.11.012

1580. Dominguez, P. R. (2013). Development and Acquisition of Flavor and Food Preferences in Children: An Update Until 2010. *Journal of Food Research*, *3*(1), 1. https://doi.org/10.5539/jfr.v3n1p1

Page 222 and 223. *Anthropologists Edward Hagen*. These references apply to the next five paragraphs as well. Note that the data cited by Hagen et al. (2013) are from: Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention (1999-2010).

1581. CDC. (n.d.). *NHANES Questionnaires, Datasets, and Related Documentation*. National Health and Nutrition Examination Survey. https://wwwn.cdc.gov/nchs/nhanes/Default.aspx

1582. Sullivan, R. J., & Hagen, E. H. (2002). Psychotropic substance-seeking: evolutionary pathology or adaptation? *Addiction*, *97*(4), 389–400. https://doi.org/10.1046/j.1360-0443.2002.00024.x

1583. Sullivan, R. J., Hagen, E. H., & Hammerstein, P. (2008). Revealing the paradox of drug reward in human evolution. *Proceedings of the Royal Society B: Biological Sciences*, *275*(1640), 1231–1241. https://doi.org/10.1098/rspb.2007.1673

1584. Degenhardt, L., Chiu, W.-T., Sampson, N., Kessler, R. C., Anthony, J. C., Angermeyer, M., Bruffaerts, R., de Girolamo, G., Gureje, O., Huang, Y., Karam, A., Kostyuchenko, S., Lepine, J. P., Mora, M. E. M., Neumark, Y., Ormel, J. H., Pinto-Meza, A., Posada-Villa, J., Stein, D. J., … Wells, J. E. (2008). Toward a Global View of Alcohol, Tobacco, Cannabis, and Cocaine Use: Findings from the WHO World Mental Health Surveys. *PLoS Medicine*, *5*(7), e141. https://doi.org/10.1371/journal.pmed.0050141

1585. Hagen, E. H., Roulette, C. J., & Sullivan, R. J. (2013). Explaining Human Recreational Use of 'pesticides': The Neurotoxin Regulation Model of Substance Use vs. the Hijack Model and Implications for Age and Sex Differences in Drug Consumption. *Frontiers in Psychiatry*, *4*. https://doi.org/10.3389/fpsyt.2013.00142

1586. Hagen, E. H., & Tushingham, S. (2019). The prehistory of psychoactive drug use. In *Handbook of cognitive archaeology* (pp. 471-498). Routledge.

1587. Hagen, E. H., Blackwell, A. D., Lightner, A. D., & Sullivan, R. J. (2023). *Homo medicus* : The transition to meat eating increased pathogen pressure and the use of pharmacological plants in *Homo*. *American Journal of Biological Anthropology*, *180*(4), 589–617. https://doi.org/10.1002/ajpa.24718

Page 223. *Yet there is virtually no coffee*.

1588. Knight, C. A., Knight, I., Mitchell, D. C., & Zepp, J. E. (2004). Beverage caffeine intake in US consumers and subpopulations of interest: estimates from the Share of Intake Panel survey. *Food and Chemical Toxicology*, *42*(12), 1923–1930. https://doi.org/10.1016/j.fct.2004.05.002

Page 223. *The best explanation*.

1589. Lawless, H. (1985). Sensory development in children: Research in taste and olfaction. *Journal of the American Dietetic Association*, *85*(5), 577–583. https://doi.org/10.1016/S0002-8223(21)03656-7

1590. Bartoshuk, L. M., Duffy, V. B., & Miller, I. J. (1994). PTC/PROP tasting: Anatomy, psychophysics, and sex effects. *Physiology & Behavior*, *56*(6), 1165–1171. https://doi.org/10.1016/0031-9384(94)90361-1

1591. Prutkin, J., Duffy, V. B., Etter, L., Fast, K., Gardner, E., Lucchina, L. A., Snyder, D. J., Tie, K., Weiffenbach, J., & Bartoshuk, L. M. (2000). Genetic variation and inferences about perceived taste intensity in mice and men. *Physiology & Behavior*, *69*(1–2), 161–173. https://doi.org/10.1016/S0031-9384(00)00199-2

1592. Segovia, C., Hutchinson, I., Laing, D. G., & Jinks, A. L. (2002). A quantitative study of fungiform papillae and taste pore density in adults and children. *Developmental Brain Research*, *138*(2), 135–146. https://doi.org/10.1016/S0165-3806(02)00463-7

1593. Wardle, J., & Cooke, L. (2008). Genetic and environmental determinants of children's food preferences. *British Journal of Nutrition*, *99*(S1), S15–S21. https://doi.org/10.1017/S000711450889246X

1594. Dovey, T. M., Staples, P. A., Gibson, E. L., & Halford, J. C. G. (2008). Food neophobia and 'picky/fussy' eating in children: A review. *Appetite*, *50*(2–3), 181–193. https://doi.org/10.1016/j.appet.2007.09.009

1595. Mennella, J. A., & Bobowski, N. K. (2015). The sweetness and bitterness of childhood: Insights from basic research on taste preferences. *Physiology & Behavior*, *152*, 502–507. https://doi.org/10.1016/j.physbeh.2015.05.015

1596. Hoffman, A. C., Salgado, R. V., Dresler, C., Faller, R. W., & Bartlett, C. (2016). Flavour preferences in youth versus adults: a review. *Tobacco Control*, *25*(Suppl 2), ii32–ii39. https://doi.org/10.1136/tobaccocontrol-2016-053192

Page 224. *Intriguingly, researchers have also found*.

1597. Bartoshuk, L. M., Duffy, V. B., & Miller, I. J. (1994). PTC/PROP tasting: Anatomy, psychophysics, and sex effects. *Physiology & Behavior*, *56*(6), 1165–1171. https://doi.org/10.1016/0031-9384(94)90361-1

Page 224. *The vast majority*.

1598. Hook, E. (1978). Dietary cravings and aversions during pregnancy. *The American Journal of Clinical Nutrition*, *31*(8), 1355–1362. https://doi.org/10.1093/ajcn/31.8.1355

1599. Profet, M. (1992). Pregnancy sickness as adaptation: A deterrent to maternal ingestion of teratogens. In J. H. Barkow, L. Cosmides, & J. Tooby (Eds.), *The adapted mind: Evolutionary psychology and the generation of culture* (pp. 327–365). Oxford University Press.

1600. Kölble, N., Hummel, T., von Mering, R., Huch, A., & Huch, R. (2001). Gustatory and olfactory function in the first trimester of pregnancy. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, *99*(2), 179–183. https://doi.org/10.1016/S0301-2115(01)00408-0

1601. Nordin, S., Broman, D. A., Olofsson, J. K., & Wulff, M. (2004). A longitudinal descriptive study of self-reported abnormal smell and taste perception in pregnant women. *Chemical Senses*, *29*(5), 391–402. https://doi.org/10.1093/chemse/bjh040

1602. Lawson, C. C., LeMasters, G. K., & Wilson, K. A. (2004). Changes in caffeine consumption as a signal of pregnancy. *Reproductive Toxicology*, *18*(5), 625–633. https://doi.org/10.1016/j.reprotox.2004.03.004

1603. Pepper, G. v, & Craig Roberts, S. (2006). Rates of nausea and vomiting in pregnancy and dietary characteristics across populations. *Proceedings of the Royal Society B: Biological Sciences*, *273*(1601), 2675–2679. https://doi.org/10.1098/rspb.2006.3633

1604. Patil, C. L., Abrams, E. T., Steinmetz, A. R., & Young, S. L. (2012). Appetite Sensations and Nausea and Vomiting in Pregnancy: An Overview of the Explanations. *Ecology of Food and Nutrition*, *51*(5), 394–417. https://doi.org/10.1080/03670244.2012.696010

1605. Hagen, E. H., Roulette, C. J., & Sullivan, R. J. (2013). Explaining Human Recreational Use of 'pesticides': The Neurotoxin Regulation Model of Substance Use vs. the Hijack Model and Implications for Age and Sex Differences in Drug Consumption. *Frontiers in Psychiatry*, *4*. https://doi.org/10.3389/fpsyt.2013.00142

1606. Isoherranen, N., & Thummel, K. E. (2013). Drug Metabolism and Transport During Pregnancy: How Does Drug Disposition Change during Pregnancy and What Are the Mechanisms that Cause Such Changes? *Drug Metabolism and Disposition*, *41*(2), 256–262. https://doi.org/10.1124/dmd.112.050245

Page 224. *For example*.

1607. James, J. E. (2021). Maternal caffeine consumption and pregnancy outcomes: a narrative review with implications for advice to mothers and mothers-to-be. *BMJ Evidence-Based Medicine*, *26*(3), 114–115. https://doi.org/10.1136/bmjebm-2020-111432

Page 224. *Thalidomide*. As discussed in Hagen et al. (2013).

1608. von Moos, R., Stolz, R., Cerny, T., & Gillessen, S. (2003). Thalidomide: from tragedy to promise. *Swiss Medical Weekly*, *133*(5–6), 77–87. https://doi.org/10.4414/smw.2003.09947

1609. Hagen, E. H., Roulette, C. J., & Sullivan, R. J. (2013). Explaining Human Recreational Use of 'pesticides': The Neurotoxin Regulation Model of Substance Use vs. the Hijack Model and Implications for Age and Sex Differences in Drug Consumption. *Frontiers in Psychiatry*, *4*. https://doi.org/10.3389/fpsyt.2013.00142

Page 224 and 224. *Ethanol, nicotine*.

1610. Ozturk, F., Sheldon, E., Sharma, J., Canturk, K. M., Otu, H. H., & Nawshad, A. (2016). Nicotine Exposure During Pregnancy Results in Persistent Midline Epithelial Seam With Improper Palatal Fusion. *Nicotine & Tobacco Research*, *18*(5), 604–612. https://doi.org/10.1093/ntr/ntv227

1611. Hoyme, H. E., Kalberg, W. O., Elliott, A. J., Blankenship, J., Buckley, D., Marais, A.-S., Manning, M. A., Robinson, L. K., Adam, M. P., Abdul-Rahman, O., Jewett, T., Coles, C. D., Chambers, C., Jones, K. L., Adnams, C. M., Shah, P. E., Riley, E. P., Charness, M. E., Warren, K. R., & May, P. A. (2016). Updated Clinical Guidelines for Diagnosing Fetal Alcohol Spectrum Disorders. *Pediatrics*, *138*(2). https://doi.org/10.1542/peds.2015-4256

1612. McGrath-Morrow, S. A., Gorzkowski, J., Groner, J. A., Rule, A. M., Wilson, K., Tanski, S. E., Collaco, J. M., & Klein, J. D. (2020). The Effects of Nicotine on Development. *Pediatrics*, *145*(3). https://doi.org/10.1542/peds.2019-1346

Page 225. *Hagen and collaborators*.

1613. Hagen, E. H., Roulette, C. J., & Sullivan, R. J. (2013). Explaining Human Recreational Use of 'pesticides': The Neurotoxin Regulation Model of Substance Use vs. the Hijack Model and Implications for Age and Sex Differences in Drug Consumption. *Frontiers in Psychiatry*, *4*. https://doi.org/10.3389/fpsyt.2013.00142

Page 226. *The paradox of drug reward*.

1614. Sullivan, R. J., Hagen, E. H., & Hammerstein, P. (2008). Revealing the paradox of drug reward in human evolution. *Proceedings of the Royal Society B: Biological Sciences*, *275*(1640), 1231–1241. https://doi.org/10.1098/rspb.2007.1673

Page 226. *Of this list*.

1615. Sullivan, R. J., & Hagen, E. H. (2002). Psychotropic substance-seeking: evolutionary pathology or adaptation? *Addiction*, *97*(4), 389–400. https://doi.org/10.1046/j.1360-0443.2002.00024.x

1616. Barretto-Tesoro, G. (2003). Burial goods in the Philippines: an attempt to quantify prestige values. *Japanese Journal of Southeast Asian Studies*, *41*(3), 299-315.

1617. Zumbroich, T. J. (2008). The origin and diffusion of betel chewing: a synthesis of evidence from South Asia, Southeast Asia and beyond. *E-Journal of Indian Medicine*, *1*(3), 87.

1618. Volgin, A. D., Bashirzade, A., Amstislavskaya, T. G., Yakovlev, O. A., Demin, K. A., Ho, Y.-J., Wang, D., Shevyrin, V. A., Yan, D., Tang, Z., Wang, J., Wang, M., Alpyshov, E. T., Serikuly, N., Wappler-Guzzetta, E. A., Lakstygal, A. M., & Kalueff, A. v. (2019). DARK Classics in Chemical Neuroscience: Arecoline. *ACS Chemical Neuroscience*, *10*(5), 2176–2185. https://doi.org/10.1021/acschemneuro.8b00711

Page 227. *The oldest bona fide*.

1619. Fox, R. B. (1970). *The Tabon caves: archaeological explorations and excavations on Palawan island, Philippines*. National Museum, Manila.

1620. Barretto-Tesoro, G. (2003). Burial goods in the Philippines: an attempt to quantify prestige values. *Japanese Journal of Southeast Asian Studies*, *41*(3), 299-315.

Page 227. *All of the new terms*.

1621. Palumbo, M. J., Talcott, S. T., & Putz, F. E. (2009). *Ilex Vomitoria* Ait. (Yaupon): A Native North American Source of a Caffeinated and Antioxidant-Rich Tea. *Economic Botany*, *63*(2), 130–137. https://doi.org/10.1007/s12231-009-9078-3

1622. Schimpl, F. C., da Silva, J. F., Gonçalves, J. F. de C., & Mazzafera, P. (2013). Guarana: Revisiting a highly caffeinated plant from the Amazon. *Journal of Ethnopharmacology*, *150*(1), 14–31. https://doi.org/10.1016/j.jep.2013.08.023

1623. Dueñas, J. F., Jarrett, C., Cummins, I., & Logan–Hines, E. (2016). Amazonian Guayusa (*Ilex guayusa* Loes.): A Historical and Ethnobotanical Overview. *Economic Botany*, *70*(1), 85–91. https://doi.org/10.1007/s12231-016-9334-2

Page 228 and 229. *Ethnobotanists Eloy Rodriguez*.

1624. Rodriguez, E., Cavin, J. C., & West, J. E. (1982). The possible role of amazonian psychoactive plants in the chemotherapy of parasitic worms — a hypothesis. *Journal of Ethnopharmacology*, *6*(3), 303–309. https://doi.org/10.1016/0378-8741(82)90053-8

1625. Schultes, R. E. (1977). The Botanical and Clinical Distribution of Hallucinogens. *Journal of Psychedelic Drugs*, *9*(3), 247–263. https://doi.org/10.1080/02791072.1977.10472055

Page 229. *In Iquitos, Peru*.

1626. Luna, L. E. (1984). The concept of plants as teachers among four mestizo shamans of iquitos, Northeastern Peru. *Journal of Ethnopharmacology*, *11*(2), 135–156. https://doi.org/10.1016/0378-8741(84)90036-9

Page 229. *At least some of the chemicals*.

1627. Cavin, J. C., Krassner, S. M., & Rodriguez, E. (1987). Plant-derived alkaloids active against Trypanosoma cruzi. *Journal of Ethnopharmacology*, *19*(1), 89–94. https://doi.org/10.1016/0378-8741(87)90140-1

Page 230. *Researchers in one study*.

1628. Roulette, C. J., Kazanji, M., Breurec, S., & Hagen, E. H. (2016). High prevalence of cannabis use among Aka foragers of the Congo Basin and its possible relationship to helminthiasis. *American Journal of Human Biology*, *28*(1), 5–15. https://doi.org/10.1002/ajhb.22740

Page 231. *This chemical behavior*.

1629. Sullivan, R. J., & Hagen, E. H. (2002). Psychotropic substance-seeking: evolutionary pathology or adaptation? *Addiction*, *97*(4), 389–400. https://doi.org/10.1046/j.1360-0443.2002.00024.x

Chapter 11. The Spice of Life

Page 233. *Plants in the mustard*.

1630. Hendriks, K. P., Kiefer, C., Al-Shehbaz, I. A., Bailey, C. D., Hooft van Huysduynen, A., Nikolov, L. A., Nauheimer, L., Zuntini, A. R., German, D. A., Franzke, A., Koch, M. A., Lysak, M. A., Toro-Núñez, Ó., Özüdoğru, B., Invernón, V. R., Walden, N., Maurin, O., Hay, N. M., Shushkov, P., … Lens, F. (2023). Global Brassicaceae phylogeny based on filtering of 1,000-gene dataset. *Current Biology*, *33*(19), 4052-4068.e6. https://doi.org/10.1016/j.cub.2023.08.026

1631. Warwick, S. I. (2011). Brassicaceae in Agriculture. In *Genetics and Genomics of the Brassicaceae* (pp. 33–65). Springer New York. https://doi.org/10.1007/978-1-4419-7118-0_2

1632. Lysak, M. A. (2018). Brassicales: an update on chromosomal evolution and ancient polyploidy. *Plant Systematics and Evolution*, *304*(6), 757–762. https://doi.org/10.1007/s00606-018-1507-2

1633. Mabry, M. E., Turner-Hissong, S. D., Gallagher, E. Y., McAlvay, A. C., An, H., Edger, P. P., Moore, J. D., Pink, D. A. C., Teakle, G. R., Stevens, C. J., Barker, G., Labate, J., Fuller, D. Q., Allaby, R. G., Beissinger, T., Decker, J. E., Gore, M. A., & Pires, J. C. (2021). The Evolutionary History of Wild, Domesticated, and Feral *Brassica oleracea* (Brassicaceae). *Molecular Biology and Evolution*, *38*(10), 4419–4434. https://doi.org/10.1093/molbev/msab183

1634. Mabry, M. E., Brose, J. M., Blischak, P. D., Sutherland, B., Dismukes, W. T., Bottoms, C. A., Edger, P. P., Washburn, J. D., An, H., Hall, J. C., McKain, M. R., Al-Shehbaz, I., Barker, M. S., Schranz, M. E., Conant, G. C., & Pires, J. C. (2020). Phylogeny and multiple independent whole-genome duplication events in the Brassicales. *American Journal of Botany*, *107*(8), 1148–1164. https://doi.org/10.1002/ajb2.1514

Page 233. *The function of mustard oils*. Note that there are many potential functions, including in signaling, defense, etc. This is a good example of the defensive functions that these chemicals can play.

1635. Lichtenstein, E. P., Strong, F. M., & Morgan, D. G. (1962). Naturally Occurring Insecticides, Identification of 2-Phenylethylisothiocyanate As an

Insecticide Occurring Naturally in the Edible Part of Turnips. *Journal of Agricultural and Food Chemistry*, *10*(1), 30–33. https://doi.org/10.1021/jf60119a009

1636. Lichtenstein, E. P., Morgan, D. G., & Mueller, C. H. (1964). Insecticides in Nature, Naturally Occurring Insecticides in Cruciferous Crops. *Journal of Agricultural and Food Chemistry*, *12*(2), 158–161. https://doi.org/10.1021/jf60132a017

1637. Lichtenstein, E. P. (1966) Insecticides occurring naturally in crops. *Natural Pest Control Agents.*pp 34-38. https://doi.org/10.1021/ba-1966-0053.ch004

Page 233. *Mustard oils serve.*

1638. Matile, Ph. (1980). „Die Senfolbombe": Zur Kompartimentierung des Myrosinasesystems. *Biochemie Und Physiologie Der Pflanzen*, *175*(8–9), 722–731. https://doi.org/10.1016/S0015-3796(80)80059-X

1639. Li, Q., Eigenbrode, S. D., Stringam, G. R., & Thiagarajah, M. R. (2000). Feeding and Growth of Plutella xylostella and Spodoptera eridania on Brassica juncea with Varying Glucosinolate Concentrations and Myrosinase Activities. *Journal of Chemical Ecology*, *26*(10), 2401–2419. https://doi.org/10.1023/A:1005535129399

1640. Ratzka, A., Vogel, H., Kliebenstein, D. J., Mitchell-Olds, T., & Kroymann, J. (2002). Disarming the mustard oil bomb. *Proceedings of the National Academy of Sciences*, *99*(17), 11223–11228. https://doi.org/10.1073/pnas.172112899

1641. Halkier, B. A., & Gershenzon, J. (2006). Biology and biochemistry of glucosinolates. *Annual Review of Plant Biology*, *57*, 303–333. https://doi.org/10.1146/annurev.arplant.57.032905.105228

1642. Kazana, E., Pope, T. W., Tibbles, L., Bridges, M., Pickett, J. A., Bones, A. M., Powell, G., & Rossiter, J. T. (2007). The cabbage aphid: a walking mustard oil bomb. *Proceedings of the Royal Society B: Biological Sciences*, *274*(1623), 2271–2277. https://doi.org/10.1098/rspb.2007.0237

1643. Hunziker, P., Lambertz, S. K., Weber, K., Crocoll, C., Halkier, B. A., & Schulz, A. (2021). Herbivore feeding preference corroborates optimal defense theory for specialized metabolites within plants. *Proceedings of the National Academy of Sciences*, *118*(47). https://doi.org/10.1073/pnas.2111977118

Page 233. *This is why*.

1644. Bell, L., Oloyede, O. O., Lignou, S., Wagstaff, C., & Methven, L. (2018). Taste and Flavor Perceptions of Glucosinolates, Isothiocyanates, and Related Compounds. *Molecular Nutrition & Food Research*, *62*(18). https://doi.org/10.1002/mnfr.201700990

Page 234. *Most commercially available wasabi*. See this quote from Köppel and Bucher (2016): "In ten of the products, which claim to contain wasabi, no wasabi signal was detected. In consequence, we concluded that the product does not contain wasabi and is therefore fraudulent. In all of these products, horseradish was detected, confirming correct DNA isolation and amplification." The algae used to color "wasabi" paste green is often *Spirulina* spp. Other coloring agents are also used.

1645. Chadwick, C. I., Lumpkin, T. A., & Elberson, L. R. (1993). The botany, uses and production of *Wasabia japonica* (Miq.) (Cruciferae) Matsum. *Economic Botany*, *47*(2), 113–135. https://doi.org/10.1007/BF02862015

1646. Bewicke, D., & Potter, B. A. (2009). *Chlorella: the emerald food*. Ronin Publishing.

1647. Koller, M., Muhr, A., & Braunegg, G. (2014). Microalgae as versatile cellular factories for valued products. *Algal Research*, *6*, 52–63. https://doi.org/10.1016/j.algal.2014.09.002

1648. Köppel, R., & Bucher, T. B. (2016). Duplex real-time PCR for the determination of wasabi (*Eutrema wasabi*) contents in horseradish (*Armoracia rusticana*) products applying the ΔΔct-method. *European Food Research and Technology*, *242*(7), 1111–1115. https://doi.org/10.1007/s00217-015-2615-7

1649. Herrera, M., Viera, I., & Roca, M. (2023). Study of the authentic composition of the novel green foods: Food colorants and coloring foods. *Food Research International*, *170*, 112974. https://doi.org/10.1016/j.foodres.2023.112974

1650. Spiegel, A. (2015, October 12). *Think You've Been Eating Wasabi All This Time? Think Again*. Huffpost. https://www.huffpost.com/entry/fake-wasabi-horseradish_n_561bd666e4b0082030a33959

1651. Petruzzello, M. (2023, August 22). wasabi. Encyclopedia Britannica. https://www.britannica.com/topic/wasabi

1652. Greaves, V. (2016, May 10). *What's Really In That Green Paste You Call Wasabi?* Allrecipes. https://www.allrecipes.com/article/are-you-really-eating-wasabi/

Page 234. *Kimchi and sauerkraut*.

1653. Ciska, E., & Pathak, D. R. (2004). Glucosinolate Derivatives in Stored Fermented Cabbage. *Journal of Agricultural and Food Chemistry*, *52*(26), 7938–7943. https://doi.org/10.1021/jf048986+

1654. Kim, S.-Y., Yang, J., Dang, Y.-M., & Ha, J.-H. (2022). Effect of fermentation stages on glucosinolate profiles in kimchi: Quantification of 14 intact glucosinolates using ultra-performance liquid chromatography-tandem mass spectrometry. *Food Chemistry: X*, *15*, 100417. https://doi.org/10.1016/j.fochx.2022.100417

Page 235. *Our gut bacteria have other plans*. There are two important points. The glucosinolate "protoxin" is hydrolyzed by glucosidases from bacteria in the human gut, producing, among other products, isothiocyanates, which are the "mustard oils." These toxins are then further degraded by hydrolases in some bacteria into hydrogen sulfide, carbon dioxide, and an amine as was first reported by Tang et al. (1972).

1655. Tang, C.-S., Bhothipaksa, K., & Frank, H. A. (1972). Bacterial Degradation of Benzyl Isothiocyanate. *Applied Microbiology*, *23*(6), 1145–1148. https://doi.org/10.1128/am.23.6.1145-1148.1972

1656. Fenwick, G. R., Heaney, R. K., Mullin, W. J., & VanEtten, C. H. (1983). Glucosinolates and their breakdown products in food and food plants. *C R C Critical Reviews in Food Science and Nutrition*, *18*(2), 123–201. https://doi.org/10.1080/10408398209527361

1657. Li, F., Hullar, M. A. J., Beresford, S. A. A., & Lampe, J. W. (2011). Variation of glucoraphanin metabolism *in vivo* and *ex vivo* by human gut bacteria. *British Journal of Nutrition*, *106*(3), 408–416. https://doi.org/10.1017/S0007114511000274

1658. Luang-In, V., Narbad, A., Nueno-Palop, C., Mithen, R., Bennett, M., & Rossiter, J. T. (2014). The metabolism of methylsulfinylalkyl- and methylthioalkyl-glucosinolates by a selection of human gut bacteria. *Molecular Nutrition & Food Research*, *58*(4), 875–883. https://doi.org/10.1002/mnfr.201300377

1659. Liou, C. S., Sirk, S. J., Diaz, C. A. C., Klein, A. P., Fischer, C. R., Higginbottom, S. K., Erez, A., Donia, M. S., Sonnenburg, J. L., & Sattely, E. S. (2020). A Metabolic Pathway for Activation of Dietary Glucosinolates by a Human Gut Symbiont. *Cell*, *180*(4), 717-728.e19. https://doi.org/10.1016/j.cell.2020.01.023

1660. Watanabe, H., Usami, R., Kishino, S., Osada, K., Aoki, Y., Morisaka, H., Takahashi, M., Izumi, Y., Bamba, T., Aoki, W., Suganuma, H., & Ogawa, J. (2021). Enzyme systems involved in glucosinolate metabolism in Companilactobacillus farciminis KB1089. *Scientific Reports*, *11*(1), 23715. https://doi.org/10.1038/s41598-021-03064-7

Page 234. *Not only are mustard oils.*

1661. Fahey, J. W., Haristoy, X., Dolan, P. M., Kensler, T. W., Scholtus, I., Stephenson, K. K., Talalay, P., & Lozniewski, A. (2002). Sulforaphane inhibits extracellular, intracellular, and antibiotic-resistant strains of *Helicobacter pylori* and prevents benzo[*a*]pyrene-induced stomach tumors. *Proceedings of the National Academy of Sciences*, *99*(11), 7610–7615. https://doi.org/10.1073/pnas.112203099

1662. Zhao, J., Moore, A. N., Clifton, G. L., & Dash, P. K. (2005). Sulforaphane enhances aquaporin-4 expression and decreases cerebral edema following traumatic brain injury. *Journal of Neuroscience Research*, *82*(4), 499–506. https://doi.org/10.1002/jnr.20649

1663. Zhao, J., Moore, A. N., Redell, J. B., & Dash, P. K. (2007). Enhancing Expression of Nrf2-Driven Genes Protects the Blood–Brain Barrier after Brain Injury. *The Journal of Neuroscience*, *27*(38), 10240–10248. https://doi.org/10.1523/JNEUROSCI.1683-07.2007

1664. Dash, P. K., Zhao, J., Orsi, S. A., Zhang, M., & Moore, A. N. (2009). Sulforaphane improves cognitive function administered following traumatic brain injury. *Neuroscience Letters*, *460*(2), 103–107. https://doi.org/10.1016/j.neulet.2009.04.028

1665. Kensler, T. W., Ng, D., Carmella, S. G., Chen, M., Jacobson, L. P., Muñoz, A., Egner, P. A., Chen, J. G., Qian, G. S., Chen, T. Y., Fahey, J. W., Talalay, P., Groopman, J. D., Yuan, J.-M., & Hecht, S. S. (2012). Modulation of the metabolism of airborne pollutants by glucoraphanin-rich and sulforaphane-rich broccoli sprout beverages in Qidong, China. *Carcinogenesis*, *33*(1), 101–107. https://doi.org/10.1093/carcin/bgr229

1666. Houghton, C. A., Fassett, R. G., & Coombes, J. S. (2013). Sulforaphane: translational research from laboratory bench to clinic. *Nutrition Reviews*, *71*(11), 709–726. https://doi.org/10.1111/nure.12060

1667. Egner, P. A., Chen, J.-G., Zarth, A. T., Ng, D. K., Wang, J.-B., Kensler, K. H., Jacobson, L. P., Muñoz, A., Johnson, J. L., Groopman, J. D., Fahey, J. W., Talalay, P., Zhu, J., Chen, T.-Y., Qian, G.-S., Carmella, S. G., Hecht, S. S., & Kensler, T. W. (2014). Rapid and Sustainable Detoxication of Airborne Pollutants by Broccoli Sprout Beverage: Results of a Randomized Clinical Trial in China. *Cancer Prevention Research*, *7*(8), 813–823. https://doi.org/10.1158/1940-6207.CAPR-14-0103

1668. Singh, K., Connors, S. L., Macklin, E. A., Smith, K. D., Fahey, J. W., Talalay, P., & Zimmerman, A. W. (2014). Sulforaphane treatment of autism spectrum disorder (ASD). *Proceedings of the National Academy of Sciences*, *111*(43), 15550–15555. https://doi.org/10.1073/pnas.1416940111

1669. Singh, K., & W. Zimmerman, A. (2016). Sulforaphane Treatment of Young Men with Autism Spectrum Disorder. *CNS & Neurological Disorders - Drug Targets*, *15*(5), 597–601. https://doi.org/10.2174/1871527315666160413122525

1670. Zhou, Q., Chen, B., Wang, X., Wu, L., Yang, Y., Cheng, X., Hu, Z., Cai, X., Yang, J., Sun, X., Lu, W., Yan, H., Chen, J., Ye, J., Shen, J., & Cao, P. (2016). Sulforaphane protects against rotenone-induced neurotoxicity in vivo: Involvement of the mTOR, Nrf2 and autophagy pathways. *Scientific Reports*, *6*(1), 32206. https://doi.org/10.1038/srep32206

1671. Liu, F., Huang, J., Hei, G., Wu, R., & Liu, Z. (2020). Effects of sulforaphane on cognitive function in patients with frontal brain damage: study protocol for a randomised controlled trial. *BMJ Open*, *10*(10), e037543. https://doi.org/10.1136/bmjopen-2020-037543

1672. Search results for Isothiocyanate. ClinicalTrials.gov. https://clinicaltrials.gov/search?term=isothiocyanate

1673. Search results for Sulforaphane. ClinicalTrials.gov. https://clinicaltrials.gov/search?term=sulforaphane

Page 234 and 235. *Other studies*. Note an earlier study did examine the effects of sulforaphane (an isothiocyanate) on lifespan in *Drosophila melanogaster*.

1674. Li, Y. M., Chan, H. Y. E., Yao, X. Q., Huang, Y., & Chen, Z. Y. (2008). Green tea catechins and broccoli reduce fat-induced mortality in Drosophila melanogaster. *The Journal of Nutritional Biochemistry*, *19*(6), 376–383. https://doi.org/10.1016/j.jnutbio.2007.05.009

1675. Villatoro-Pulido, M., Font, R., Saha, S., Obregón-Cano, S., Anter, J., Muñoz-Serrano, A., de Haro-Bailón, A., Alonso-Moraga, A., & del Río- Celestino, M. (2012). In vivo biological activity of rocket extracts (*Eruca vesicaria* subsp. sativa (Miller) Thell) and sulforaphane. *Food and Chemical Toxicology*, *50*(5), 1384–1392. https://doi.org/10.1016/j.fct.2012.02.017

1676. Grünwald, S., Stellzig, J., Adam, I. v., Weber, K., Binger, S., Boll, M., Knorr, E., Twyman, R. M., Vilcinskas, A., & Wenzel, U. (2013). Longevity in the red flour beetle *Tribolium castaneum* is enhanced by broccoli and depends on *nrf-2*, *jnk-1* and *foxo-1* homologous genes. *Genes & nutrition*, *8*, 439-448. https://doi.org/10.1007/s12263-012-0330-6

1677. Qi, Z., Ji, H., Le, M., Li, H., Wieland, A., Bauer, S., Liu, L., Wink, M., & Herr, I. (2021). Sulforaphane promotes C. elegans longevity and healthspan via DAF-16/DAF-2 insulin/IGF-1 signaling. *Aging*, *13*(2), 1649–1670. https://doi.org/10.18632/aging.202512

Page 235. *Called Nrf2*.

1678. Moi, P., Chan, K., Asunis, I., Cao, A., & Kan, Y. W. (1994). Isolation of NF-E2-related factor 2 (Nrf2), a NF-E2-like basic leucine zipper transcriptional activator that binds to the tandem NF-E2/AP1 repeat of the beta-globin locus control region. *Proceedings of the National Academy of Sciences*, *91*(21), 9926–9930. https://doi.org/10.1073/pnas.91.21.9926

1679. Dinkova-Kostova, A. T., Holtzclaw, W. D., Cole, R. N., Itoh, K., Wakabayashi, N., Katoh, Y., Yamamoto, M., & Talalay, P. (2002). Direct evidence that sulfhydryl groups of Keap1 are the sensors regulating induction of phase 2 enzymes that protect against carcinogens and oxidants. *Proceedings of the National Academy of Sciences*, *99*(18), 11908–11913. https://doi.org/10.1073/pnas.172398899

1680. Zhang, D. D., & Hannink, M. (2003). Distinct Cysteine Residues in Keap1 Are Required for Keap1-Dependent Ubiquitination of Nrf2 and for Stabilization of Nrf2 by Chemopreventive Agents and Oxidative Stress. *Molecular and Cellular Biology*, *23*(22), 8137–8151. https://doi.org/10.1128/MCB.23.22.8137-8151.2003

1681. Motohashi, H., Katsuoka, F., Engel, J. D., & Yamamoto, M. (2004). Small Maf proteins serve as transcriptional cofactors for keratinocyte differentiation in the Keap1–Nrf2 regulatory pathway. *Proceedings of the National Academy of Sciences*, *101*(17), 6379–6384. https://doi.org/10.1073/pnas.0305902101

1682. McMahon, M., Thomas, N., Itoh, K., Yamamoto, M., & Hayes, J. D. (2004). Redox-regulated Turnover of Nrf2 Is Determined by at Least Two Separate Protein Domains, the Redox-sensitive Neh2 Degron and the Redox-insensitive Neh6 Degron. *Journal of Biological Chemistry*, *279*(30), 31556–31567. https://doi.org/10.1074/jbc.M403061200

Page 235. *Another hint about why*. Rather than a single study, there are actually a series of studies that have used both paraquat and rotenone in the diet as generators of reactive oxygen species in the context of lifespan, stress, and/or Parkinson's Disease in *Drosophila melanogaster* and mice. Other studies then tested how pre-treatment with extracts from mustards or sulforaphane itself extends lifespan and/or rescues Parksinon's Disease-like effects in mutant model animals. As the Coulom and Birman (2004) study suggests: "The selectivity of rotenone action is likely attributable to a specific sensitivity of *Drosophila* dopaminergic neurons to reactive oxygen species and oxidative damages."

1683. Coulom, H., & Birman, S. (2004). Chronic Exposure to Rotenone Models Sporadic Parkinson's Disease in *Drosophila melanogaster*. *The Journal of Neuroscience*, *24*(48), 10993–10998. https://doi.org/10.1523/JNEUROSCI.2993-04.2004

1684. Trinh, K., Moore, K., Wes, P. D., Muchowski, P. J., Dey, J., Andrews, L., & Pallanck, L. J. (2008). Induction of the Phase II Detoxification Pathway Suppresses Neuron Loss in *Drosophila* Models of Parkinson's Disease. *The Journal of Neuroscience*, *28*(2), 465–472. https://doi.org/10.1523/JNEUROSCI.4778-07.2008

1685. Li, Y. M., Chan, H. Y. E., Huang, Y., & Chen, Z. Y. (2008). Broccoli (*Brassica oleracea* var. botrytis L.) improves the survival and up-regulates endogenous antioxidant enzymes in *Drosophila melanogaster* challenged with reactive oxygen species. *Journal of the Science of Food and Agriculture*, *88*(3), 499–506. https://doi.org/10.1002/jsfa.3113

1686. Lyles, J. T., Luo, L., Liu, K., Jones, D. P., Jones, R. M., & Quave, C. L. (2021). Cruciferous vegetables (*Brassica oleracea*) confer cytoprotective effects in *Drosophila* intestines. *Gut Microbes*, *13*(1). https://doi.org/10.1080/19490976.2021.1921926

1687. Zhou, Q., Chen, B., Wang, X., Wu, L., Yang, Y., Cheng, X., Hu, Z., Cai, X., Yang, J., Sun, X., Lu, W., Yan, H., Chen, J., Ye, J., Shen, J., & Cao, P. (2016). Sulforaphane protects against rotenone-induced neurotoxicity in vivo: Involvement of the mTOR, Nrf2 and autophagy pathways. *Scientific Reports*, *6*(1), 32206. https://doi.org/10.1038/srep32206

1688. Cheng, J., Wang, H., Bartlett, M., Stevenson, D., Pan, Y., Ho, M. S., & Ren, Y. (2021). Antioxidant Blend of Curcumin and Broccoli Seed Extract Exhibits Protective Effect on Neurodegeneration and Promotes *Drosophila* Lifespan. *ASN Neuro*, *13*, 175909142110150. https://doi.org/10.1177/17590914211015033

1689. Lawana, V., & Cannon, J. R. (2020). Rotenone neurotoxicity: Relevance to Parkinson's disease. In M. Aschner & L. G. Costa (Eds.), *Advances in Neurotoxicology* (Vol. 4, pp. 209–254). Academic Press. https://doi.org/https://doi.org/10.1016/bs.ant.2019.11.004

Page 235. *Rotenone is an isoflavonoid*.

1690. Clark, E. P. (1929). The Occurrence of Rotenone in the Peruvian Fish Poison "Cube." *Science*, *70*(1820), 478–479. https://doi.org/10.1126/science.70.1820.478.b

1691. Davidson, W. M. (1930). Rotenone as a Contact Insecticide. *Journal of Economic Entomology*, *23*(5), 868–874. https://doi.org/10.1093/jee/23.5.868

1692. la Forge, F. B., Haller, H. L., & Smith, L. E. (1933). The Determination of the Structure of Rotenone. *Chemical Reviews*, *12*(2), 181–213. https://doi.org/10.1021/cr60042a001

1693. Krukoff, B. A., & Smith, A. C. (1937). Rotenone-Yielding Plants of South America. *American Journal of Botany*, *24*(9), 573. https://doi.org/10.2307/2436635

1694. Leonard, J. W. (1939). Notes on the Use of Derris as a Fish Poison. *Transactions of the American Fisheries Society*, *68*(1), 269–280. https://doi.org/https://doi.org/10.1577/1548-8659(1938)68[269:NOTUOD]2.0.CO;2

1695. Hansberry, R., & Cecil, L. (1943). The Yam Bean, Pachyrrhizus erosus Urban, as a Possible Insecticide. *Journal of Economic Entomology*, *36*(2), 351–352. https://doi.org/10.1093/jee/36.2.351

1696. Heizer, R. F. (1946). Fish poisons. *Handbook of South American Indians: The comparative ethnology of South American Indians*, *143*, 277. US Government Printing Office.

1697. Öberg, K. E. (1967). The reversibility of the respiratory inhibition in gills and the ultrastructural changes in chloride cells from the rotenone-poisoned marine teleost, Gadus callarias L. *Experimental Cell Research*, *45*(3), 590–602. https://doi.org/10.1016/0014-4827(67)90162-0

1698. Schrœder, C. A. (1968). Sociological aspects of the Jicama in Mexico. *Ethnos*, *33*(1–4), 78–90. https://doi.org/10.1080/00141844.1968.9980999

1699. Cannon, J. G., Burton, R. A., Wood, S. G., & Owen, N. L. (2004). Naturally Occurring Fish Poisons from Plants. *Journal of Chemical Education*, *81*(10), 1457. https://doi.org/10.1021/ed081p1457

Page 235. *Rotenone can produce*.

1700. Betarbet, R., Sherer, T. B., MacKenzie, G., Garcia-Osuna, M., Panov, A. v., & Greenamyre, J. T. (2000). Chronic systemic pesticide exposure reproduces features of Parkinson's disease. *Nature Neuroscience*, *3*(12), 1301–1306. https://doi.org/10.1038/81834

1701. Tanner, C. M., Kamel, F., Ross, G. W., Hoppin, J. A., Goldman, S. M., Korell, M., Marras, C., Bhudhikanok, G. S., Kasten, M., Chade, A. R., Comyns, K., Richards, M. B., Meng, C., Priestley, B., Fernandez, H. H., Cambi, F., Umbach, D. M., Blair, A., Sandler, D. P., & Langston, J. W. (2011). Rotenone, Paraquat, and Parkinson's Disease. *Environmental Health Perspectives*, *119*(6), 866–872. https://doi.org/10.1289/ehp.1002839

Page 235. *Some studies show*.

1702. Trinh, K., Moore, K., Wes, P. D., Muchowski, P. J., Dey, J., Andrews, L., & Pallanck, L. J. (2008). Induction of the Phase II Detoxification Pathway Suppresses Neuron Loss in *Drosophila* Models of Parkinson's Disease. *The Journal of Neuroscience*, *28*(2), 465–472. https://doi.org/10.1523/JNEUROSCI.4778-07.2008

1703. Morroni, F., Tarozzi, A., Sita, G., Bolondi, C., Zolezzi Moraga, J. M., Cantelli-Forti, G., & Hrelia, P. (2013). Neuroprotective effect of sulforaphane in 6-hydroxydopamine-lesioned mouse model of Parkinson's disease. *NeuroToxicology*, *36*, 63–71. https://doi.org/10.1016/j.neuro.2013.03.004

1704. Zhou, Q., Chen, B., Wang, X., Wu, L., Yang, Y., Cheng, X., Hu, Z., Cai, X., Yang, J., Sun, X., Lu, W., Yan, H., Chen, J., Ye, J., Shen, J., & Cao, P. (2016). Sulforaphane protects against rotenone-induced neurotoxicity in vivo: Involvement of the mTOR, Nrf2 and autophagy pathways. *Scientific Reports*, *6*(1), 32206. https://doi.org/10.1038/srep32206

Page 235 and 236. *Scientists have dug deeper*.

1705. Maries, E., Dass, B., Collier, T. J., Kordower, J. H., & Steece-Collier, K. (2003). The role of α-synuclein in Parkinson's disease: insights from animal models. *Nature Reviews Neuroscience*, *4*(9), 727–738. https://doi.org/10.1038/nrn1199

1706. Polymeropoulos, M. H., Lavedan, C., Leroy, E., Ide, S. E., Dehejia, A., Dutra, A., Pike, B., Root, H., Rubenstein, J., Boyer, R., Stenroos, E. S., Chandrasekharappa, S., Athanassiadou, A., Papapetropoulos, T., Johnson, W. G., Lazzarini, A. M., Duvoisin, R. C., di Iorio, G., Golbe, L. I., & Nussbaum, R. L. (1997). Mutation in the α-Synuclein Gene Identified in Families with Parkinson's Disease. *Science*, *276*(5321), 2045–2047. https://doi.org/10.1126/science.276.5321.2045

1707. Spillantini, M. G., Schmidt, M. L., Lee, V. M.-Y., Trojanowski, J. Q., Jakes, R., & Goedert, M. (1997). α-Synuclein in Lewy bodies. *Nature*, *388*(6645), 839–840. https://doi.org/10.1038/42166

1708. Zarranz, J. J., Alegre, J., Gómez-Esteban, J. C., Lezcano, E., Ros, R., Ampuero, I., Vidal, L., Hoenicka, J., Rodriguez, O., Atarés, B., Llorens, V., Tortosa, E. G., del Ser, T., Muñoz, D. G., & de Yebenes, J. G. (2004). The new mutation, E46K, of α-synuclein causes parkinson and Lewy body dementia. *Annals of Neurology*, *55*(2), 164–173. https://doi.org/10.1002/ana.10795

1709. Walker, Z., Possin, K. L., Boeve, B. F., & Aarsland, D. (2015). Lewy body dementias. *The Lancet*, *386*(10004), 1683–1697. https://doi.org/10.1016/S0140-6736(15)00462-6

1710. Visanji, N. P., Brotchie, J. M., Kalia, L. v., Koprich, J. B., Tandon, A., Watts, J. C., & Lang, A. E. (2016). α-Synuclein-Based Animal Models of Parkinson's Disease: Challenges and Opportunities in a New Era. *Trends in Neurosciences*, *39*(11), 750–762. https://doi.org/10.1016/j.tins.2016.09.003

1711. Ayers, J. I., Lee, J., Monteiro, O., Woerman, A. L., Lazar, A. A., Condello, C., Paras, N. A., & Prusiner, S. B. (2022). Different α-synuclein prion strains cause dementia with Lewy bodies and multiple system atrophy. *Proceedings of the National Academy of Sciences*, *119*(6). https://doi.org/10.1073/pnas.2113489119

Page 236. *To better study Parkinson's*.

1712. Feany, M. B., & Bender, W. W. (2000). A Drosophila model of Parkinson's disease. *Nature*, *404*(6776), 394–398. https://doi.org/10.1038/35006074

1713. Auluck, P. K., Chan, H. Y. E., Trojanowski, J. Q., Lee, V. M.-Y., & Bonini, N. M. (2002). Chaperone Suppression of α-Synuclein Toxicity in a *Drosophila* Model for Parkinson's Disease. *Science*, *295*(5556), 865–868. https://doi.org/10.1126/science.1067389

1714. Chen, L., & Feany, M. B. (2005). α-Synuclein phosphorylation controls neurotoxicity and inclusion formation in a Drosophila model of Parkinson disease. *Nature Neuroscience*, *8*(5), 657–663. https://doi.org/10.1038/nn1443

Page 236. *Flies are useful*.

1715. Strausfeld, N. J. (2012). *Arthropod brains: evolution, functional elegance, and historical significance*. Harvard University Press.

1716. Bridi, J. C., Ludlow, Z. N., Kottler, B., Hartmann, B., vanden Broeck, L., Dearlove, J., Göker, M., Strausfeld, N. J., Callaerts, P., & Hirth, F. (2020). Ancestral regulatory mechanisms specify conserved midbrain circuitry in arthropods and vertebrates. *Proceedings of the National Academy of Sciences*, *117*(32), 19544–19555. https://doi.org/10.1073/pnas.1918797117

Page 236. *When the diet*.

1717. Trinh, K., Moore, K., Wes, P. D., Muchowski, P. J., Dey, J., Andrews, L., & Pallanck, L. J. (2008). Induction of the Phase II Detoxification Pathway Suppresses Neuron Loss in *Drosophila* Models of Parkinson's Disease. *The Journal of Neuroscience*, *28*(2), 465–472. https://doi.org/10.1523/JNEUROSCI.4778-07.2008

1718. Morroni, F., Tarozzi, A., Sita, G., Bolondi, C., Zolezzi Moraga, J. M., Cantelli-Forti, G., & Hrelia, P. (2013). Neuroprotective effect of sulforaphane in 6-hydroxydopamine-lesioned mouse model of Parkinson's disease. *NeuroToxicology*, *36*, 63–71. https://doi.org/10.1016/j.neuro.2013.03.004

Page 236 and 237. *Nrf2 is normally*.

1719. Zhang, D. D., & Hannink, M. (2003). Distinct Cysteine Residues in Keap1 Are Required for Keap1-Dependent Ubiquitination of Nrf2 and for Stabilization of Nrf2 by Chemopreventive Agents and Oxidative Stress. *Molecular and Cellular Biology*, *23*(22), 8137–8151. https://doi.org/10.1128/MCB.23.22.8137-8151.2003

1720. Hong, F., Freeman, M. L., & Liebler, D. C. (2005). Identification of Sensor Cysteines in Human Keap1 Modified by the Cancer Chemopreventive Agent Sulforaphane. *Chemical Research in Toxicology*, *18*(12), 1917–1926. https://doi.org/10.1021/tx0502138

1721. Dinkova-Kostova, A. T., Fahey, J. W., Kostov, R. v., & Kensler, T. W. (2017). KEAP1 and done? Targeting the NRF2 pathway with sulforaphane. *Trends in Food Science & Technology*, *69*, 257–269. https://doi.org/10.1016/j.tifs.2017.02.002

Page 237. *If GSH is like a sponge*.

1722. Gasper, A. v, Al-janobi, A., Smith, J. A., Bacon, J. R., Fortun, P., Atherton, C., Taylor, M. A., Hawkey, C. J., Barrett, D. A., & Mithen, R. F. (2005). Glutathione S-transferase M1 polymorphism and metabolism of sulforaphane from standard and high-glucosinolate broccoli. *The American Journal of Clinical Nutrition*, *82*(6), 1283–1291. https://doi.org/10.1093/ajcn/82.6.1283

Page 237. *People who die of paracetamol*.

1723. Davidson, D. G., & Eastham, W. N. (1966). Acute liver necrosis following overdose of paracetamol. *BMJ*, *2*(5512), 497–499. https://doi.org/10.1136/bmj.2.5512.497

1724. Prescott, L. F., Illingworth, R. N., Critchley, J. A., Stewart, M. J., Adam, R. D., & Proudfoot, A. T. (1979). Intravenous N-acetylcystine: the treatment of choice for paracetamol poisoning. *BMJ*, *2*(6198), 1097–1100. https://doi.org/10.1136/bmj.2.6198.1097

1725. Waring, W. S. (2012). Novel acetylcysteine regimens for treatment of paracetamol overdose. *Therapeutic Advances in Drug Safety*, *3*(6), 305–315. https://doi.org/10.1177/2042098612464265

Page 238. *Hormesis, which comes from*.

1726. Calabrese, E. J., & Baldwin, L. A. (2003). Hormesis: The Dose-Response Revolution. *Annual Review of Pharmacology and Toxicology*, *43*(1), 175–197. https://doi.org/10.1146/annurev.pharmtox.43.100901.140223

1727. Calabrese, E. J. (2008). Hormesis and medicine. *British Journal of Clinical Pharmacology*, *66*(5), 594–617. https://doi.org/10.1111/j.1365-2125.2008.03243.x

1728. Berry, R., & López-Martínez, G. (2020). A dose of experimental hormesis: When mild stress protects and improves animal performance. *Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology*, *242*, 110658. https://doi.org/10.1016/j.cbpa.2020.110658

Page 238. *Heat-shock proteins*.

1729. Dudley, R. (2002). Fermenting fruit and the historical ecology of ethanol ingestion: is alcoholism in modern humans an evolutionary hangover? *Addiction*, *97*(4), 381–388. https://doi.org/10.1046/j.1360-0443.2002.00002.x

1730. Calabrese, E. J., & Baldwin, L. A. (2003). Ethanol and Hormesis. *Critical Reviews in Toxicology*, *33*(3–4), 407–424. https://doi.org/10.1080/713611043

1731. Singh, I. S., & Hasday, J. D. (2013). Fever, hyperthermia and the heat shock response. *International Journal of Hyperthermia*, *29*(5), 423–435. https://doi.org/10.3109/02656736.2013.808766

1732. Peake, J. M., Markworth, J. F., Nosaka, K., Raastad, T., Wadley, G. D., & Coffey, V. G. (2015). Modulating exercise-induced hormesis: Does less equal more? *Journal of Applied Physiology*, *119*(3), 172–189. https://doi.org/10.1152/japplphysiol.01055.2014

1733. Henderson, K. N., Killen, L. G., O'Neal, E. K., & Waldman, H. S. (2021). The Cardiometabolic Health Benefits of Sauna Exposure in Individuals with High-Stress Occupations. A Mechanistic Review. *International Journal of Environmental Research and Public Health*, *18*(3), 1105. https://doi.org/10.3390/ijerph18031105

Page 238 and 239. *On average*.

1734. Griswold, M. G., Fullman, N., Hawley, C., Arian, N., Zimsen, S. R. M., Tymeson, H. D., Venkateswaran, V., Tapp, A. D., Forouzanfar, M. H., Salama, J. S., Abate, K. H., Abate, D., Abay, S. M., Abbafati, C., Abdulkader, R. S., Abebe, Z., Aboyans, V., Abrar, M. M., Acharya, P., … Gakidou, E. (2018). Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*, *392*(10152), 1015–1035. https://doi.org/10.1016/S0140-6736(18)31310-2

1735. Bryazka, D., Reitsma, M. B., Griswold, M. G., Abate, K. H., Abbafati, C., Abbasi-Kangevari, M., Abbasi-Kangevari, Z., Abdoli, A., Abdollahi, M., Abdullah, A. Y. M., Abhilash, E. S., Abu-Gharbieh, E., Acuna, J. M., Addolorato, G., Adebayo, O. M., Adekanmbi, V., Adhikari, K., Adhikari, S., Adnani, Q. E. S., … Gakidou, E. (2022). Population-level risks of alcohol consumption by amount, geography, age, sex, and year: a systematic analysis for the Global Burden of Disease Study 2020. *The Lancet*, *400*(10347), 185–235. https://doi.org/10.1016/S0140-6736(22)00847-9

1736. Ding, C., O'Neill, D., Bell, S., Stamatakis, E., & Britton, A. (2021). Association of alcohol consumption with morbidity and mortality in patients with cardiovascular disease: original data and meta-analysis of 48,423 men and women. *BMC Medicine*, *19*(1), 167. https://doi.org/10.1186/s12916-021-02040-2

Page 239. *One terrific*. This reference supports the next paragraph as well.

1737. Howitz, K. T., & Sinclair, D. A. (2008). Xenohormesis: Sensing the Chemical Cues of Other Species. *Cell*, *133*(3), 387–391. https://doi.org/10.1016/j.cell.2008.04.019

Page 239. *One last finding*.

1738. Trinh, K., Moore, K., Wes, P. D., Muchowski, P. J., Dey, J., Andrews, L., & Pallanck, L. J. (2008). Induction of the Phase II Detoxification Pathway Suppresses Neuron Loss in *Drosophila* Models of Parkinson's Disease. *The Journal of Neuroscience*, *28*(2), 465–472. https://doi.org/10.1523/JNEUROSCI.4778-07.2008

Page 239. *This matters because*.

1739. Gloss, A. D., Vassão, D. G., Hailey, A. L., Nelson Dittrich, A. C., Schramm, K., Reichelt, M., Rast, T. J., Weichsel, A., Cravens, M. G., Gershenzon, J., Montfort, W. R., & Whiteman, N. K. (2014). Evolution in an Ancient Detoxification Pathway Is Coupled with a Transition to Herbivory in the Drosophilidae. *Molecular Biology and Evolution*, *31*(9), 2441–2456. https://doi.org/10.1093/molbev/msu201

Page 240. *Small clinical trials*.

1740. Singh, K., & W. Zimmerman, A. (2016). Sulforaphane Treatment of Young Men with Autism Spectrum Disorder. *CNS & Neurological Disorders - Drug Targets*, *15*(5), 597–601. https://doi.org/10.2174/1871527315666160413122525

1741. Singh, K., Connors, S. L., Macklin, E. A., Smith, K. D., Fahey, J. W., Talalay, P., & Zimmerman, A. W. (2014). Sulforaphane treatment of autism spectrum disorder (ASD). *Proceedings of the National Academy of Sciences*, *111*(43), 15550–15555. https://doi.org/10.1073/pnas.1416940111

1742. Lynch, R., Diggins, E. L., Connors, S. L., Zimmerman, A. W., Singh, K., Liu, H., Talalay, P., & Fahey, J. W. (2017). Sulforaphane from Broccoli Reduces Symptoms of Autism: A Follow-up Case Series from a Randomized Double-blind Study. *Global Advances in Health and Medicine*, *6*, 2164957X1773582. https://doi.org/10.1177/2164957X17735826

1743. Momtazmanesh, S., Amirimoghaddam-Yazdi, Z., Moghaddam, H. S., Mohammadi, M. R., & Akhondzadeh, S. (2020). Sulforaphane as an adjunctive treatment for irritability in children with autism spectrum disorder: A randomized, double-blind, placebo-controlled clinical trial. *Psychiatry and Clinical Neurosciences*, *74*(7), 398–405. https://doi.org/10.1111/pcn.13016

1744. Zimmerman, A. W., Singh, K., Connors, S. L., Liu, H., Panjwani, A. A., Lee, L.-C., Diggins, E., Foley, A., Melnyk, S., Singh, I. N., James, S. J., Frye, R. E., & Fahey, J. W. (2021). Randomized controlled trial of sulforaphane and metabolite discovery in children with Autism Spectrum Disorder. *Molecular Autism*, *12*(1), 38. https://doi.org/10.1186/s13229-021-00447-5

1745. Ou, J., Smith, R. C., Tobe, R. H., Lin, J., Arriaza, J., Fahey, J. W., Liu, R., Zeng, Y., Liu, Y., Huang, L., Shen, Y., Li, Y., Cheng, D., Cornblatt, B., Davis, J. M., Zhao, J., Wu, R., & Jin, H. (2022). Efficacy of Sulforaphane in Treatment of Children with Autism Spectrum Disorder: A Randomized Double-Blind Placebo-Controlled Multi-center Trial. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-022-05784-9

Page 240. *Our food is not only*.

1746. Johns, T. (1990). *With bitter herbs they shall eat it: chemical ecology and the origins of human diet and medicine*. University of Arizona Press.

1747. Pollan, M. (2002). *The botany of desire: A plant's-eye view of the world*. Random house trade paperbacks.

1748. Nabhan, G. P. (2004). *Why some like it hot: food, genes, and cultural diversity*. Island Press.

1749. Nabhan, G. P. (2013). *Food, genes, and culture: eating right for your origins*. Washington, DC: Island Press.

Page 240. *Anthropologist Solomon Katz.*

1750. Katz, S. H. (1990). An evolutionary theory of cuisine. *Human Nature*, *1*(3), 233–259. https://doi.org/10.1007/BF02733985

Page 241 and 242. *In 1999, biologists Paul Sherman.* These citations cover the next five paragraphs as well.

1751. Syed Ziauddin, K., Subba Rao, H., & Fairoze, N. (1996). Effect of organic acids and spices on quality and shelf-life of meats at ambient temperature. *Journal of food science and technology (Mysore)*, *33*(3), 255-258.

1752. Billing, J., & Sherman, P. W. (1998). Antimicrobial Functions of Spices: Why Some Like it Hot. *The Quarterly Review of Biology*, *73*(1), 3–49. https://doi.org/10.1086/420058

1753. Sherman, P. W., & Billing, J. (1999). Darwinian Gastronomy: Why We Use Spices. *BioScience*, *49*(6), 453–463. https://doi.org/10.2307/1313553

1754. Flaxman, S. M., & Sherman, P. W. (2000). Morning Sickness: A Mechanism for Protecting Mother and Embryo. *The Quarterly Review of Biology*, *75*(2), 113–148. https://doi.org/10.1086/393377

1755. Sherman, P. W., & Hash, G. A. (2001). Why vegetable recipes are not very spicy. *Evolution and Human Behavior*, *22*(3), 147–163. https://doi.org/10.1016/S1090-5138(00)00068-4

1756. Sherman, P., & Flaxman, S. (2001). Protecting Ourselves from Food. *American Scientist*, *89*(2), 142. https://doi.org/10.1511/2001.18.142

Page 242 and 243. *As groundbreaking as.*

1757. Abdel-Salam, O. M. E. (2016). Preference for hot pepper: A complex interplay of personal, cultural, and pharmacological effects. *Temperature*, *3*(1), 39–40. https://doi.org/10.1080/23328940.2015.1111289

1758. Bromham, L., Skeels, A., Schneemann, H., Dinnage, R., & Hua, X. (2021). There is little evidence that spicy food in hot countries is an adaptation to reducing infection risk. *Nature Human Behaviour*, *5*(7), 878–891. https://doi.org/10.1038/s41562-020-01039-8

1759. Martello, J. L. (2022). *Associations among Proxies for Pathogen Stress and Consumption of Plant Secondary Compounds: A Country-Level Analysis*. Washington State University.

1760. Hagen, E. H., Blackwell, A. D., Lightner, A. D., & Sullivan, R. J. (2023). *Homo medicus* : The transition to meat eating increased pathogen pressure and the use of pharmacological plants in *Homo*. *American Journal of Biological Anthropology*, *180*(4), 589–617. https://doi.org/10.1002/ajpa.24718

Page 243. *For example, a little-supported*.

1761. Spence, C. (2018). Why is piquant/spicy food so popular? *International Journal of Gastronomy and Food Science*, *12*, 16–21. https://doi.org/10.1016/j.ijgfs.2018.04.002

Page 243. *They enhance our experience*.

1762. Bourgeois, J. A., Parthasarathi, U., & Hategan, A. (2014). Taking the spice route: psychoactive properties of culinary spices. *Curr Psychiatry*, *13*(4), 21-32. https://cdn.mdedge.com/files/s3fs-public/Document/September-2017/021_0414CP_Bourgeois_FINAL.pdf

1763. Smalheiser, N. R. (2019). A Neglected Link Between the Psychoactive Effects of Dietary Ingredients and Consciousness-Altering Drugs. *Frontiers in Psychiatry*, *10*. https://doi.org/10.3389/fpsyt.2019.00591

Page 243. *A more recent article*.

1764. Johnson-Arbor, K., & Smolinske, S. (2021). Stoned on spices: a mini-review of three commonly abused household spices. *Clinical Toxicology*, *59*(2), 101–105. https://doi.org/10.1080/15563650.2020.1840579

Page 243. *One interesting example*.

1765. X, Malcolm; Haley, Alex (1965). *The Autobiography of Malcolm X* (1st ed.). New York: Grove Press.

1766. Weil, A. T. (1971). Nutmeg as a Psychoactive Drug. *Journal of Psychedelic Drugs*, *3*(2), 72–80. https://doi.org/10.1080/02791072.1971.10471380

1767. Kalbhen, D. A. (1971). Nutmeg as a Narcotic. A Contribution to the Chemistry and Pharmacology of Nutmeg *(Myristica fragrans)*. *Angewandte Chemie International Edition in English*, *10*(6), 370–374. https://doi.org/10.1002/anie.197103701

Page 244. *Take the case of D.*

1768. Hategan, S. J. (2013). Effects of chronic nutmeg abuse. *Current Psychiatry*, *12*(12), e1.

Page 244. *Could the subtle.*

1769. Smalheiser, N. R. (2019). A Neglected Link Between the Psychoactive Effects of Dietary Ingredients and Consciousness-Altering Drugs. *Frontiers in Psychiatry*, *10*. https://doi.org/10.3389/fpsyt.2019.00591

Page 244 and 245. *Saffron is widely used.*

1770. Basker, D., & Negbi, M. (1983). Uses of saffron. *Economic Botany*, *37*(2), 228–236. https://doi.org/10.1007/BF02858789

1771. Forsyth, P.Y. (2000). The Medicinal Use of Saffron in the Aegean Bronze Age. *Echos du monde classique: Classical views* *44*(2), 145-166. https://www.muse.jhu.edu/article/650900.

1772. Willard, P. (2002). *Secrets of saffron: the vagabond life of the world's most seductive spice*. Beacon press.

Page 245. *Small double-blind.*

1773. Noorbala, A. A., Akhondzadeh, S., Tahmacebi-Pour, N., & Jamshidi, A. H. (2005). Hydro-alcoholic extract of *Crocus sativus* L. versus fluoxetine in the treatment of mild to moderate depression: a double-blind, randomized pilot trial. *Journal of Ethnopharmacology*, *97*(2), 281–284. https://doi.org/10.1016/j.jep.2004.11.004

1774. Basti, A. A., Moshiri, E., Noorbala, A. A., Jamshidi, A. H., Abbasi, S. H., & Akhondzadeh, S. (2007). Comparison of petal of *Crocus sativus* L. and fluoxetine in the treatment of depressed outpatients: A pilot double-blind randomized trial. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *31*(2), 439–442. https://doi.org/10.1016/j.pnpbp.2006.11.010

1775. Lopresti, A. L., & Drummond, P. D. (2014). Saffron (*Crocus sativus*) for depression: a systematic review of clinical studies and examination of underlying antidepressant mechanisms of action. *Human Psychopharmacology: Clinical and Experimental*, *29*(6), 517–527. https://doi.org/10.1002/hup.2434

1776. Shahmansouri, N., Farokhnia, M., Abbasi, S.-H., Kassaian, S. E., Noorbala Tafti, A.-A., Gougol, A., Yekehtaz, H., Forghani, S., Mahmoodian, M., Saroukhani, S., Arjmandi-Beglar, A., & Akhondzadeh, S. (2014). A randomized, double-blind, clinical trial comparing the efficacy and safety of *Crocus sativus* L. with fluoxetine for improving mild to moderate depression in post percutaneous coronary intervention patients. *Journal of Affective Disorders*, *155*, 216–222. https://doi.org/10.1016/j.jad.2013.11.003

1777. Hausenblas, H. A., Heekin, K., Mutchie, H. L., & Anton, S. (2015). A systematic review of randomized controlled trials examining the effectiveness of saffron (Crocus sativus L.) on psychological and behavioral outcomes. *Journal of Integrative Medicine*, *13*(4), 231–240. https://doi.org/10.1016/S2095-4964(15)60176-5

1778. Sahraian, A., Jelodar, S., Javid, Z., Mowla, A., & Ahmadzadeh, L. (2016). Study the effects of saffron on depression and lipid profiles: A double blind comparative study. *Asian Journal of Psychiatry*, *22*, 174–176. https://doi.org/10.1016/j.ajp.2015.10.012

1779. Kashani, L., Eslatmanesh, S., Saedi, N., Niroomand, N., Ebrahimi, M., Hosseinian, M., Foroughifar, T., Salimi, S., & Akhondzadeh, S. (2016). Comparison of Saffron versus Fluoxetine in Treatment of Mild to Moderate Postpartum Depression: A Double-Blind, Randomized Clinical Trial. *Pharmacopsychiatry*, *50*(02), 64–68. https://doi.org/10.1055/s-0042-115306

1780. Shafiee, M., Arekhi, S., Omranzadeh, A., & Sahebkar, A. (2018). Saffron in the treatment of depression, anxiety and other mental disorders: Current evidence and potential mechanisms of action. *Journal of Affective Disorders*, *227*, 330–337. https://doi.org/10.1016/j.jad.2017.11.020

1781. Khaksarian, M., Behzadifar, M., Behzadifar, M., Alipour, M., Jahanpanah, F., Re, T. S., Firenzuoli, F., Zerbetto, R., & Bragazzi, N. L. (2019). The efficacy of *Crocus sativus* (Saffron) versus placebo and Fluoxetine in treating depression: a systematic review and meta-analysis. *Psychology Research and Behavior Management*, *Volume 12*, 297–305. https://doi.org/10.2147/PRBM.S199343

1782. Tóth, B., Hegyi, P., Lantos, T., Szakács, Z., Kerémi, B., Varga, G., Tenk, J., Pétervári, E., Balaskó, M., Rumbus, Z., Rakonczay, Z., Bálint, E., Kiss, T., & Csupor, D. (2019). The Efficacy of Saffron in the Treatment of Mild to Moderate Depression: A Meta-analysis. *Planta Medica*, *85*(01), 24–31. https://doi.org/10.1055/a-0660-9565

Page 245. *The most interesting study*.

1783. Georgiadou, G., Tarantilis, P. A., & Pitsikas, N. (2012). Effects of the active constituents of *Crocus sativus* L., crocins, in an animal model of obsessive–compulsive disorder. *Neuroscience Letters*, *528*(1), 27–30. https://doi.org/10.1016/j.neulet.2012.08.081

1784. Kazemi, F., Vosough, I., Sepahi, S., & Mohajeri, S. A. (2021). Effect of crocin versus fluoxetine in treatment of mild to moderate obsessive-compulsive disorder: A double blind randomized clinical trial. *Human Psychopharmacology: Clinical and Experimental*, *36*(4). https://doi.org/10.1002/hup.2780

Page 246. *Saffranal also has anticonvulsant*.

1785. Hosseinzadeh, H., & Sadeghnia, H. R. (2007). Protective effect of safranal on pentylenetetrazol-induced seizures in the rat: Involvement of GABAergic and opioids systems. *Phytomedicine*, *14*(4), 256–262. https://doi.org/10.1016/j.phymed.2006.03.007

1786. Sadeghnia, H., Cortez, M., Liu, D., Hosseinzadeh, H., & Snead, O. C. (2008). Antiabsence Effects of Safranal in Acute Experimental Seizure Models: EEG and Autoradiography. *Journal of Pharmacy & Pharmaceutical Sciences*, *11*(3), 1. https://doi.org/10.18433/J38G6J

1787. Pitsikas, N., & Tarantilis, P. A. (2020). The GABAA-Benzodiazepine Receptor Antagonist Flumazenil Abolishes the Anxiolytic Effects of the Active Constituents of *Crocus sativus* L. Crocins in Rats. *Molecules*, *25*(23), 5647. https://doi.org/10.3390/molecules25235647

Page 246. *Relief from physical pain*.

1788. Navratilova, E., & Porreca, F. (2014). Reward and motivation in pain and pain relief. *Nature Neuroscience*, *17*(10), 1304–1312. https://doi.org/10.1038/nn.3811

Page 246. *So, when we consume.*

1789. Rozin, P., & Schiller, D. (1980). The nature and acquisition of a preference for chili pepper by humans. *Motivation and Emotion*, *4*(1), 77–101. https://doi.org/10.1007/BF00995932

1790. Mohr, C., Leyendecker, S., Mangels, I., Machner, B., Sander, T., & Helmchen, C. (2008). Central representation of cold-evoked pain relief in capsaicin induced pain: An event-related fMRI study. *Pain*, *139*(2), 416–430. https://doi.org/10.1016/j.pain.2008.05.020

1791. Nilius, B., & Appendino, G. (2013). Spices: the savory and beneficial science of pungency. *Reviews of Physiology, Biochemistry and Pharmacology*, *164*, 1–76. https://doi.org/10.1007/112_2013_11

1792. Bastian, B., Jetten, J., & Hornsey, M. J. (2014). Gustatory pleasure and pain. The offset of acute physical pain enhances responsiveness to taste. *Appetite*, *72*, 150–155. https://doi.org/10.1016/j.appet.2013.10.011

1793. Dalton, P., & Byrnes, N. (2016). Psychology of chemesthesis – why would anyone want to be in pain? In *Chemesthesis* (pp. 8–31). Wiley. https://doi.org/10.1002/9781118951620.ch2

1794. Elman, I., & Borsook, D. (2016). Common Brain Mechanisms of Chronic Pain and Addiction. *Neuron*, *89*(1), 11–36. https://doi.org/10.1016/j.neuron.2015.11.027

Page 246. *Beyond activating our sense of smell.*

1795. Jordt, S.-E., McKemy, D. D., & Julius, D. (2003). Lessons from peppers and peppermint: the molecular logic of thermosensation. *Current Opinion in Neurobiology*, *13*(4), 487–492. https://doi.org/10.1016/S0959-4388(03)00101-6

1796. Basbaum, A. I., Bautista, D. M., Scherrer, G., & Julius, D. (2009). Cellular and Molecular Mechanisms of Pain. *Cell*, *139*(2), 267–284. https://doi.org/10.1016/j.cell.2009.09.028

Page 246. *The "wasabi receptor"*.

1797. Caterina, M. J., Schumacher, M. A., Tominaga, M., Rosen, T. A., Levine, J. D., & Julius, D. (1997). The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature*, *389*(6653), 816–824. https://doi.org/10.1038/39807

1798. McKemy, D. D., Neuhausser, W. M., & Julius, D. (2002). Identification of a cold receptor reveals a general role for TRP channels in thermosensation. *Nature*, *416*(6876), 52–58. https://doi.org/10.1038/nature719

1799. Peier, A. M., Moqrich, A., Hergarden, A. C., Reeve, A. J., Andersson, D. A., Story, G. M., Earley, T. J., Dragoni, I., McIntyre, P., Bevan, S., & Patapoutian, A. (2002). A TRP Channel that Senses Cold Stimuli and Menthol. *Cell*, *108*(5), 705–715. https://doi.org/10.1016/S0092-8674(02)00652-9

1800. Story, G. M., Peier, A. M., Reeve, A. J., Eid, S. R., Mosbacher, J., Hricik, T. R., Earley, T. J., Hergarden, A. C., Andersson, D. A., Hwang, S. W., McIntyre, P., Jegla, T., Bevan, S., & Patapoutian, A. (2003). ANKTM1, a TRP-like Channel Expressed in Nociceptive Neurons, Is Activated by Cold Temperatures. *Cell*, *112*(6), 819–829. https://doi.org/10.1016/S0092-8674(03)00158-2

1801. Jordt, S.-E., Bautista, D. M., Chuang, H., McKemy, D. D., Zygmunt, P. M., Högestätt, E. D., Meng, I. D., & Julius, D. (2004). Mustard oils and cannabinoids excite sensory nerve fibres through the TRP channel ANKTM1. *Nature*, *427*(6971), 260–265. https://doi.org/10.1038/nature02282

1802. Bandell, M., Story, G. M., Hwang, S. W., Viswanath, V., Eid, S. R., Petrus, M. J., Earley, T. J., & Patapoutian, A. (2004). Noxious Cold Ion Channel TRPA1 Is Activated by Pungent Compounds and Bradykinin. *Neuron*, *41*(6), 849–857. https://doi.org/10.1016/S0896-6273(04)00150-3

1803. Woo, S.-H., Ranade, S., Weyer, A. D., Dubin, A. E., Baba, Y., Qiu, Z., Petrus, M., Miyamoto, T., Reddy, K., Lumpkin, E. A., Stucky, C. L., & Patapoutian, A. (2014). Piezo2 is required for Merkel-cell mechanotransduction. *Nature*, *509*(7502), 622–626. https://doi.org/10.1038/nature13251

1804. Hill, R. Z., Loud, M. C., Dubin, A. E., Peet, B., & Patapoutian, A. (2022). PIEZO1 transduces mechanical itch in mice. *Nature*, *607*(7917), 104–110. https://doi.org/10.1038/s41586-022-04860-5

Page 247. *More generally*.

1805. Kang, K., Pulver, S. R., Panzano, V. C., Chang, E. C., Griffith, L. C., Theobald, D. L., & Garrity, P. A. (2010). Analysis of Drosophila TRPA1 reveals an ancient origin for human chemical nociception. *Nature*, *464*(7288), 597–600. https://doi.org/10.1038/nature08848

1806. Sabry, Z., Ho, A., Ireland, D., Rabeler, C., Cochet-Escartin, O., & Collins, E.-M. S. (2019). Pharmacological or genetic targeting of Transient Receptor Potential (TRP) channels can disrupt the planarian escape response. *PLOS ONE*, *14*(12), e0226104. https://doi.org/10.1371/journal.pone.0226104

1807. Smith, E. St. J., Park, T. J., & Lewin, G. R. (2020). Independent evolution of pain insensitivity in African mole-rats: origins and mechanisms. *Journal of Comparative Physiology A*, *206*(3), 313–325. https://doi.org/10.1007/s00359-020-01414-w

Page 247. *In fact, every spice.*

1808. Vennekens, R., Vriens, J., & Nilius, B. (2008). Herbal Compounds and Toxins Modulating TRP Channels. *Current Neuropharmacology*, *6*(1), 79–96. https://doi.org/10.2174/157015908783769644

1809. Nilius, B., & Appendino, G. (2013). Spices: the savory and beneficial science of pungency. *Reviews of Physiology, Biochemistry and Pharmacology*, *164*, 1–76. https://doi.org/10.1007/112_2013_11

1810. Meotti, F. C., Lemos de Andrade, E., & Calixto, J. B. (2014). TRP Modulation by Natural Compounds. In B. Nilius & V. Flockerzi (Eds.), *Mammalian Transient Receptor Potential (TRP) Cation Channels: Volume II* (pp. 1177–1238). Springer International Publishing. https://doi.org/10.1007/978-3-319-05161-1_19

1811. Friedland, K., & Harteneck, C. (2017). Spices and Odorants as TRP Channel Activators. In *Springer Handbook of Odor* (pp. 85–86). Springer International Publishing. https://doi.org/10.1007/978-3-319-26932-0_34

1812. Silver, W. L., & Saunders, C. J. (2020). A TRP Along the Silk Roads: In *Silk Roads* (pp. 65–80). Oxbow Books. https://doi.org/10.2307/j.ctv13nb9gn.11

Page 247. *Consequently, each of these spices.*

1813. Aroke, E., Powell-Roach, K., Jaime-Lara, R., Tesfaye, M., Roy, A., Jackson, P., & Joseph, P. (2020). Taste the Pain: The Role of TRP Channels in Pain and

Taste Perception. *International Journal of Molecular Sciences*, *21*(16), 5929. https://doi.org/10.3390/ijms21165929

Page 248. *The same goes for carbonated.*

1814. Chandrashekar, J., Mueller, K. L., Hoon, M. A., Adler, E., Feng, L., Guo, W., Zuker, C. S., & Ryba, N. J. P. (2000). T2Rs Function as Bitter Taste Receptors. *Cell*, *100*(6), 703–711. https://doi.org/10.1016/S0092-8674(00)80706-0

1815. Carstens, E., Iodi Carstens, M., Dessirier, J.-M., O'Mahony, M., Simons, C. T., Sudo, M., & Sudo, S. (2002). It hurts so good: oral irritation by spices and carbonated drinks and the underlying neural mechanisms. *Food Quality and Preference*, *13*(7–8), 431–443. https://doi.org/10.1016/S0950-3293(01)00067-2

1816. Chandrashekar, J., Yarmolinsky, D., von Buchholtz, L., Oka, Y., Sly, W., Ryba, N. J. P., & Zuker, C. S. (2009). The Taste of Carbonation. *Science*, *326*(5951), 443–445. https://doi.org/10.1126/science.1174601

1817. Wang, Y. Y., Chang, R. B., & Liman, E. R. (2010). TRPA1 Is a Component of the Nociceptive Response to CO_2. *The Journal of Neuroscience*, *30*(39), 12958–12963. https://doi.org/10.1523/JNEUROSCI.2715-10.2010

1818. Turner, H. N., & Liman, E. R. (2022). The Cellular and Molecular Basis of Sour Taste. *Annual Review of Physiology*, *84*(1), 41–58. https://doi.org/10.1146/annurev-physiol-060121-041637

Page 248. *An understanding of why your body.*

1819. Chang, M. M., Leeman, S. E., & Niall, H. D. (1971). Amino-acid Sequence of Substance P. *Nature New Biology*, *232*(29), 86–87. https://doi.org/10.1038/newbio232086a0

1820. Pert, C. B., & Snyder, S. H. (1973). Opiate Receptor: Demonstration in Nervous Tissue. *Science*, *179*(4077), 1011–1014. https://doi.org/10.1126/science.179.4077.1011

1821. Hughes, J., Smith, T. W., Kosterlitz, H. W., Fothergill, L. A., Morgan, B. A., & Morris, H. R. (1975). Identification of two related pentapeptides from the brain with potent opiate agonist activity. *Nature*, *258*(5536), 577–579. https://doi.org/10.1038/258577a0

1822. Simantov, R., & Snyder, S. H. (1976). Morphine-like peptides in mammalian brain: isolation, structure elucidation, and interactions with the opiate receptor. *Proceedings of the National Academy of Sciences*, *73*(7), 2515–2519. https://doi.org/10.1073/pnas.73.7.2515

1823. Hollmann, M., O'Shea-Greenfield, A., Rogers, S. W., & Heinemann, S. (1989). Cloning by functional expression of a member of the glutamate receptor family. *Nature*, *342*(6250), 643–648. https://doi.org/10.1038/342643a0

1824. Enna, S. J., & McCarson, K. E. (2006). The role of GABA in the mediation and perception of pain. *Advances in Pharmacology (San Diego, Calif.)*, *54*, 1–27. https://doi.org/10.1016/s1054-3589(06)54001-3

1825. Garland, E. L. (2012). Pain Processing in the Human Nervous System. *Primary Care: Clinics in Office Practice*, *39*(3), 561–571. https://doi.org/10.1016/j.pop.2012.06.013

1826. Markovic, T., Pedersen, C. E., Massaly, N., Vachez, Y. M., Ruyle, B., Murphy, C. A., Abiraman, K., Shin, J. H., Garcia, J. J., Yoon, H. J., Alvarez, V. A., Bruchas, M. R., Creed, M. C., & Morón, J. A. (2021). Pain induces adaptations in ventral tegmental area dopamine neurons to drive anhedonia-like behavior. *Nature Neuroscience*, *24*(11), 1601–1613. https://doi.org/10.1038/s41593-021-00924-3

Page 249. *What does the hot pan.*

1827. Rozin, P., Ebert, L., & Schull, J. (1982). Some like it hot: A temporal analysis of hedonic responses to chili pepper. *Appetite*, *3*(1), 13–22. https://doi.org/10.1016/S0195-6663(82)80033-0

1828. Gear, R. W., Aley, K. O., & Levine, J. D. (1999). Pain-Induced Analgesia Mediated by Mesolimbic Reward Circuits. *The Journal of Neuroscience*, *19*(16), 7175–7181. https://doi.org/10.1523/JNEUROSCI.19-16-07175.1999

1829. Leknes, S., & Tracey, I. (2008). A common neurobiology for pain and pleasure. *Nature Reviews Neuroscience*, *9*(4), 314–320. https://doi.org/10.1038/nrn2333

1830. Lee, J.-S., Kim, S.-G., Kim, H.-K., Baek, S.-Y., & Kim, C.-M. (2012). Acute Effects of Capsaicin on Proopioimelanocortin mRNA Levels in the Arcuate Nucleus of Sprague-Dawley Rats. *Psychiatry Investigation*, *9*(2), 187. https://doi.org/10.4306/pi.2012.9.2.187

1831. Choy, M., el Fassi, S., & Treur, J. (2021). An adaptive network model for pain and pleasure through spicy food and its desensitization. *Cognitive Systems Research*, *66*, 211–220. https://doi.org/10.1016/j.cogsys.2020.10.006

Page 249 and 250. *Some of us*.

1832. Volpicelli, J., Balaraman, G., Hahn, J., Wallace, H., & Bux, D. (1999). The role of uncontrollable trauma in the development of PTSD and alcohol addiction. *Alcohol Research & Health : The Journal of the National Institute on Alcohol Abuse and Alcoholism*, *23*(4), 256–262.

1833. Volkow, N. D., Fowler, J. S., Wang, G.-J., Swanson, J. M., & Telang, F. (2007). Dopamine in Drug Abuse and Addiction. *Archives of Neurology*, *64*(11), 1575. https://doi.org/10.1001/archneur.64.11.1575

1834. Maté, G. (2008). *In the realm of hungry ghosts: Close encounters with addiction*. Random House Digital, Inc.

1835. Mazei-Robison, M. S., Bowton, E., Holy, M., Schmudermaier, M., Freissmuth, M., Sitte, H. H., Galli, A., & Blakely, R. D. (2008). Anomalous Dopamine Release Associated with a Human Dopamine Transporter Coding Variant. *The Journal of Neuroscience*, *28*(28), 7040–7046. https://doi.org/10.1523/JNEUROSCI.0473-08.2008

1836. Dreher, J.-C., Kohn, P., Kolachana, B., Weinberger, D. R., & Berman, K. F. (2009). Variation in dopamine genes influences responsivity of the human reward system. *Proceedings of the National Academy of Sciences*, *106*(2), 617–622. https://doi.org/10.1073/pnas.0805517106

1837. Frascella, J., Potenza, M. N., Brown, L. L., & Childress, A. R. (2010). Shared brain vulnerabilities open the way for nonsubstance addictions: Carving addiction at a new joint? *Annals of the New York Academy of Sciences*, *1187*(1), 294–315. https://doi.org/10.1111/j.1749-6632.2009.05420.x

1838. Heim, C., Shugart, M., Craighead, W. E., & Nemeroff, C. B. (2010). Neurobiological and psychiatric consequences of child abuse and neglect. *Developmental Psychobiology*, *52*(7), 671–690. https://doi.org/10.1002/dev.20494

1839. Maté, G. (2012). Addiction: Childhood trauma, stress and the biology of addiction. *Journal of Restorative Medicine*, *1*(1), 56-63.

1840. Pearce, E., Wlodarski, R., Machin, A., & Dunbar, R. I. M. (2017). Variation in the β-endorphin, oxytocin, and dopamine receptor genes is associated with different dimensions of human sociality. *Proceedings of the National Academy of Sciences*, *114*(20), 5300–5305. https://doi.org/10.1073/pnas.1700712114

Page 250. *It is easy to see*.

1841. Jones, G. A. (1989). Alcohol abuse and traumatic brain injury. *Alcohol Health & Research World*, *13*(2), 104-110.

1842. Dube, S. R., Felitti, V. J., Dong, M., Chapman, D. P., Giles, W. H., & Anda, R. F. (2003). Childhood Abuse, Neglect, and Household Dysfunction and the Risk of Illicit Drug Use: The Adverse Childhood Experiences Study. *Pediatrics*, *111*(3), 564–572. https://doi.org/10.1542/peds.111.3.564

1843. Widom, C. S., White, H. R., Czaja, S. J., & Marmorstein, N. R. (2007). Long-Term Effects of Child Abuse and Neglect on Alcohol Use and Excessive Drinking in Middle Adulthood. *Journal of Studies on Alcohol and Drugs*, *68*(3), 317–326. https://doi.org/10.15288/jsad.2007.68.317

Page 250. *There are complex reasons*.

1844. Maté, G. (2008). *In the realm of hungry ghosts: Close encounters with addiction*. Random House Digital, Inc.

Page 251. *However, we are unique*. Humans are considered more “altricial” than more “precocial” chimpanzees, for example, as in more like sparrow nestlings than duck nestlings right after birth (this is an extreme comparison).

1845. Portmann, A. (1969). Biologische Fragmente zu einer Lehre vom Menschen [A Zoologist Looks at Humankind](Schwabe, Basel, Germany); trans Schaefer J (1990).

1846. Kennedy, G. (2005). From the ape’s dilemma to the weanling’s dilemma: early weaning and its evolutionary context. *Journal of Human Evolution*, *48*(2), 123–145. https://doi.org/10.1016/j.jhevol.2004.09.005

1847. Neubauer, S., & Hublin, J.-J. (2012). The Evolution of Human Brain Development. *Evolutionary Biology*, *39*(4), 568–586. https://doi.org/10.1007/s11692-011-9156-1

1848. Gómez-Robles, A., Hopkins, W. D., Schapiro, S. J., & Sherwood, C. C. (2015). Relaxed genetic control of cortical organization in human brains compared with chimpanzees. *Proceedings of the National Academy of Sciences*, *112*(48), 14799–14804. https://doi.org/10.1073/pnas.1512646112

1849. Smithsonian Institute. (n.d.). Human Characteristics: Brains. https://humanorigins.si.edu/human-characteristics/brains

Page 250. *Infants that are*.

1850. Maté, G. (2012). Addiction: Childhood trauma, stress and the biology of addiction. *Journal of Restorative Medicine*, *1*(1), 56-63.

Page 251. *A particular mutation in OPRM1*.

1851. Bond, C., LaForge, K. S., Tian, M., Melia, D., Zhang, S., Borg, L., Gong, J., Schluger, J., Strong, J. A., Leal, S. M., Tischfield, J. A., Kreek, M. J., & Yu, L. (1998). Single-nucleotide polymorphism in the human mu opioid receptor gene alters β-endorphin binding and activity: Possible implications for opiate addiction. *Proceedings of the National Academy of Sciences*, *95*(16), 9608–9613. https://doi.org/10.1073/pnas.95.16.9608

1852. Smith, A. H., Jensen, K. P., Li, J., Nunez, Y., Farrer, L. A., Hakonarson, H., Cook-Sather, S. D., Kranzler, H. R., & Gelernter, J. (2017). Genome-wide association study of therapeutic opioid dosing identifies a novel locus upstream of OPRM1. *Molecular Psychiatry*, *22*(3), 346–352. https://doi.org/10.1038/mp.2016.257

1853. Ho, K. W. D., Wallace, M. R., Staud, R., & Fillingim, R. B. (2020). OPRM1, OPRK1, and COMT genetic polymorphisms associated with opioid effects on experimental pain: a randomized, double-blind, placebo-controlled study. *The Pharmacogenomics Journal*, *20*(3), 471–481. https://doi.org/10.1038/s41397-019-0131-z

1854. Yee, L., Capule, F. R., & Makmor-Bakry, M. (2022). Genetic polymorphisms of *OPRM1* on the efficacy and safety of anesthetic and analgesic agents: a systematic review. *Pharmacogenomics*, *23*(10), 609–617. https://doi.org/10.2217/pgs-2022-0042

1855. Gaddis, N., Mathur, R., Marks, J., Zhou, L., Quach, B., Waldrop, A., Levran, O., Agrawal, A., Randesi, M., Adelson, M., Jeffries, P. W., Martin, N. G., Degenhardt, L., Montgomery, G. W., Wetherill, L., Lai, D., Bucholz, K., Foroud, T., Porjesz, B., … Johnson, E. O. (2022). Multi-trait genome-wide association study of opioid addiction: OPRM1 and beyond. *Scientific Reports*, *12*(1), 16873. https://doi.org/10.1038/s41598-022-21003-y

Page 251. *A small but*.

1856. Jeong, H. J., Kim, S. G., Kim, J. H., Park, S. H., & Kang, C. J. (2007). The impact of hot food preferences on naltrexone's effects on subjective acute responses to alcohol in social drinkers. *Journal of Korean Neuropsychiatric Association*, 566-572.

1857. Park, J.-H., Kim, S.-G., Kim, J.-H., Lee, J.-S., Jung, W.-Y., & Kim, H.-K. (2017). Spicy Food Preference and Risk for Alcohol Dependence in Korean. *Psychiatry Investigation*, *14*(6), 825. https://doi.org/10.4306/pi.2017.14.6.825

Page 251. *As ethnobotanist Gary Nabhan*.

1858. Nabhan, G. P. (2004). *Why some like it hot: food, genes, and cultural diversity*. Island Press.

Page 251 and 252. *Paul Freedman*. This reference supports the next seven paragraphs.

1859. Freedman, P. (2008). *Out of the East: spices and the medieval imagination*. Yale University Press.

Page 252. *Out of Mithridate's paranoia*.

1860. Grévin, J. (1568). Deux liures des venins: ausquels il est amplement discouru des bestes venimeuses, theriaques, poisons & contrepoisons. Anvers.

1861. Tidicaeus, F. (1607). De theriaca et eius multiplici utilitate, ac recta conficiendi ratione in Andromachi Senioris […] carmen Graecum de theriaca ex viperis inscriptum, commentarius. Thorun.

1862. Karamanou, M., & Androutsos, G. (2014). Theriaca Magna. In *History of Toxicology and Environmental Health* (pp. 35–43). Elsevier. https://doi.org/10.1016/B978-0-12-800045-8.00005-8

1863. Karamanou, M., & Androutsos, G. (2019). Theriaca magna: the glorious cure-all remedy. In *Toxicology in Antiquity* (pp. 175–184). Elsevier. https://doi.org/10.1016/B978-0-12-815339-0.00012-3

Page 252. *The recipe called for*.

1864. Mayor, A. (2019). Mithridates of Pontus and His Universal Antidote. In *Toxicology in Antiquity* (pp. 161–174). Elsevier. https://doi.org/10.1016/B978-0-12-815339-0.00011-1

Page 252. *In the first century.* See from Karaberopoulus et al. (2012) reference below: "But Galen did not just administer his theriac, he also experimented with it on animals. In *De Theriaca ad Pisonem* he describes how he took roosters and divided them into two groups: in one group he gave the theriac and in the other group he did not. Then he brought both groups into contact with snakes; Galen observed that the roosters who had not been given the theriac died immediately after being bitten, whereas those who had been given the theriac survived. Moreover, he points out that this experiment could be used in cases where someone wants to make sure whether a theriac is in its natural form or has been adulterated."

1865. Karaberopoulos, D., Karamanou, M., & Androutsos, G. (2012). The theriac in antiquity. *The Lancet*, *379*(9830), 1942–1943. https://doi.org/10.1016/S0140-6736(12)60846-0

Chapter 12. Nutmeg, Tea, Opium and Cinchona

Page 254. *Spices flowed into*. The references below are relied upon heavily throughout this chapter.

1866. Lane, F. C. (1940). The Mediterranean Spice Trade Further Evidence of its Revival in the Sixteenth Century. *The American Historical Review*, *45*(3), 581. https://doi.org/10.2307/1840697

1867. Chittick, N. (1979). Early ports in the Horn of Africa. *International Journal of Nautical Archaeology*, *8*(4), 273–277. https://doi.org/10.1111/j.1095-9270.1979.tb01131.x

1868. Ashtor, E. (1980). The volume of mediaeval spice trade. *Journal of European Economic History*, *9*(3), 753.

1869. Casson, L. (1980). Rome's Trade with the East: The Sea Voyage to Africa and India. *Transactions of the American Philological Association (1974-)*, *110*, 21. https://doi.org/10.2307/284208

1870. Chaudhuri, K. N. (1985). *Trade and civilisation in the Indian Ocean: an economic history from the rise of Islam to 1750*. Cambridge University Press.

1871. Laurioux, B. (1985). Spices in the medieval diet: A new approach. *Food and Foodways*, *1*(1–2), 43–75. https://doi.org/10.1080/07409710.1985.9961877

1872. Di Cosmo, N. (2005). Venice, Genoa, The Golden Horde, and the Limits of European Expansion in Asia. *Venice, Genoa, the Golden Horde, and the Limits of European Expansion in Asia*, 1000-1018.

1873. Smith, S. H. (2007). Demystifying a Change in Taste: Spices, Space, and Social Hierarchy in Europe, 1380-1750. *The International History Review*, *29*(2), 237–257. http://www.jstor.org/stable/40110784

1874. Freedman, P. (2008). *Out of the East: spices and the medieval imagination*. Yale University Press.

1875. Turner, J. (2008). *Spice: the History of a Temptation*. Vintage.

1876. Livarda, A. (2011). Spicing up life in northwestern Europe: exotic food plant imports in the Roman and medieval world. *Vegetation History and Archaeobotany*, *20*(2), 143–164. https://doi.org/10.1007/s00334-010-0273-z

1877. Freedman, P. (2012). The Medieval Spice Trade. In *The Oxford Handbook of Food History* (pp. 324–340). Oxford University Press. https://doi.org/10.1093/oxfordhb/9780199729937.013.0018

1878. Warmington, E. H. (2014). *The commerce between the Roman Empire and India*. Cambridge university press.

1879. Boerner, L., & Severgnini, B. (2015). Genoa and Venice: Traders of Prosperity, Growth, and Death. In G. Christ (Ed.), *Union in Separation Diasporic Groups and Identities in the Eastern Mediterranean (1100-1800)* (pp. 105-122). Viella. Viella Historical Research No. 1

1880. Freedman, P. (2015). Health, wellness and the allure of spices in the Middle Ages. *Journal of Ethnopharmacology*, *167*, 47–53. https://doi.org/10.1016/j.jep.2014.10.065

1881. van der Veen, M., & Morales, J. (2015). The Roman and Islamic spice trade: New archaeological evidence. *Journal of Ethnopharmacology*, *167*, 54–63. https://doi.org/10.1016/j.jep.2014.09.036

Page 254. *Genoese traders established*.

1882. Vasil'ev, A. A. (1936). *The Goths in the Crimea*. Mediaeval academy of America. https://books.google.com/books?id=9f4gAQAAMAAJ

1883. Grousset, R. (1970). *The empire of the steppes: a history of Central Asia*. Rutgers University Press.

1884. Khvalkov, E. A. (2018). Europeans in the Black Sea Area during the Late Middle Ages: The Genoese Colony of Caffa. *Mediaevistik*, *31*(1), 213–234. https://doi.org/10.3726/med.2018.1.11

1885. Barker, H. (2021). Laying the Corpses to Rest: Grain, Embargoes, and *Yersinia pestis* in the Black Sea, 1346–48. *Speculum*, *96*(1), 97–126. https://doi.org/10.1086/711596

1886. Mayor, A. (2022). *Greek Fire, Poison Arrows, and Scorpion Bombs: Unconventional Warfare in the Ancient World*. Princeton University Press.

1887. Spyrou, M. A., Musralina, L., Gnecchi Ruscone, G. A., Kocher, A., Borbone, P.-G., Khartanovich, V. I., Buzhilova, A., Djansugurova, L., Bos, K. I., Kühnert, D., Haak, W., Slavin, P., & Krause, J. (2022). The source of the Black Death in fourteenth-century central Eurasia. *Nature*, *606*(7915), 718–724. https://doi.org/10.1038/s41586-022-04800-3

1888. Ferreira, C., Doursout, M.-F. J., & Balingit, J. S. (2023). The Plagues Pandemics: 2000 Years of Recurrent Devastations: The Black Death. In *2000 Years of Pandemics* (pp. 17–59). Springer International Publishing. https://doi.org/10.1007/978-3-031-10035-2_2

1889. Schaub, G. A., & Vogel, P. U. B. (2023). Plague Disease: From Asia to Europe and Back along the Silk Road. In H. Mehlhorn, X. Wu, & Z. Wu (Eds.), *Infectious Diseases along the Silk Roads: The Spread of Parasitoses and Culture Past and Today* (pp. 83–112). Springer International Publishing. https://doi.org/10.1007/978-3-031-35275-1_7

Page 255. *With no knowledge of*.

1890. Dixon, A. (1908). A note on three cases of plague treated by Yersin's serum. *The Lancet*, *171*(4407), 494-495. https://doi.org/10.1016/S0140-6736(00)66513-3

1891. Riddle, J. M. (1964). Pomum ambrae: Amber and Ambergris in Plague Remedies. *Sudhoffs Archiv Für Geschichte Der Medizin Und Der Naturwissenschaften*, *48*(2), 111–122. http://www.jstor.org/stable/20775083

1892. Dubois, E. (1980). How to Face the Plague: Some Seventeenth-Century Practices. *Seventeenth-Century French Studies Newsletter*, *2*(1), 29–36. https://doi.org/10.1179/c17.1980.2.1.29

1893. Milton, G. (1999). *Nathaniel's Nutmeg, Or, The True and Incredible Adventures of the Spice Trader who Changed the Course of History*. Macmillan.

1894. Fabbri, C. N. (2007). Treating Medieval Plague: The Wonderful Virtues of Theriac. *Early Science and Medicine*, *12*(3), 247–283. http://www.jstor.org/stable/20617676

1895. Freedman, P. (2008). *Out of the East: spices and the medieval imagination*. Yale University Press.

1896. Turner, J. (2008). *Spice: the History of a Temptation*. Vintage.

1897. Nam, J. K. (2014). Medieval European Medicine and Asian Spices. *Korean Journal of Medical History*, *23*(2), 319–342. https://doi.org/10.13081/kjmh.2014.23.319

1898. Pagano, T., Goik, M., Templeton, D. C., Ross, A. D., & Smith, S. B. (2016). Exploring nutmeg's intriguing place in history using narrative and project-based approaches in the science laboratory. *Journal of Laboratory Chemical Education*, *4*(1), 9-18.

Page 255. *It was not only the fall*. Quote by Freedman is in reference below.

1899. Freedman, P. (2008). *Out of the East: spices and the medieval imagination*. Yale University Press.

Page 255. *Christopher Columbus.*

1900. Keegan, W. F., & Mitchell, S. W. (1987). The archaeology of Christopher Columbus' voyage through the Bahamas, 1492. *American Archaeology*, *6*(2), 102-108.

Page 256. *Columbus sailed.*

1901. Crosby, A. W. (1972). *The Columbian Exchange; Biological and cultural consequences of 1492*. Greenwood Press.

1902. McNeill, J. (2023, September 29). *Columbian Exchange*. *Encyclopedia Britannica*. https://www.britannica.com/event/Columbian-exchange

1903. Daru, B. H., Davies, T. J., Willis, C. G., Meineke, E. K., Ronk, A., Zobel, M., Pärtel, M., Antonelli, A., & Davis, C. C. (2021). Widespread homogenization of plant communities in the Anthropocene. *Nature Communications*, *12*(1), 6983. https://doi.org/10.1038/s41467-021-27186-8

1904. Hancock, J. F. (2023). Fifty Years Later—The Legacy of Alfred Crosby's "The Columbian Exchange: Biological and Cultural Consequences of 1492." *Economic Botany*, *77*(1), 82–102. https://doi.org/10.1007/s12231-022-09563-6

1905. Philippsen, B., Feveile, C., Olsen, J., & Sindbæk, S. M. (2022). Single-year radiocarbon dating anchors Viking Age trade cycles in time. *Nature*, *601*(7893), 392–396. https://doi.org/10.1038/s41586-021-04240-5

Page 256. *Meanwhile the.*

1906. Corrêa, G. (1869). *The three voyages of Vasco da Gama, and his viceroyalty* (No. 42). B. Franklin.

1907. Keay, J. (2011). *India: A history*. Open Road+ Grove/Atlantic.

1908. Ravenstein, E. G. (Ed.). (2017). *A journal of the first voyage of Vasco da Gama, 1497-1499*. Taylor & Francis.

1909. O'Rourke, K. H., & Williamson, J. G. (2009). Did Vasco da Gama Matter for European Markets? *The Economic History Review*, *62*(3), 655–684. http://www.jstor.org/stable/20542963

Page 256 and 257. *Not long after*. These references support the next six paragraphs as well.

1910. Freedman, P. (2008). *Out of the East: spices and the medieval imagination*. Yale University Press.

1911. Turner, J. (2008). *Spice: the History of a Temptation*. Vintage.

Page 257. *In 1667, the Treaty*.

1912. Loth, V. C. (1995). Armed Incidents and Unpaid Bills: Anglo-Dutch Rivalry in the Banda Islands in the Seventeenth Century. *Modern Asian Studies*, *29*(4), 705–740. http://www.jstor.org/stable/312802

1913. Van Ittersum, M. (2020). Arguing over empire: international law and Anglo-Dutch rivalry in the Banda Islands, 1616-67. In *War, Trade and the State: Anglo-Dutch Conflict 1652-89* (pp. 248-269). Boydell Press.

Page 257. *However, as demand for spices*.

1914. Wilson, S. M. (1984). Coffee, Tea, or Opium?. *Natural History*.

1915. Guotu, Z. (1993). Tea, Silver, Opium and War: From Commercial Expansion to Military Invasion. *Itinerario*, *17*(2), 10–36. https://doi.org/10.1017/S0165115300024384

1916. Bard, S. (2000). Tea and Opium. *Journal of the Hong Kong Branch of the Royal Asiatic Society*, *40*, 1-19. http://www.jstor.org/stable/23895257

1917. Zhong, W. (2010). The Roles of Tea and Opium in Early Economic Globalization: A Perspective on China's Crisis in the 19th Century. *Frontiers of History in China*, *5*(1), 86–105. https://doi.org/10.1007/s11462-010-0004-0

1918. Derks, H. (2012). Tea for Opium Vice Versa. In *History of the Opium Problem* (pp. 49-86). Brill.

Page 258. *The Treaty of Breda*. See references above (Page 257. *In 1667, the Treaty*.) and below.

1919. Lesaffer, R., & Martell, G. (2018). Peace of Breda (1667). In *The Encyclopedia of Diplomacy*. Wiley.

1920. Rommelse, G. (2010). The role of mercantilism in Anglo-Dutch political relations, 1650–74. *The Economic History Review*, *63*(3), 591-611. https://www.jstor.org/stable/40929818

Page 258. *In the seventeenth century*.

1921. Freedman, P. (2008). *Out of the East: spices and the medieval imagination*. Yale University Press.

1922. Page 258 to 262. *As historian Stephen Platt*. This reference supports the next 13 paragraphs.

1923. Platt, S. R. (2019). *Imperial Twilight: The Opium War and the End of China's Last Golden Age*. Vintage.

Page 261. *Opium dependence*.

1924. Newman, R. K. (1995). Opium Smoking in Late Imperial China: A Reconsideration. *Modern Asian Studies*, *29*(4), 765–794. https://doi.org/10.1017/S0026749X00016176

1925. Slack, E. R. (2000). *Opium, state, and society: China's narco-economy and the Guomindang, 1924-1937*. University of Hawaii Press.

1926. Zheng, Y. (2003). The Social Life of Opium in China, 1483-1999. *Modern Asian Studies*, *37*(1), 1–39. http://www.jstor.org/stable/3876550

1927. Windle, J. (2013). Harms caused by China's 1906–17 opium suppression intervention. *International Journal of Drug Policy*, *24*(5), 498–505. https://doi.org/10.1016/j.drugpo.2013.03.001

1928. Liang, B. (2013). Drugs and drug control in the People's Republic of China (1949–present). In *The Routledge Handbook of Chinese Criminology*. Routledge. https://doi.org/10.4324/9780203766774.ch15

1929. Zhang, S. X., & Chin, K. (2018). China's New Long March to Control Illicit Substance Use: From a Punitive Regime towards Harm Reduction. *Journal of Drug Policy Analysis*, *11*(1). https://doi.org/10.1515/jdpa-2015-0023

1930. Paulès, X. (2022). Opium Detoxification Places in Guangzhou (1839–1952). *East Asian Science, Technology, and Medicine*, 1–30. https://doi.org/10.1163/26669323-20220002

Page 262. *Although internal strife*.

1931. Dikötter, F., Laamann, L., & Xun, Z. (2002). Narcotic culture: A Social History of Drug Consumption in China. *The British Journal of Criminology*, *42*(2), 317–336. http://www.jstor.org/stable/23638784

1932. Vassilev, R. (2010). China's Opium Wars: Britain as the World's First Narco-State. *New Politics*, *13*(1), 75-80.

1933. Rowe, W. T. (2014). White Lotus Rebels and South China Pirates: Crisis and Reform in the Qing Empire by Wensheng Wang. *Harvard Journal of Asiatic Studies*, *74*(2), 379–385. https://doi.org/10.1353/jas.2014.0021

1934. Blessing, O. L. E. (2015). China Weeps: The Opium Wars and Chinas Stolen History. *Collections*, *11*(1), 27–40. https://doi.org/10.1177/155019061501100104

1935. Mao, H. (2016). *The Qing Empire and the Opium War*. Cambridge University Press.

1936. Chen, S. C. (2017). *Merchants of war and peace: British knowledge of China in the making of the opium war*. Hong Kong University Press.

1937. Keller, W., & Shiue, C. H. (2021). *The economic consequences of the opium war* (No. w29404). National Bureau of Economic Research.

Page 262. *By the latter half of the twentieth.*

1938. Scott, D. (2008). *China and the international system, 1840-1949: power, presence, and perceptions in a century of humiliation*. State University of New York Press.

1939. Kaufman, A. A. (2010). The "Century of Humiliation," Then and Now: Chinese Perceptions of the International Order. *Pacific Focus*, *25*(1), 1–33. https://doi.org/10.1111/j.1976-5118.2010.01039.x

Page 262. *The waves continue to ripple.*

1940. Woolf, S. H. (2023). Falling Behind: The Growing Gap in Life Expectancy Between the United States and Other Countries, 1933–2021. *American Journal of Public Health*, *113*(9), 970–980. https://doi.org/10.2105/AJPH.2023.307310

1941. Feng, J. (2022, September 8). Fact Check: Has China Overtaken U.S. in Life Expectancy for First Time? *Newsweek*. https://www.newsweek.com/china-us-life-expectancy-birth-2021-fact-check-1740991

1942. Miles, T. (2018, May 30). China overtakes U.S. for healthy lifespan: WHO data. *Reuters*. https://www.reuters.com/article/us-health-lifespan/china-overtakes-u-s-for-healthy-lifespan-who-data-idUSKCN1IV15L

1943. Rosner, M., Ortiz-Ospina, E., & Ritchie, H. (2013). Life Expectancy. *Our World in Data*. https://ourworldindata.org/life-expectancy#rising-life-expectancy-around-the-world

Page 262. *In an ironic twist*. These references support the next two paragraphs.

1944. Felbab-Brown, V., 2022. *China and synthetic drugs control: Fentanyl, methamphetamines, and precursors*, Brookings Institution. United States of America. https://policycommons.net/artifacts/4136111/china-and-synthetic-drugs-control/4944618/

1945. Wang, C., Lassi, N., Zhang, X., & Sharma, V. (2022). The Evolving Regulatory Landscape for Fentanyl: China, India, and Global Drug Governance. *International Journal of Environmental Research and Public Health*, *19*(4), 2074. https://doi.org/10.3390/ijerph19042074

1946. Lassi, N. (2023). Strengthening pill press control to combat fentanyl: Legislative and law enforcement imperatives. *Exploratory Research in Clinical and Social Pharmacy*, *11*, 100321. https://doi.org/10.1016/j.rcsop.2023.100321

1947. DEA Intelligence Report. (2020). *Fentanyl Flow to the United States*. https://www.dea.gov/documents/2020/2020-03/2020-03-06/fentanyl-flow-united-states

1948. U.S. Department of the Treasury. (2023, May 30). *Treasury Sanctions China- and Mexico-Based Enablers of Counterfeit, Fentanyl-Laced Pill Production*. https://home.treasury.gov/news/press-releases/jy1507

1949. The White House Briefing Room. (2023, April 11). *FACT SHEET: Biden-Harris Administration Announces Strengthened Approach to Crack Down on Illicit Fentanyl Supply Chains*. https://www.whitehouse.gov/briefing-room/statements-releases/2023/04/11/fact-sheet-biden-harris-administration-announces-strengthened-approach-to-crack-down-on-illicit-fentanyl-supply-chains/

1950. U.S. Drug Enforcement Administration. (2021, May). *National Drug Threat Assessment*. https://www.justice.gov/usao-mdpa/page/file/1425276/download

1951. Gupta, R. (2023). *Countering Illicit Fentanyl Trafficking*. https://www.foreign.senate.gov/imo/media/doc/f4597c23-de04-fa71-e612-bcbc49b6826c/021523_Gupta_Testimony.pdf

1952. Congressional Research Service. (2023). *China Primer: Illicit Fentanyl and China's Role*. https://crsreports.congress.gov/product/pdf/IF/IF10890

Page 263. *As Donald Trump*. The quote is paraphrased from Donald J. Trump's victory speech on electron night in 2016.

1953. Gottschalk, M. (2023). The Opioid Crisis: The War on Drugs Is Over. Long Live the War on Drugs. *Annual Review of Criminology*, *6*(1), 363–398. https://doi.org/10.1146/annurev-criminol-030421-040140

1954. Keiffer, C. (2023). Landscapes of Despair: Book Covers and the Visual Culture of the Opioid Crisis. *Art Journal*, *82*(1), 58–73. https://doi.org/10.1080/00043249.2023.2180278

1955. Gage, B. (2016, November). Who Is the "Forgotten Man." *The New Tork Times*. https://www.nytimes.com/interactive/projects/cp/opinion/election-night-2016/who-is-the-forgotten-man

1956. Trump, D., & Federal News Service. (2016, November 9). Transcript: Donald Trump's Victory Speech. *The New York Times*. https://www.nytimes.com/2016/11/10/us/politics/trump-speech-transcript.html

Page 263. *Although the Trump*.

1957. Wen, L. S., & Sadeghi, N. B. (2020). The opioid crisis and the 2020 US election: crossroads for a national epidemic. *The Lancet*, *396*(10259), 1316–1318. https://doi.org/10.1016/S0140-6736(20)32113-9

1958. *Watch Trump's full speech on opioids*. (2017, October 26). The Washington Post. https://www.youtube.com/watch?v=KJHAm87W8NM

1959. Mann, B. (2020, October 29). *Opioid Crisis: Critics Say Trump Fumbled Response To Another Deadly Epidemic*. NPR. https://www.npr.org/2020/10/29/927859091/opioid-crisis-critics-say-trump-fumbled-response-to-another-deadly-epidemic

1960. H.R.6 - 115th Congress (2017-2018): SUPPORT for Patients and Communities Act. (2018, October 24). https://www.congress.gov/bill/115th-congress/house-bill/6

1961. Keith, T. (2017, May 5). Leaked Document Indicates Big Proposed Cuts To Drug Czar's Office. *NPR*. https://www.npr.org/2017/05/05/527076657/leaked-document-indicates-big-proposed-cuts-to-drug-czars-office

1962. United States Government Accountability Office. (2019). *The Office of National Drug Control Policy Should Develop Key Planning Elements to Meet Statutory Requirements*. https://www.gao.gov/assets/gao-20-124.pdf

1963. Anderson, S. (2023, March 2). Synthetic Opioid Overdose Deaths Soared While Trump Was President. *Forbes*. https://www.forbes.com/sites/stuartanderson/2023/03/02/synthetic-opioid-overdose-deaths-soared-while-trump-was-president/

Page 246. *Following a small dip*.

1964. Wilson, N., Kariisa, M., Seth, P., Smith, H., & Davis, N. L. (2020). Drug and Opioid-Involved Overdose Deaths — United States, 2017–2018. *MMWR. Morbidity and Mortality Weekly Report*, *69*(11), 290–297. https://doi.org/10.15585/mmwr.mm6911a4

1965. Hedegaard, H., Miniño, A., Spencer, M. R., & Warner, M. (2021). *Drug Overdose Deaths in the United States, 1999–2020*. https://doi.org/10.15620/cdc:112340

1966. CDC. (2023). *Opioid Data Analysis and Resources*. https://www.cdc.gov/opioids/data/analysis-resources.html

Page 263. *A landmark study*.

1967. Case, A., & Deaton, A. (2015). Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *Proceedings of the National Academy of Sciences*, *112*(49), 15078–15083. https://doi.org/10.1073/pnas.1518393112

Page 263. *After 2013*.

1968. Alexander, M. J., Kiang, M. v., & Barbieri, M. (2018). Trends in Black and White Opioid Mortality in the United States, 1979–2015. *Epidemiology*, *29*(5), 707–715. https://doi.org/10.1097/EDE.0000000000000858

1969. Shiels, M. S., Freedman, N. D., Thomas, D., & Berrington de Gonzalez, A. (2018). Trends in U.S. Drug Overdose Deaths in Non-Hispanic Black, Hispanic, and Non-Hispanic White Persons, 2000–2015. *Annals of Internal Medicine*, *168*(6), 453. https://doi.org/10.7326/M17-1812

1970. Lippold, K. M., Jones, C. M., Olsen, E. O., & Giroir, B. P. (2019). Racial/Ethnic and Age Group Differences in Opioid and Synthetic Opioid–Involved Overdose Deaths Among Adults Aged ≥18 Years in Metropolitan Areas — United States, 2015–2017. *MMWR. Morbidity and Mortality Weekly Report*, *68*(43), 967–973. https://doi.org/10.15585/mmwr.mm6843a3

1971. Friedman, J. R., & Hansen, H. (2022). Evaluation of Increases in Drug Overdose Mortality Rates in the US by Race and Ethnicity Before and During the COVID-19 Pandemic. *JAMA Psychiatry*, *79*(4), 379. https://doi.org/10.1001/jamapsychiatry.2022.0004

1972. Friedman, J., Beletsky, L., & Jordan, A. (2022). Surging Racial Disparities in the U.S. Overdose Crisis. *American Journal of Psychiatry*, *179*(2), 166–169. https://doi.org/10.1176/appi.ajp.2021.21040381

1973. Mason, M., Soliman, R., Kim, H. S., & Post, L. A. (2022). Disparities by Sex and Race and Ethnicity in Death Rates Due to Opioid Overdose Among Adults 55 Years or Older, 1999 to 2019. *JAMA Network Open*, *5*(1), e2142982. https://doi.org/10.1001/jamanetworkopen.2021.42982

1974. Qeadan, F., Madden, E. F., Mensah, N. A., Tingey, B., Herron, J., Hernandez-Vallant, A., Venner, K. L., English, K., & Dixit, A. (2022). Epidemiological trends in opioid-only and opioid/polysubstance-related death rates among American Indian/Alaska Native populations from 1999 to 2019: a retrospective longitudinal ecological study. *BMJ Open*, *12*(5), e053686. https://doi.org/10.1136/bmjopen-2021-053686

1975. Romero, R., Friedman, J. R., Goodman-Meza, D., & Shover, C. L. (2023). US drug overdose mortality rose faster among hispanics than non-hispanics from 2010 to 2021. *Drug and Alcohol Dependence*, *246*, 109859. https://doi.org/10.1016/j.drugalcdep.2023.109859

Page 263. *After 2010, life expectancy*.

1976. Case, A., & Deaton, A. (2015). Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *Proceedings of the National Academy of Sciences*, *112*(49), 15078–15083. https://doi.org/10.1073/pnas.1518393112

1977. Olfson, M., Cosgrove, C., Altekruse, S. F., Wall, M. M., & Blanco, C. (2021). Deaths Of Despair: Adults At High Risk For Death By Suicide, Poisoning, Or Chronic Liver Disease In The US. *Health Affairs*, *40*(3), 505–512. https://doi.org/10.1377/hlthaff.2020.01573

1978. Kuo, C.-T., & Kawachi, I. (2023). County-Level Income Inequality, Social Mobility, and Deaths of Despair in the US, 2000-2019. *JAMA Network Open*, *6*(7), e2323030. https://doi.org/10.1001/jamanetworkopen.2023.23030

1979. Nudy, M., Galper, K., George, D. R., Williams, B. A., Kraschnewski, J. L., Sinoway, L., & Brignone, E. (2023). Association between diseases of despair and atherosclerotic cardiovascular disease among insured adults in the USA: a retrospective cohort study from 2017 to 2021. *BMJ Open*, *13*(9), e074102. https://doi.org/10.1136/bmjopen-2023-074102

Page 264. *Like the isoprene*. These references support the paragraphs through the end of this chapter.

1980. Taylor, N. (1943). Quinine: The Story of Cinchona. *The Scientific Monthly*, *57*(1), 17–32. http://www.jstor.org/stable/18210

1981. Steere, W. C. (1945). The Botanical Work of the Cinchona Missions in South America. *Science*, *101*(2616), 177–178. https://doi.org/10.1126/science.101.2616.177

1982. Steere, W. C. (1945). The Cinchona-Bark Industry of South America. *The Scientific Monthly*, *61*(2), 114–126. http://www.jstor.org/stable/18623

1983. Hodge, W. H. (1948). Wartime cinchona procurement in latin america. *Economic Botany*, *2*(3), 229–257. https://doi.org/10.1007/BF02859067

1984. Smocovitis, V. B. (2003). Desperately seeking quining: The malaria threat drove the Allies' WWII "Cinchona Mission". *Modern Drug Discovery, American Chemical Society, 6(5), 57-58.* https://pubsapp.acs.org/subscribe/archive/mdd/v06/i05/pdf/503timeline.pdf

1985. Kaufman, T. S., & Rúveda, E. A. (2005). The Quest for Quinine: Those Who Won the Battles and Those Who Won the War. *Angewandte Chemie International Edition*, *44*(6), 854–885. https://doi.org/10.1002/anie.200400663

1986. Cuvi, N. (2011). The Cinchona Program (1940-1945): science and imperialism in the exploitation of a medicinal plant. *Dynamis*, *31*(1), 183–206. https://doi.org/10.4321/S0211-95362011000100009

1987. Goss, A. (2014). Building the world's supply of quinine: Dutch colonialism and the origins of a global pharmaceutical industry. *Endeavour*, *38*(1), 8–18. https://doi.org/10.1016/j.endeavour.2013.10.002

1988. Crawford, M. J. (2016). *The Andean wonder drug: Cinchona bark and imperial science in the Spanish Atlantic, 1630-1800*. University of Pittsburgh Press.

Page 264 and 265. *Although only 350,000 pounds*.

1989. Turrion, A. (1989). Quina del Nuevo Mundo para la Corona española. *Asclepio*, *41*(1), 305-323.

Page 265. *In 1942 alone*.

1990. Smocovitis, V. B. (2003). Desperately seeking quining: The malaria threat drove the Allies' WWII "Cinchona Mission". *Modern Drug Discovery, American Chemical Society, 6(5), 57-58.* https://pubsapp.acs.org/subscribe/archive/mdd/v06/i05/pdf/503timeline.pdf

Page 265 and 266. *More quinine was needed*. These references support the next three paragraphs.

1991. Steere, W. C. (1945). The Botanical Work of the Cinchona Missions in South America. *Science*, *101*(2616), 177–178. https://doi.org/10.1126/science.101.2616.177

1992. Steere, W. C. (1945). The Cinchona-Bark Industry of South America. *The Scientific Monthly*, *61*(2), 114–126. http://www.jstor.org/stable/18623

1993. Roosevelt, F. D. (1943, July 15). *Executive Order 9361 Establishing the Office of Economic Warfare.* https://www.presidency.ucsb.edu/documents/executive-order-9361-establishing-the-office-economic-warfare

1994. National Museum of Natural History. (n.d.). *Cinchona Missions Expedition*. https://naturalhistory.si.edu/research/botany/about/historical-expeditions/cinchona-missions

Page 266. *From 1941 to 1945*.

1995. Cuvi, N. (2011). The Cinchona Program (1940-1945): science and imperialism in the exploitation of a medicinal plant. *Dynamis*, *31*(1), 183–206. https://doi.org/10.4321/S0211-95362011000100009

Page 266. *Perhaps more cryptically but arguably.*

1996. Guzmán, M. D. P., & Quevedo, E. (1999). La cooperación técnica norteamericana en salud pública en Colombia durante la Segunda Guerra Mundial. *Biomédica*, *19*(1), 5. https://doi.org/10.7705/biomedica.v19i1.1002

1997. Cuvi, N. (2011). The Cinchona Program (1940-1945): science and imperialism in the exploitation of a medicinal plant. *Dynamis*, *31*(1), 183–206. https://doi.org/10.4321/S0211-95362011000100009

Page 266. *But at the beginning*. These references support the next two paragraphs.

1998. Sayre, F. B. (1937). *The" good Neighbor" Policy and Trade Agreements* (Vol. 998). US Government Printing Office.

1999. Stuart, G. (1939). The Results of the Good Neighbor Policy In Latin America. *World Affairs*, *102*(3), 166–170. http://www.jstor.org/stable/20663306

2000. Wilgus, A. C. (1943). Will the Good Neighbor Policy Outlast the War?. *International Social Science Review*, *18*(4), 193.

2001. Huberman, M. A. (1948). Our Good Neighbors' Forestry. *Journal of Forestry*, *46*(2), 81–98. https://doi.org/10.1093/jof/46.2.81

2002. Van Deusen, R. C. (1961). *Good Neighbor idealism in the Roosevelt era*. American University.

2003. Varg, P. A. (1976). The Economic Side of the Good Neighbor Policy: The Reciprocal Trade Program and South America. *Pacific Historical Review*, *45*(1), 47–71. https://doi.org/10.2307/3637300

2004. Yerxa, D. A. (1987). The United States Navy in Caribbean Waters during World War I. *Military Affairs*, *51*(4), 182. https://doi.org/10.2307/1987947

2005. Berger, M. T. (1993). Civilising the South: The US Rise to Hegemony in the Americas and the Roots of "Latin American Studies" 1898-1945. *Bulletin of Latin American Research*, *12*(1), 1. https://doi.org/10.2307/3338811

2006. Gellman, I. (2019). *Good Neighbor Diplomacy: United States Policies in Latin America, 1933-1945*. JHU Press.

2007. Cuvi, N. (2011). The Cinchona Program (1940-1945): science and imperialism in the exploitation of a medicinal plant. *Dynamis*, *31*(1), 183–206. https://doi.org/10.4321/S0211-95362011000100009

2008. Marcilhacy, D. (2022). 1914, between two oceans, between two empires: a turning point for Latin America. *National Identities*, *24*(1), 21–37. https://doi.org/10.1080/14608944.2020.1738365

Chapter 13. The Future Pharmacopoeia

Page 268. *There is grandeur in this view of life.* This is the last quote in the chapter XIV of Charle's Darwin's masterpiece that usually is known by the abbreviated title *On the Origin of Species*. This particular quote is from the first British edition published in 1859 and three additional words were added to that quote such that by 1872 (the last edition) the words "by the Creator" were inserted after "breathed into" for reasons covered by historians.

2009. Darwin, C. R. (1859). *On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life*. London: Murray. [1st ed.]

Page 269. *Most of these natural toxins*. The notes that follow provide context and support for the entire paragraph that starts with this sentence and the following one that begins: *Scientists have shown that*.

In 1976 botanist Donald Levin published the first truly quantitative study on how plant secondary chemical diversity correlates with latitude such that there are fewer made by plants at the poles or at high elevation than in the tropics or low elevation. He first found that across the planet's latitudes, the percentage of plants with alkaloids increased from the poles to the tropics (like spice use in us). The proportion of plant species from tropical countries containing alkaloids (45%) is nearly double the proportion from temperate countries containing alkaloids (27%). In an attempt tease apart why, Levin cleverly used the German polymath Alexander von Humboldt's observation that the biomes of the planet that so predictably change across latitude, from the rainforests of the tropics to the tundra of the poles, could also be mirrored across changes in altitude, from the base of a tall tropical mountain to its summit. Levin used an alkaloid dataset across such an elevational gradient in the large tropical island of Papua New Guinea, which fit the bill owing to its lush lowland rainforests and treeless alpine habitats. Sure enough, he found that plant species bearing alkaloids were more prevalent in the three rainforest communities, with the most (21.5%) in the lowland rain forest and the fewest in the subalpine and alpine biomes (0%)—although my guess is that the instruments may not have been sensitive enough for us to really know that there aren't *any* in the plants he tested in the latter. Other notable papers buttressing this paragraph in the book are also listed below. One by Levin and York also concludes that the toxicity of the alkaloids made by tropical plants is higher than those made by temperate plants (and that there were no salient differences in toxicity in herbaceous vs. wood plants in that regard). This further supports the working hypothesis that the strength of biotic interactions is higher in the tropics than the temperate zones. In a review, Coley and Barone in 1996 concluded that rates of herbivory are higher in the tropics than in temperate zones. In a series of papers Janzen also proposes some specific hypotheses as to why this is generally the case. MacArthur and Wilson propose why there may be more species in the tropics than in the temperate zone. A general review of whether biotic interactions were stronger in the tropics than the temperate zone was published by Schemske et al. in 2009 and the analysis was in support of this working hypothesis.

2010. Levin, D. A. (1976). Alkaloid-Bearing Plants: An Ecogeographic Perspective. *The American Naturalist*, *110*(972), 261–284. https://doi.org/10.1086/283063

2011. Levin, D. A. (1976). The Chemical Defenses of Plants to Pathogens and Herbivores. *Annual Review of Ecology and Systematics*, *7*(1), 121–159. https://doi.org/10.1146/annurev.es.07.110176.001005

2012. Levin, D. A., & York, B. M. (1978). The toxicity of plant alkaloids: an Ecogeographic perspective. *Biochemical Systematics and Ecology*, *6*(1), 61–76. https://doi.org/10.1016/0305-1978(78)90026-1

2013. Coley, P. D., & Barone, J. A. (1996). Herbivory and Plant Defenses in Tropical Forests. *Annual Review of Ecology and Systematics*, *27*, 305–335. http://www.jstor.org/stable/2097237

2014. Janzen, D. H. (1968). Host Plants as Islands in Evolutionary and Contemporary Time. *The American Naturalist*, *102*(928), 592–595. http://www.jstor.org/stable/2459347

2015. Janzen, D. H. (1973). Community structure of secondary compounds in plants. In *Chemistry in Evolution and Systematics*, ed T. Swain, pp. 529-38. New York: Russak.

2016. Janzen, D. H. (1974). Tropical Blackwater Rivers, Animals, and Mast Fruiting by the Dipterocarpaceae. *Biotropica*, *6*(2), 69. https://doi.org/10.2307/2989823

2017. Hutchinson, G. E. (1959). Homage to Santa Rosalia or Why Are There So Many Kinds of Animals? *The American Naturalist*, *93*(870), 145–159. http://www.jstor.org/stable/2458768

2018. Schemske, D. W., Mittelbach, G. G., Cornell, H. v., Sobel, J. M., & Roy, K. (2009). Is There a Latitudinal Gradient in the Importance of Biotic Interactions? *Annual Review of Ecology, Evolution, and Systematics*, *40*(1), 245–269. https://doi.org/10.1146/annurev.ecolsys.39.110707.173430

Pages 269-270. *If you or a loved one*. This section also applies to the four paragraphs that follow the first. Note that the quote "West Indian shrub" is from the Noble et al. paper from 1958 below.

2019. John Innes Centre. (2018, March 28). *Vinblastine and vincristine: life-saving drugs from a periwinkle*. https://www.jic.ac.uk/blog/vinblastine-and-vincristine-life-saving-drugs-from-a-periwinkle/

2020. *Rosy periwinkle*. (n.d.). Oxford Plants 400. https://herbaria.plants.ox.ac.uk/bol/plants400/Profiles/CD/Catharanthus

2021. Wittenauer, C. (2003, August 3). Saving Rare Plants From Extinction Is Botanists' Mission. *The Washington Post*. https://www.washingtonpost.com/archive/politics/2003/08/03/saving-rare-plants-from-extinction-is-botanists-mission/5f74806f-6b9c-4deb-af2c-5a30e10f5d2c/

2022. Duffin, J. (2000). Poisoning the Spindle: Serendipity and Discovery of the Anti-Tumor Properties of the Vinca Alkaloids. *Canadian Bulletin of Medical History*, *17*(1), 155–192. https://doi.org/10.3138/cbmh.17.1.155

2023. Noble, R. L., Beer, C. T., & Cutts, J. H. (1958). Role of chance observations in chemotherapy: *Vinca rosea*. *Annals of the New York Academy of Sciences*, *76*(3), 882–894. https://doi.org/10.1111/j.1749-6632.1958.tb54906.x

2024. O'Connor, S. E., & Maresh, J. J. (2006). Chemistry and biology of monoterpene indole alkaloid biosynthesis. *Natural Product Reports*, *23*(4), 532. https://doi.org/10.1039/b512615k

2025. Kumar, S., Singh, B., & Singh, R. (2022). Catharanthus roseus (L.) G. Don: A review of its ethnobotany, phytochemistry, ethnopharmacology and toxicities. *Journal of Ethnopharmacology*, *284*, 114647. https://doi.org/10.1016/j.jep.2021.114647

2026. Caputi, L., Franke, J., Farrow, S. C., Chung, K., Payne, R. M. E., Nguyen, T.-D., Dang, T.-T. T., Soares Teto Carqueijeiro, I., Koudounas, K., Dugé de Bernonville, T., Ameyaw, B., Jones, D. M., Vieira, I. J. C., Courdavault, V., & O'Connor, S. E. (2018). Missing enzymes in the biosynthesis of the anticancer drug vinblastine in Madagascar periwinkle. *Science*, *360*(6394), 1235–1239. https://doi.org/10.1126/science.aat4100

Page 270. *Many important drugs come from weedy species*. These references also apply to the next two paragraphs.

2027. Dufour, D. L. (1990). Use of Tropical Rainforests by Native Amazonians. *BioScience*, *40*(9), 652. https://doi.org/10.2307/1311432

2028. Voeks, R. A. (2004). Disturbance Pharmacopoeias: Medicine and Myth from the Humid Tropics. *Annals of the Association of American Geographers*, *94*(4), 868–888. https://doi.org/10.1111/j.1467-8306.2004.00439.x

2029. Ellis, E. C., Gauthier, N., Klein Goldewijk, K., Bliege Bird, R., Boivin, N., Díaz, S., Fuller, D. Q., Gill, J. L., Kaplan, J. O., Kingston, N., Locke, H., McMichael, C. N. H., Ranco, D., Rick, T. C., Shaw, M. R., Stephens, L., Svenning, J.-C., & Watson, J. E. M. (2021). People have shaped most of terrestrial nature for at least 12,000 years. *Proceedings of the National Academy of Sciences*, *118*(17). https://doi.org/10.1073/pnas.2023483118

2030. Bennett, B. C. (2007). Doctrine of Signatures: An Explanation of Medicinal Plant Discovery or Dissemination of Knowledge? *Economic Botany*, *61*(3), 246–255. http://www.jstor.org/stable/4257221

2031. Chazdon, R. L., & Guariguata, M. R. (2016). Natural regeneration as a tool for large-scale forest restoration in the tropics: prospects and challenges. *Biotropica*, *48*(6), 716–730. https://doi.org/10.1111/btp.12381

2032. Voeks, R. A. (2018). *The Ethnobotany of Eden: Rethinking the Jungle Medicine Narrative.* University of Chicago Press: Chicago.

2033. Roberts, P. (2021). *Jungle: How Tropical Forests Shaped the World and Us*. Viking Press: New York.

2034. Canuto, M. A., Estrada-Belli, F., Garrison, T. G., Houston, S. D., Acuña, M. J., Kováč, M., Marken, D., Nondédéo, P., Auld-Thomas, L., Castanet, C., Chatelain, D., Chiriboga, C. R., Drápela, T., Lieskovský, T., Tokovinine, A., Velasquez, A., Fernández-Díaz, J. C., & Shrestha, R. (2018). Ancient lowland Maya complexity as revealed by airborne laser scanning of northern Guatemala. *Science*, *361*(6409). https://doi.org/10.1126/science.aau0137

2035. Inomata, T., Triadan, D., Vázquez López, V. A., Fernandez-Diaz, J. C., Omori, T., Méndez Bauer, M. B., García Hernández, M., Beach, T., Cagnato, C., Aoyama, K., & Nasu, H. (2020). Monumental architecture at Aguada Fénix and the rise of Maya civilization. *Nature*, *582*(7813), 530–533. https://doi.org/10.1038/s41586-020-2343-4

2036. Ringle, W. M., Gallareta Negrón, T., May Ciau, R., Seligson, K. E., Fernandez-Diaz, J. C., & Ortegón Zapata, D. (2021). Lidar survey of ancient Maya settlement in the Puuc region of Yucatan, Mexico. *PLOS ONE*, *16*(4), e0249314. https://doi.org/10.1371/journal.pone.0249314

2037. Prümers, H., Betancourt, C. J., Iriarte, J., Robinson, M., & Schaich, M. (2022). Lidar reveals pre-Hispanic low-density urbanism in the Bolivian Amazon. *Nature*, *606*(7913), 325–328. https://doi.org/10.1038/s41586-022-04780-4

Page 271. *Our past actions have finally.*

2038. Abate, R. S., & Kronk, E. A. (2013). Commonality Among Unique Indigenous Communities: An Introduction to Climate Change and Its Impacts on Indigenous Peoples. *Tulane Environmental Law Journal*, *26*(2), 179–195. http://www.jstor.org/stable/24673665

2039. Lovejoy, T. E. and L. Hannah, Eds. 2019. *Biodiversity and Climate Change: Transforming the Biosphere*. Yale Univ. Press: New Haven.

2040. Leal Filho, W., Matandirotya, N. R., Lütz, J. M., Alemu, E. A., Brearley, F. Q., Baidoo, A. A., Kateka, A., Ogendi, G. M., Adane, G. B., Emiru, N., & Mbih, R. A. (2021). Impacts of climate change to African indigenous communities and examples of adaptation responses. *Nature Communications*, *12*(1), 6224. https://doi.org/10.1038/s41467-021-26540-0

2041. Díaz, S., Pascual, U., Stenseke, M., Martín-López, B., Watson, R. T., Molnár, Z., Hill, R., Chan, K. M. A., Baste, I. A., Brauman, K. A., Polasky, S., Church, A., Lonsdale, M., Larigauderie, A., Leadley, P. W., van Oudenhoven, A. P. E., van der Plaat, F., Schröter, M., Lavorel, S., … Shirayama, Y. (2018). Assessing nature's contributions to people. *Science*, *359*(6373), 270–272. https://doi.org/10.1126/science.aap8826

2042. Pörtner, H.-O., Scholes, R. J., Arneth, A., Barnes, D. K. A., Burrows, M. T., Diamond, S. E., Duarte, C. M., Kiessling, W., Leadley, P., Managi, S., McElwee, P., Midgley, G., Ngo, H. T., Obura, D., Pascual, U., Sankaran, M., Shin, Y. J., & Val, A. L. (2023). Overcoming the coupled climate and biodiversity crises and their societal impacts. *Science*, *380*(6642). https://doi.org/10.1126/science.abl4881

2043. *Climate Change*. (n.d.). U.N. Department of Economic and Social Affairs. https://www.un.org/development/desa/indigenouspeoples/climate-change.html

2044. *Biodiversity - our strongest natural defense against climate change*. (n.d.). U.N. Climate Action. https://www.un.org/en/climatechange/science/climate-issues/biodiversity

2045. *Climate Change and the Health of Indigenous Populations*. (n.d.). Environmental Protection Agency. https://www.epa.gov/climateimpacts/climate-change-and-health-indigenous-populations

Page 272. *As we toured museums*. These references apply to the next four paragraphs well.

2046. Brief description from the Victoria and Albert Museum: "Tapestry 'The Three Fates' ('The Triumph of Death'), Flemish, early 16th century" see: https://collections.vam.ac.uk/item/O72702/the-three-fates-tapestry-unknown/ Gallery Label from the V&A Museum: "THE TRIUMPH OF DEATH or THE THREE FATES The three fates, Clotho, Lachesis and Atropos, who spin, draw out and cut the thread of Life, represent Death in this tapestry, as they triumph over the fallen body of Chastity. This is the third subject in Petrarch's poem The Triumphs. First, Love triumphs; then Love is overcome by Chastity, Chastity by Death, Death by Fame, Fame by Time and Time by Eternity. FLEMISH (probably BRUSSELS); c. 1510-20 Museum number 65-1866 (c. 2003)."

2047. Plato. (1992). *Republic*. Translated by Sorrey (Second ed.). Hackett Publishing Company: Indianapolis.

2048. I Trifoni. (n.d.). https://petrarch.petersadlon.com/trionfi.html

2049. Parcae. (n.d.). In *McClintock and Strong Biblical Encyclopedia*. https://www.biblicalcyclopedia.com/P/parcae.html

2050. Petrarca, F. (n.d.). *The Sonnets, Triumphs, and Other Poems of Petrarch*. https://archive.org/stream/thesonnetstriump17650gut/17650.txt

2051. *Moirai*. (n.d.). Theoi Greek Mythology. https://www.theoi.com/Daimon/Moirai.html#Zeus

Page 274. *I am not a doomer*.

2052. Mann, M. (2023). *Our Fragile Moment: How Lessons from the Earth's Past Can Help Us Survive the Climate Crisis*. Hachette: New York.

2053. Hernandez, J. (2022). *Fresh Banana Leaves: Healing Indigenous Landscapes through Indigenous Science*. North Atlantic: Berkeley.

2054. Dinerstein, E., Joshi, A. R., Vynne, C., Lee, A. T. L., Pharand-Deschênes, F., França, M., Fernando, S., Birch, T., Burkart, K., Asner, G. P., & Olson, D. (2020). A "Global Safety Net" to reverse biodiversity loss and stabilize Earth's climate. *Science Advances*, *6*(36). https://doi.org/10.1126/sciadv.abb2824

2055. Etchart, L. (2017). The role of indigenous peoples in combating climate change. *Palgrave Communications*, *3*(1), 17085. https://doi.org/10.1057/palcomms.2017.85

2056. Buckley, C. (2022, March 22). 'OK Doomer' and the Climate Advocates Who Say It's Not Too Late. *The New York Times*.

https://www.nytimes.com/2022/03/22/climate/climate-change-ok-doomer.html

2057. Mann, M. E., Hassol, S. J., & Toles, T. (2017, July 12). Doomsday Scenarios are as Harmful as Climate Change Denial. *The Washington Post*. https://www.washingtonpost.com/opinions/doomsday-scenarios-are-as-harmful-as-climate-change-denial/2017/07/12/880ed002-6714-11e7-a1d7-9a32c91c6f40_story.html

2058. IPBES-IPCC Co-Sponsored Workshop on Biodiversity and Climate Change. (2021). https://www.ipbes.net/events/ipbes-ipcc-co-sponsored-workshop-biodiversity-and-climate-change

Page 275. *Once we lose a species.*

2059. Raup, D. M., & Sepkoski, J. J. (1982). Mass Extinctions in the Marine Fossil Record. *Science*, *215*(4539), 1501–1503. https://doi.org/10.1126/science.215.4539.1501

2060. Benton, M. J. (1995). Diversification and Extinction in the History of Life. *Science*, *268*(5207), 52–58. https://doi.org/10.1126/science.7701342

2061. Kirchner, J. W., & Weil, A. (2000). Delayed biological recovery from extinctions throughout the fossil record. *Nature*, *404*(6774), 177–180. https://doi.org/10.1038/35004564

2062. Erwin, D. H. (2001). Lessons from the past: Biotic recoveries from mass extinctions. *Proceedings of the National Academy of Sciences*, *98*(10), 5399–5403. https://doi.org/10.1073/pnas.091092698

2063. Lowery, C. M., Bralower, T. J., Owens, J. D., Rodríguez-Tovar, F. J., Jones, H., Smit, J., Whalen, M. T., Claeys, P., Farley, K., Gulick, S. P. S., Morgan, J. v., Green, S., Chenot, E., Christeson, G. L., Cockell, C. S., Coolen, M. J. L., Ferrière, L., Gebhardt, C., Goto, K., … Zylberman, W. (2018). Rapid recovery of life at ground zero of the end-Cretaceous mass extinction. *Nature*, *558*(7709), 288–291. https://doi.org/10.1038/s41586-018-0163-6

Page 275. *The tropics hold most.*

2064. Stehli, F. G., Douglas, R. G., & Newell, N. D. (1969). Generation and Maintenance of Gradients in Taxonomic Diversity. *Science*, *164*(3882), 947–949. https://doi.org/10.1126/science.164.3882.947

2065. Willig, M. R., Kaufman, D. M., & Stevens, R. D. (2003). Latitudinal Gradients of Biodiversity: Pattern, Process, Scale, and Synthesis. *Annual Review of Ecology, Evolution, and Systematics*, *34*(1), 273–309. https://doi.org/10.1146/annurev.ecolsys.34.012103.144032

2066. Brown, J. H. (2014). Why are there so many species in the tropics? *Journal of Biogeography*, *41*(1), 8–22. https://doi.org/10.1111/jbi.12228

2067. Garnett, S. T., Burgess, N. D., Fa, J. E., Fernández-Llamazares, Á., Molnár, Z., Robinson, C. J., Watson, J. E. M., Zander, K. K., Austin, B., Brondizio, E. S., Collier, N. F., Duncan, T., Ellis, E., Geyle, H., Jackson, M. v., Jonas, H., Malmer, P., McGowan, B., Sivongxay, A., & Leiper, I. (2018). A spatial overview of the global importance of Indigenous lands for conservation. *Nature Sustainability*, *1*(7), 369–374. https://doi.org/10.1038/s41893-018-0100-6

2068. Fa, J. E., Watson, J. E., Leiper, I., Potapov, P., Evans, T. D., Burgess, N. D., Molnár, Z., Fernández-Llamazares, Á., Duncan, T., Wang, S., Austin, B. J., Jonas, H., Robinson, C. J., Malmer, P., Zander, K. K., Jackson, M. v, Ellis, E., Brondizio, E. S., & Garnett, S. T. (2020). Importance of Indigenous Peoples' lands for the conservation of Intact Forest Landscapes. *Frontiers in Ecology and the Environment*, *18*(3), 135–140. https://doi.org/10.1002/fee.2148

2069. O'Bryan, C. J., Garnett, S. T., Fa, J. E., Leiper, I., Rehbein, J. A., Fernández-Llamazares, Á., Jackson, M. v., Jonas, H. D., Brondizio, E. S., Burgess, N. D., Robinson, C. J., Zander, K. K., Molnár, Z., Venter, O., & Watson, J. E. M. (2021). The importance of Indigenous Peoples' lands for the conservation of terrestrial mammals. *Conservation Biology*, *35*(3), 1002–1008. https://doi.org/10.1111/cobi.13620

2070. Walker, W. S., Gorelik, S. R., Baccini, A., Aragon-Osejo, J. L., Josse, C., Meyer, C., Macedo, M. N., Augusto, C., Rios, S., Katan, T., de Souza, A. A., Cuellar, S., Llanos, A., Zager, I., Mirabal, G. D., Solvik, K. K., Farina, M. K., Moutinho, P., & Schwartzman, S. (2020). The role of forest conversion, degradation, and disturbance in the carbon dynamics of Amazon indigenous territories and protected areas. *Proceedings of the National Academy of Sciences*, *117*(6), 3015–3025. https://doi.org/10.1073/pnas.1913321117

2071. Fletcher, M.-S., Hamilton, R., Dressler, W., & Palmer, L. (2021). Indigenous knowledge and the shackles of wilderness. *Proceedings of the National Academy of Sciences*, *118*(40). https://doi.org/10.1073/pnas.2022218118

2072. Harris, N. L., Gibbs, D. A., Baccini, A., Birdsey, R. A., de Bruin, S., Farina, M., Fatoyinbo, L., Hansen, M. C., Herold, M., Houghton, R. A., Potapov, P. v., Suarez, D. R., Roman-Cuesta, R. M., Saatchi, S. S., Slay, C. M., Turubanova, S. A., & Tyukavina, A. (2021). Global maps of twenty-first century forest carbon fluxes. *Nature Climate Change*, *11*(3), 234–240. https://doi.org/10.1038/s41558-020-00976-6

2073. Sze, J. S., Childs, D. Z., Carrasco, L. R., & Edwards, D. P. (2022). Indigenous lands in protected areas have high forest integrity across the tropics. *Current Biology*, *32*(22), 4949-4956.e3. https://doi.org/10.1016/j.cub.2022.09.040

2074. Hernandez, J., Meisner, J., Bardosh, K., & Rabinowitz, P. (2022). Prevent pandemics and halt climate change? Strengthen land rights for Indigenous peoples. *The Lancet Planetary Health*, *6*(5), e381–e382. https://doi.org/10.1016/S2542-5196(22)00069-9

2075. Grounded. (2020). Why protecting Indigenous communities can also help save the Earth. *The Guardian*. https://www.theguardian.com/climate-academy/2020/oct/12/indigenous-communities-protect-biodiversity-curb-climate-crisis

2076. Veit, P., Gibbs, D., & Reytar, K. (2023, January 6). *Indigenous Forests Are Some of the Amazon's Last Carbon Sinks*. World Resources Institute. https://www.wri.org/insights/amazon-carbon-sink-indigenous-forests?utm_source=miragenews&utm_medium=miragenews&utm_campaign=news#

2077. FAO Regional Office for Latin America and the Caribbean. (2021). *New UN report to show evidence of key role that Indigenous and Tribal Peoples play in preserving forests and reducing carbon emission.* https://www.fao.org/americas/noticias/ver/en/c/1381870/

2078. FAO Regional Office for Latin America and the Caribbean. (2021). *Forest Governance by Indigenous and Tribal Peoples*. https://www.fao.org/americas/publicaciones-audio-video/forest-gov-by-indigenous/en/ and https://www.fao.org/documents/card/en/c/cb2953en

2079. *Indigenous Peoples*. (2023). The World Bank. https://www.worldbank.org/en/topic/indigenouspeoples

2080. Sobrevila, C. (2008). *The Role of Indigenous Peoples in Biodiversity Conservation*. https://documents1.worldbank.org/curated/en/995271468177530126/pdf/443000WP0BOX321onservation01PUBLIC1.pdf

2081. Henning, S. (2020, September 19). *Is 80% of the world's biodiversity found in Indigenous lands?* GigaFact. https://gigafact.org/fact-briefs/is-80-of-the-worlds-biodiversity-found-in-indigenous-lands

Page 274. *There is no Planet B*.

2082. Herries, A. I. R., Martin, J. M., Leece, A. B., Adams, J. W., Boschian, G., Joannes-Boyau, R., Edwards, T. R., Mallett, T., Massey, J., Murszewski, A., Neubauer, S., Pickering, R., Strait, D. S., Armstrong, B. J., Baker, S., Caruana, M. v., Denham, T., Hellstrom, J., Moggi-Cecchi, J., … Menter, C. (2020). Contemporaneity of *Australopithecus* , *Paranthropus* , and early *Homo erectus* in South Africa. *Science*, *368*(6486). https://doi.org/10.1126/science.aaw7293

Page 274. *In Braiding Sweetgrass.* The quote is from Page 419 of the book referenced below.

2083. Kimmerer, R. W. 2013. *Braiding Sweetgrass: Indigenous Wisdom, Scientific Knowledge, and the Teachings of Plants.* Milkweed Editions: Minneapolis.