

### Appendix: Plant-Derived Toxins Commonly Used as Stimulants

Plant toxin (number of daily users worldwide)	Common name of source (Latin name), plant family; geographical origin	Neurotransmitter mimicked, receptor target, or neurotransmitter enzyme inhibited	Pharmaceutical or recreational drugs derived from, or modeled after, the natural product's structure
Arecoline (600 million)	Areca palm nut or betel nut <sup>a</sup> ( <i>Areca catechu</i> ), Arecaceae; Asia and Oceania	An acetylcholine mimic that binds to muscarinic receptors as partial agonists	Arecoline injection for Alzheimer's disease symptoms; arecoline has carcinogenic properties
Caffeine and related methylxanthines like theobromine and theophylline (>4 billion)	Cocoa bean ( <i>Theobroma cacao</i> ), Malvaceae; South America  Coffee bean ( <i>Coffea arabica</i> and <i>C. canephora</i> ), Rubiaceae; Africa  Cola nut or kola nut ( <i>Cola nitida</i> and <i>C.</i>	An adenosine mimic that binds to the adenosine receptors as antagonists and independently inhibits phosphodiesterases	Caffeine citrate (Cafcit) for apnea management in infants  Caffeine (e.g., NoDoz, Vivarin)  Caffeine in combination with aspirin and acetaminophen (Excedrin Migraine)  In the antiemetic drug dimenhydrinate (Dramamine) contains both the antihistamine diphenhydramine (e.g., Benadryl, Compoz) and the caffeine analog 8-chlorotheophylline, a stimulant that counters the sedative effects of diphenhydramine (e.g., Benadryl, Compoz)

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	<p><i>acuminata</i>), Malvaceae; Africa</p> <p>Guayusa leaf (<i>Ilex guayusa</i>), Aquifoliaceae; South America</p> <p>Guarana seed (<i>Paullinia cupana</i>), Sapindaceae; South America</p> <p>Tea leaf (<i>Camellia sinensis</i>), Theaceae; Asia</p> <p>Yaupon leaf (<i>Ilex vomitoria</i>), Aquifoliaceae; North America</p> <p>Yerba maté leaf (<i>Ilex paraguariensis</i>), Aquifoliaceae; South America</p>		
Cathinone (20 million)	Khat leaf ( <i>Catha edulis</i> ), Celastraceae; Africa	Binds directly to dopamine, noradrenaline, and serotonin reuptake transporters and inhibits	Methylenedioxypropylone (street names Bath Salts, Monkey Dust)

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		their function, increasing levels of the corresponding neurotransmitters	4-methylmethcathinone (methedrone, street names include Drone, Meow, White Magic, M-cat)
Cocaine (>5 million)	Coca leaf ( <i>Erythroxylum coca</i> ), Erythroxylaceae; South America	Binds directly to the dopamine transporter and inhibits its function, increasing levels of dopamine <sup>b</sup>	Cocaine as a powder (street names Blow, Nose Candy, etc.), a powder adulterated with a base (crack cocaine), or mixed with heroin (street name Speedball)  Lidocaine injection <sup>b</sup>  Procaine (Novocain) injection <sup>b</sup>  Tetracaine injection <sup>b</sup>
Ephedrine and pseudoephedrine (>1 billion)	Ephedra, ma huang ( <i>Ephedra</i> spp.), Ephedraceae; Asia and North America	A norepinephrine (noradrenaline) mimic that binds to adrenergic receptors as agonists	Amphetamine sulfate inhaler (Benzedrine)  Dextroamphetamine (D-Amphetamine) pills (Dexedrine)  D-Amphetamine and Levoamphetamine (L-amphetamine) pills (Adderall; street names Greenies, Beans)  Ephedrine sulfate injection  Fenfluramine and phentermine pills (Fen-Phen)  3,4-Methylenedioxymethamphetamine (MDMA; street names Ecstasy, E, Molly)  3-methoxy-4,5-methylenedioxyamphetamine (MMDA)

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			<p>Methamphetamine pills, smoked or injection (Desoxyn, early formulations of Obitrol; street names Bennies, Pep Pills, Crystal Meth, Speed)</p> <p>Methylphenidate pills (Ritalin), and lisdexamfetamine dimesylate pills (Vyvanse)</p> <p>Pseudoephedrine hydrochloride pills (e.g., Sudafed) singly or in combination with other drugs (e.g., Allegra D, Zyrtec-D, Advil Cold and Sinus)</p>
Nicotine (>3 billion)	<p>Tobacco leaf (<i>Nicotiana tabacum</i> and <i>N. rustica</i>), Solanaceae; North and South America</p> <p>Pituri leaf (<i>Duboisia hopwoodii</i> and various <i>Nicotiana</i> species), Solanaceae; Australia</p>	<p>An acetylcholine mimic that binds to the nicotinic acetylcholine receptor as an agonist (and, less importantly, as an antagonist), increasing dopamine levels in the brain</p>	<p>Tobacco used in chewing, smoking and snuff</p> <p>Pure nicotine and flavor additives in vaping products</p> <p>Nicotine polacrilex in chewing gums and lozenges (e.g., Nicorette) and nicotine slow-release skin patches (e.g., NicoDerm) for nicotine replacement therapy</p> <p>Bupropion (Wellbutrin) and varenicline (Chantix), which block nicotine from binding to acetylcholine receptors for smoking cessation</p>

<sup>a</sup>Paan and betel quid combine areca nut with betle leaf, slaked lime, spices, and sweeteners.

<sup>b</sup>Cocaine has targets in the nervous system beyond the dopamine reuptake transporter, including voltage-gated sodium channels and calcium channels, which it blocks. This blocking of the two types of channels is thought to underlie the drug's utility.