Unlocking Nature's Potential: A Comprehensive Review of CNS-Stimulant Activity in Natural Herbs

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**1. INTRODUCTION:**

CNS-stimulants are the hallucinatory pills that cause transient upgrades in intellectual and bodily feature through bettering the pastime of central apprehensive device. They concede superb advantages for a vary of issues but nonetheless they are extensively used as illicit resources of abuse. In children with Attention Deficit Hyperactivity Disorder (ADHD), amphetamine and methylphenidate are given medications. According to the National Department of Health, between 2.5% and 3.5% of individuals in the USA utilize these capsules. It produces generalized motion which on greater doses may additionally produce convulsions [1]. Ephedra vulgaris (Ma huang), Catha edulis (Khat), and Erythroxylum coca (Coca) are a few examples of tablets that have been used historically and are known to have CNS stimulating properties. The Chinese herb ma huang, which is having central stimulating activity, has been used as a circulatory stimulant, diaphoretic, antipyretic, and antitussive agent [2] for some over 5100 years. After ephedrine is remoted from plant which was once used in remedy of allergies and comparable prerequisites [2]. Improved alertness, awareness, wakefulness, endurance, productivity, motivation, increased arousal, motility, coronary heart rate, and blood pressure are just a few of the unique effects that CNS stimulants induce.Inhibition of urge for food and reduce in the ingestion of meals is the frequent method of the pills which are performing on catecholamine or serotonergic structures consequently they are extensively used in weight discount therapy [3]. These are used to deal with medical despair and bipolar disorder, especially odd despair and remedy resistant despair. Orthostatic hypotension, postural orthostatic tachycardia syndrome, and nasal congestion are all effectively relieved.The impact of stimulants relies upon upon the substance, its efficiency and dosage; it reduces hyperactivity and being commonly free of serious facet results at average doses used in medical medicinal drug. The most notable pharmacological mechanisms used by stimulants to produce their effects include nicotine acetylcholine receptor agonist, adenosine receptor antagonist, and amplify norepinephrine (noradrenaline) and/or dopamine exercise through monoamine transporter inhibition.

**2.** **CLASSIFICATION OF CNS STIMULANTS:**

CNS stimulants are categorized on the foundation of its pharmacological motion such as psychostimulants, psychoanaleptics, and brain-boosting substances. In the United States, more than 15 million people consume high-dose vitamins or natural remedies$17.7 billion of the $37.1 billion spent on weight-loss products in 2001 came from natural dropping pounds supplements. These figures increased by 6% to 7% annually. The use of natural products for medicinal and disease-prevention purposes has been growing. [4]. other natural remedies that have a negative impact on the cardiovascular system include St. John's wort and gingko biloba. In the US, St. John's wort is one of the most popular herbs. Because St. John's wort causes the hepatic cytochrome P450 device, which is responsible for drug metabolism, as well as subsequent recurrence of arrhythmia, hypertension, and other adverse effects, use of the herb should likely result in major adverse responses. Both hypertension and hypotensive effects are associated with ginseng [5].

**[2.1] Herbal CNS Psychostimulants:**

**2.1.1. Cocaine**: Cocaine is an alkaloid obtained from the erythroxylum coca plant. Because free base is unstable, it is extracted as a paste and then transformed into a salt form, such as hydrochloride or sulfate. Depending on how you consume cocaine, such as by IV injection or snorting, this salt can be made in a number of different ways. However, due to its more subdued stimulant properties, it has been utilized for thousands of years in Central and South America. [6]. Dopamine is released from nerve terminals into the synaptic cleft, bind to dopamine receptor and gives its pharmacological action then it is taken up by dopamine reuptake transporters and metabolized by monoamine oxidase enzyme (MAO). But cocaine in the periphery, blocks uptake of NA, adrenaline and dopamine into adrenergic nerve endings, resulting in higher concentrations of transmitter around the receptor and causes CNS stimulation. By inhibiting Na+ channels, cocaine also functions as a local anesthetic. Only in the United States is its medical use approved. Recent research, however, points to NMDA receptor blockage as the potential cause of cocaine's convulsigenic effects [6]. Cocaine's addictive and reinforcing qualities have been directly linked to dopamine reuptake blockade. Cocaine usage that is both acute and prolonged may result in cardio toxic and neurovascular issues. The therapy dose determines how severe the condition is. Although it's rarely utilized in medicine, some people say that ophthalmic use requires 4 mg/kg per day of cocaine. Caffeine works by actively inhibiting adenosine receptors and phosphodiesterase, which raises levels of dopamine, adrenaline, and serotonin and stimulates the central nervous system [7]. Caffeine has been found to boost mental alertness, decrease weariness, and increase attention [8]. It may also lessen the symptoms of Parkinson's disease and other metabolic diseases, such as obesity. When consumed regularly (less than 400 mg/day, or 6.5 mg/kg/day for an adult weighing 70 kg), caffeine generally has little negative consequences [8]. Caffeine toxicity is uncommon; the lethal dose is 150–200 mg/kg, or 10–20 grams per day [8]. Because they contain caffeine, subsequent plants have been used as CNS stimulants.

**2.1.3 Tea (Camellia sinensis**): After water, tea is a popular beverage. Tea lowers glucose levels, lipids, weight, and blood pressure while improving metabolic profiles and reducing the risk of depression and stroke. The caffeine level of tea leaves ranges from 3 mg/g to 30 mg/g, making a cup of tea with 7.5 mg to 75 mg of tea leaves caffeine-rich. Caffeine levels vary depending on the tea plant's many components, including Caffeine content is higher in leaf buds (tips) and younger leaves than in mature and older leaves. Heavy tea consumption may result in sleeplessness, anxiety, restlessness, and tachycardia due to the high caffeine content.

**2.1.4 Coffee (Coffea robusta/arabica**): In western nations, coffee ranks third in terms of beverage consumption and primary source of caffeine [7]. Caffeine content in coffee varies depending on the species: 1.45% in C. arabica and 2.38% in C. robusta (C. canephora) [9]. High doses of caffeine should not be consumed by the patient as they may result in insomnia and anxiety. In addition to coffee's CNS stimulating properties Giulia Runti also noted that high caffeine intake may increase the excretion of calcium and magnesium in the urine, which may have an impact on the bone health of women. Arabica coffee extract also exhibits antibacterial action against Staphylococcus epidermidis and Enterococcus faecalis.

**2.1.5 Cocoa (Theobroma cacao):** The plant from which cocoa, also known as cacao, is derived. Minerals, methylxanthines (theobromine 1% to 4% and caffeine 0.07% to 0.36%) and polyphenols are all components of cocoa, along with cocoa butter. Its flavonoid content has neuroprotective and neuromodulatory effects. The flavanols operate in two ways: 1) directly on cells and through cell cascades, resulting in the expression of neuroprotective and neuromodulatory proteins, promoting neurogenesis, and improving neuronal function; and 2) by increasing blood flow in brain and sensory tissues. It has therefore been utilized for its improved cognition, protection against insulin resistance, and anti-inflammatory properties.Due to the conversion of tryptophan from cocoa into serotonin in one animal, consumption of cocoa has been shown to prevent melancholy. Although it is generally accepted, cocoa can occasionally causethe constipation, prolonged heart rate, prolonged urine, and adverse skin reaction.

**2.1.6 Cola Nut ((Cola nitida/acuminata):** The cola plant is native to Western Africa. Theobromine and caffeine are two components that kola nuts must have. Cola acuminata and Cola nitida seeds are used to grow cola nuts. 1.5% to 3.8% of the natural Cola nut extract contains caffeine. It can be used to treat migraines, depression, physical and mental exhaustion, and weight loss. Additionally, it is employed in the food industry as a flavoring agent. It should no longer be administered to pregnant women due to its potential to cause gastrointestinal infections.

**2.1.7 Guarana(Paullinia):** The Guarana plant originated in the central Amazonian Basin and is a common component in Brazilian smooth drinks. Caffeine, which makes up 2.5–5% of the dry weight of the extract, is what gives guarana its CNS stimulant properties, however other purine alkaloids like theophylline and theobromine also exist in modest amounts. A high amount of both saponins and tannins is also thought to be responsible for the guarana's 111 International Journal of Herbal Medicine psychoactive property [10]. Due to its ability to reduce physical or psychological pressures, guarana is not frequently consumed on its own but rather in combination with ginseng [11]. It has been stated that mental health problems might have negative effects such as anxiety, restlessness, and irritation guarana-infused energy drinks.

**2.1.8 Yerba Mate (Ilex paraguariensis):** The dried leaves of the Aquifoliaceae genus Ilex paraguariensis are what make up yerba mate. It is frequently used as a source of caffeine and for its medical properties in southern Latin American nations such southern Brazil, Argentina, Paraguay, and Uruguay. It is commercially available in the United States in the form of tea bags that have been packaged, pills that are taken orally, as well as in the food and nutritional supplement sectors. The high awareness of caffeine (1% to 2% of dry weight) is what causes CNS stimulation. Chronic usage may also help treat kidney, bladder, lung, esophagus, and oral malignancies.

**2.2 Psychoanaleptics:**

**2.2.1 Ephedra:** Since ancient times, MA huang, also known as an ephedra, has been recognized in China. The most common form of ephedra is ephedra sinica. It is made up of ephedrine and pseudoephedrine and has CNS stimulant properties similar to amphetamines. Ephedrine has a central action that increases the release of noradrenaline and adrenaline while inhibiting their absorption, which reduces appetite and promotes fullness by way of the hypothalamic centers in charge of controlling demand for food. Ephedrine will boost metabolic rate, which aids in weight loss. Its effect on thermogenesis is brought on via activating receptors. The FDA outlawed the sale of dietary supplements containing ephedra in the US in 2004. These dietary supplements, according to the FDA, pose an unjustified risk of harm or illness.

**2.2.2 Khat Khat** Catha edulis leaves or young shoots are used as a CNS stimulant. East Africa and the Arabian Peninsula are two places where the plant is frequently grown [12]. Khat has a wide variety of unusual chemical elements. The majority of khat's psychedelic properties are caused by cathinone, the primary alkaloid found in it and a structural analog of amphetamine. The effects of cathinone and amphetamine on metabolism and appetite suppression may be similar [12]. Even though ghrelin or Peptide YY secretion are not traded, loyal consumers' feelings of famine and fullness are expanded [13].

**2.2.3 St. John's wort:** The name "st. John's wort" is frequently used to refer to the yellow-flowered perennial herb Hypericum perforatum, which is native to North America, West Asia, and Europe. Recent research points to the effectiveness of this herb in treating a variety of conditions, including cancer, disorders associated with inflammation, bacterial and viral diseases, as well as acting as an antioxidant and neuroprotective agent. St. John's wort contains hypericin, an active ingredient that acts as an antidepressant. The enzyme monoamine oxidase is involved in the breakdown of amine neurotransmitters. According to studies, hypericin has the capacity to both inhibit MAO and increase the level of neurotransmitters [14].

**2.3 Cognition Enhancers:**

**2.3.1 Ginkgo:** It is made up of the dried leaves of the Ginkgo biloba tree, which has been grown in China for thousands of years for its medicinal properties. It is used in the treatment of vertigo, temporary memory loss, and attention deficit disorder. Additionally, cerebral vascular issues are treated using it. According to research by Bryn Williams, ginkgo extract rapidly interacts with the glutamatergic system and improves cognition in those who are suffering from dementia. In addition to acting as a neuroprotective by preventing amyloid- neurotoxicity and providing protection from hypoxic challenges and increased oxidative stress, ginkgo biloba also has a role as a radical scavenger [15].

**2.3.2 Gotu Kola:** It is a herb from the hallucinogenic medical plant Centella asiatica. Triterpenoid glycosides, asiaticoside, madecassoside, Asiatic acid, and madecassic acid are the active components of Centella asiatica [16]. According to Nora E. Grey et al., plant extract will boost the mitochondrial respiratory and antioxidant genes whether amyloid exposure is present or not. This method of action is linked to the disease Alzheimer's as well as other conditions where oxidative stress and mitochondrial dysfunction are present. Due of glutamate's ability to overstimulate NMDA receptors, neuronal degeneration can be triggered. Additionally, asiatic acid limits the quantity of intracellular free radicals and lessens H2O2-induced cell death. Triterpene asiatic acid and its derivatives have been shown to protect cortical neurons by reducing glutamate-induced excitotoxicity in in vitro studies.Centella extract (100, 200, and 300 mg/kg) demonstrated dose-dependent protective effects against cognitive impairments and oxidative stress in rats and improved memory retention..

**2.3.3 Ginseng:** It is made up of dried Panax ginseng roots, and it has been used for over 2000 years in Asia, primarily in China, Korea, and Japan. Ginseng extract is recommended as a cognitive enhancer in the treatment of Alzheimer's disease, according to studies [17]. Ginseng's active ingredients prevent the buildup of amyloid and protect rats' spatial memory [18]. Additionally, it prevents the production of advanced glycation end product (AGE), which inhibits it. In rat cortical cells, red ginseng water extract (0.3–3 mg/mL) prevents the development of reactive oxygen species (ROS) and neuronal death that are induced by glutamate, N-methyl-D-aspartate, or beta-amyloid.

**[3] Herbal CNS Stimulants in research:**

**Alpinia galanga:**

It is made up of dried Alpinia galanga L. (Zingiberaceae) rhizomes.It is used exclusively in cooking. The herb is widely distributed over several regions of Southeast Asia and India. By using a variety of pharmacological experiments on crude methanolic extract and ethyl acetate fraction of A. galanga, researchers were able to assess the plant's CNS stimulating activity.The fantastic activity was demonstrated on mice using actophotometry and the rotarod test in conjunction with methanolic and ethyl acetate extract of A. galanga. Mice treated with the methanolic extract and ethyl acetate fraction of A. galanga's rhizome in dosages of 250 and 500 mg/kg showed an increase in locomotor activity. CNS stimulants increase motor coordination, which increases the amount of time spent performing**.**

**Cucurbita Maxima:**

The Cucurbitaceae family includes the short-lived shrub Cucurbita maxima [97]. The oil from the seeds is used to treat anxiety problems and debility, and the seeds have historically been used as a bitter tonic [98, 99]. The Swiss albino mice used in this study were used to study the CNS stimulant recreation [20]. A reference drug in the past was caffeine [21,20]. The crude extract had significant CNS stimulant activity when compared to the control group, and the outcomes were consistent with the work demonstrated by the reference medication [20].

Rhinacanthus nasutus (R. nasutus) leaf extract has been studied to see how it affects obese mice's impaired lipid and glucose metabolism [22]. Weight problems caused by a high-fat diet (HFD) and typical lipid metabolism can be exacerbated by blocking the release of glucose from the liver and its uptake by fat and muscle cells [22,23].In mice, obesity was once induced by feeding them a high-fat diet (60 kcal% fat) for 12 weeks. After the first six weeks of a weight loss plan, obese mice were given water extracts of R. nasutus leaves at doses of 250 and 500 mg/kg per day for the following six weeks [23]. In order to conduct a histological study, the liver and adipose tissues are removed.protein expression study.The blood glucose, lipid profiles, insulin, leptin, andadiponectin stages had been measured [23]. After 6 weeks of remedy it was once located that water extract of R. nasutus reduces

increased lipid concentrations in their serum and liver tissues in overweight mice [23]. The current research suggested that R.nasutus extract is enhancing the impaired glucose and lipid

By increasing the insulin sensitivity in the liver and adipose tissues, the International Journal of Herbal Medicine metabolism in high-fat diet-induced weight problems in mice is stimulated in 113 International journals of Herbal Medicine metabolism [23].

The use of natural products for disease prevention and treatment is increasing since herbal CNS stimulants are much safer than synthetic pills.

**[5] CONCLUSION:**

In contrast to natural CNS stimulants, which have a large margin of safety, are cheaper, and have minimal side effects compared to artificial drugs, artificial pills are more expensive, have a narrower margin of safety, and are therefore being studied more for CNS disorders.

With the exception of the addictive drugs cocaine and khat, all other medications, including caffeine and ephedra, have a far wider margin of safety and less adverse side effects than amphetamine and methylphenidate.

There is a lot of research being done on innovative techniques with an emphasis on natural CNS stimulants. Numerous problems relating to research, production, and software are sought after solutions.

A suitable delivery system must be created that can increase the drug's pharmacological activity while reducing its toxicity. Herbal pills have excellent therapeutic potential that has to be investigated using some medication delivery technologies that cost money.

**REFERENCES:**

1. Tripathi KD. CNS Stimulants and Cognition Enhancers, Essentials of Medical Pharmacology, Fifth Edition, 2003,435.

2. Chen KK, Schmidt CF. The action of ephedrine, the active principle of the Chinese drug Ma Huang. Journal

of Pharmacology and Experimental Therapeutics. 1925;24:339-357.

3. Silverstone T. Appetite suppressants—a review. Drugs.1992; 43(6):820-36

4. Valli G, Giardina EG. Benefits, adverse effects and drug interactions of herbal therapies with cardiovascular

effects. Journal of the American College of Cardiology. 2002; 39:1083-95.

5. Sung J, Han KH, Zo JH, Park HJ, Kim CH, Oh BH. Effects of red ginseng upon vascular endothelial function

in patients with essential hypertension, The American Journal of Chinese Medicine, 2000; 28:205-16.

6. Indriati E, Buikstra JE. Coca chewing in prehistoric coastal Peru: dental evidence. American Journal of

Physical Anthropology. 2001; 114:242-25

7. Lasoń W. Neurochemical and pharmacological aspects of cocaine-induced seizures, Polish journal of pharmacology. 2001; 53:57-60

8. Catterall WA, Mackie K. (Local anesthetics, in Goodman & Gilman's The Pharmacological Basis of Therapeutics, 2011, 11th ed (Brunton LL, Lazo JS, and Parker KL eds), The McGraw-Hill Companies, New York.International Journal of Herbal Medicine

9. Henman AR. Guarana (Paullinia cupana var Sorbilis): ecological and social perspective on an economic plant of the central Amazon Basin. Journal ofEthnopharmacology. 1982; 6:311-38.

10. Hechman, MA, Weil J, Mejia EG. Caffeine (1, 3, 7-Trimethylxanthine) in Foods: A Comprehensive Reviewon Consumption, Functionality, Safety, and RegulatoryMatters. Journal of Food Science, 2010; 75:R77-

11. Heck CI, De Mejia EG. Yerba Mate Tea (Ilex paraguariensis): A Comprehensive Review on Chemistry,Health Implications, and Technological Considerations.Journal of Food Science, 2007; 72:R138-R15

12. Bicho NC, Lidon FC, Ramalho JC, Leitao AE. Quality assessment of Arabica and Robusta green and roastedcoffees - A review Emirates Journal of Food andAgriculture, 2013; 25:945-950.

13. Espinola EB, Dias RF, Mattei R, Carlini EA. Pharmacological activity of Guaranan (Paullinia cupanaMart) in laboratory animals, Journal of Ethnopharmacology, 1997; 55:223-9.

14. Mattei R, Dias RF, Espínola EB, Carlini EA, BarrosSBM.Guarana(Paullina coanalytic behavioural effects in laboratory animals and anti - oxidant activity in vitro journal of ethnopharmacology 1998:60:111-116

15. Andrine M Lemieux et al., Khat use and appetite: An overview and comparison of amphetamine, khat andcathinone. Journal of Ethnopharmacology. 2015; 160:78-85.

16. Murray CD, LeRoux CW, Emmanuel AV, Halket JM, Przyborowska AM, Kamm MA et al., The effect of ~115~International Journal of Herbal Medicine Khat (Catha edulis) as an appetite suppressant isindependent of ghrelin and PYY secretion. Appetite,2008; 51:747-750.

17. Chavez ML, Chavez PI. Saint John's wort, Hospital Pharmacy Journal. 1997; 32(12):1621-32.

18. Xiaobin Tan et al., Ginseng improves cognitive deficit via the RAGE/NF-κB pathway in advanced glycation end product-induced rats, Journal of Ginseng Research. 2015;39(2):116-124.

19. Inamdar PK, Teola RD, Ghogare AB, De Souza NJ. Determination of biologically active constituents in Centella asiatica. Journal of Chromatography A. 1996;742:127-130.

20. Song XY et al., Ginsenoside Rg1 attenuates okadaic acid induced spatial memory impairment by the GSK3β/tausignaling pathway and the Aβ formation prevention inrats, European Journal of Pharmacology. 2013; 710:29-38.

21. Woelk H, Arnoldt KH et al., Ginkgo biloba special extract EGb 761 in generalized anxiety disorder and adjustment disorder with anxious mood: a randomized, double-blind, placebo-controlled trial, Journal ofPsychiatric Research. 2007; 41(6):472-80.

22. Kim HJ et al, Effect of herbal Ephedra sinica and Evodiarutaecarpa on body composition and resting metabolic rate: a randomized, double-blind clinical trial in Korean premenopausal women, Journal ofAcupuncture & Meridian Studies, 2008;1(20:128-38

23.Doke pp et al., Central nervous system stimulant effect of the oils obtained from seeds of cucurbita maxima. International Journal of Pharmaceutical Biology. 2011;1(1):30-36.