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Madhura Mestry
SVKM's Dr. Bhanuben Nanavati College of Pharmacy, V. M. Road, Vile Parle (W) Mumbai, India

Dr. Amrita Bajaj
SVKM's Dr. Bhanuben Nanavati College of Pharmacy, V. M. Road, Vile Parle (W) Mumbai, India

Dr. Meenal Rane
SVKM's Dr. Bhanuben Nanavati College of Pharmacy, V. M. Road, Vile Parle (W) Mumbai, India

Kausani Lalan
SVKM's Dr. Bhanuben Nanavati College of Pharmacy, V. M. Road, Vile Parle (W) Mumbai, India

Correspondence
Dr. Meenal Rane
SVKM's Dr. Bhanuben Nanavati College of Pharmacy, V. M. Road, Vile Parle (W) Mumbai, India

Herbal CNS stimulants

Madhura Mestry, Dr. Amrita Bajaj, Dr. Meenal Rane and Kausani Lalan

Abstract
This review article draws the attention to many plant species possessing central nervous system (CNS) stimulant activity. CNS stimulants are classified on the basis of their pharmacological action such as psychostimulants, psychoanaleptic and Cognition enhancers. Psychostimulants such as Tea, Coffee, and Cocoa are used to induce temporary improvements in mental and physical function by enhancing the (CNS). Psychoanaleptics such as Ephedra, Khat, and St. John's wort are used in weight reduction treatment. Cognition Enhancers such as Ginkgo and Gotu kola is used to improve memory and also used in treatment of vertigo, short term memory loss, lack of attention. The article also discusses the novel approaches for formulation development of herbal CNS stimulants and plants which are in research.

Keywords: Herbal CNS stimulants, psychostimulants, psychoanaleptics, cognition enhancers

1. Introduction
CNS stimulants are the psychoactive drugs which induce temporary improvements in mental and physical function by enhancing the activity of central nervous system (CNS). They provide great benefits for a range of disorders but still they are widely used as illicit substances of abuse. Amphetamine and Methylphenidate are prescribed in Attention Deficit Hyperactivity Disorder (ADHD) for children but National Department of Health reported that the these drugs are used by 2-3.5% of adults in USA [1]. It produces generalized action which on higher doses may produce convulsions [2].

The use of Ma huang (*Ephedra vulgaris*) in China, khat (*Catha edulis*) in Africa, and coca (*Erythroxylum coca*) in South America are examples of the drugs which are known to have a CNS stimulant activity from ancient time. The Chinese herb ma huang, which having central stimulating activity, has been in use as a circulatory stimulant, diaphoretic, antipyretic, and antitussive agent [3, 4] for some over 5100 years. After ephedrine is isolated from plant which was used in treatment of asthma and similar conditions [3, 4].

CNS Stimulants produce different kinds of effects such as enhanced alertness, awareness, wakefulness, endurance, productivity, motivation, increased arousal, locomotion, heart rate, blood pressure [5]. Inhibition of appetite and decrease in the ingestion of food is the common approach of the drugs which are acting on catecholamine or serotonergic systems therefore they are widely used in weight reduction treatment [6]. They are used to treat clinical depression and bipolar disorder, particularly atypical depression and treatment resistant depression [7-11]. It relieves nasal congestion as well as orthostatic hypotension and postural orthostatic tachycardia syndrome [5]. The effect of stimulants depends upon the substance, its potency and dosage, it reduces hyperactivity and being generally free of serious side effects at moderate doses used in clinical medicine [5].

CNS Stimulants exert their effects through a number of different pharmacological mechanisms, the most prominent of which include increase of norepinephrine (noradrenaline) and/or dopamine activity via monoamine transporter inhibition, adenosine receptor antagonism, and nicotine acetylcholine receptor agonism [1].

CNS stimulants are classified on the basis of its pharmacological action such as psychostimulants, psychoanaleptics and Cognition enhancers.

More than 15 million people in the U.S. consume herbal remedies or high-dose vitamins [12]. $37.1 billion spent for weight-loss products in 2001, $17.7 billion was on herbal weight-loss supplements, these numbers increased by 6% to 7% per year [12, 13]. The use of herbal products is increasing for prevention of diseases and therapeutic purposes [14]. Different herbal remedies that produce adverse effects on the cardiovascular system include St. John's wort, gingko biloba. St. John's wort is one of the bestselling herbs in US [15]. Use of St. John's wort could potentially result in serious adverse reactions because it induces the hepatic cytochrome P450 system which causes drug metabolism [16], it also causes subsequent recurrence of arrhythmia, hypertension and other undesirable effect [17]. Ginseng has hypertensive and hypotensive side effects [18]. In Chinese medicine, ginseng is used for myocardial infarction, congestive heart

failure (CHF), and angina pectoris [19]; however. Ginseng abuse may cause hypertension, behavioral changes, and diarrhea [20] therefore current evidence does not support its use for cardiovascular conditions [19].

This article deals with the information on various herbal CNS stimulant plants which are widely used as well as the novel approaches of formulation development for the same.

2. Herbal CNS stimulants

2.1 Psychostimulants

2.1.1 Cocaine

Cocaine is an alkaloid derived from the coca plant (*Erythroxylum coca*), it is extracted in form of paste and converted into a salt form such as hydrochloride or sulphate because free base is unstable. This salt can be prepared in a variety of ways which depends upon the intake of cocaine such as i.v. injection or snorting. However, it has been used from thousands of years in Central and South America for its more modest stimulant effects [21, 22].

Dopamine is released from nerve terminals into synaptic cleft, bind to dopamine receptor and gives its pharmacological action then it is taken up by dopamine reuptake transporters and metabolized by monoaminooxidase enzyme (MAO).But cocaine in the periphery, it blocks uptake of NA, and adrenaline and dopamine into adrenergic nerve endings, resulting in higher concentrations of transmitter around the receptor and causes CNS stimulation. [23]

Cocaine also acts as a local anaesthetic by blocking Na^+ channels [24, 25]. Its medical use is approved only in United States However, recent evidence suggests that cocaine's convulsigenic effects may be due to blocking of NMDA receptors [26]. Blocking of dopamine reuptake has been closely associated with the reinforcing and addictive properties of cocaine [27].

Prolonged and acute use of cocaine may cause cardiotoxic [28] and neurovascular [29] complications. The severity depends upon the dose which is used for treatment. Medical use of cocaine is very rare but sometimes argued to be used for ophthalmic and ear surgeries because it causes vasoconstriction which controls the bleeding and swelling and it also has local anaesthetic action [30, 31].

2.1.2 Caffeine

Caffeine is most widely used as a CNS Stimulant [32]. Natural source of caffeine is found in more than 60 plants species such as coffee (*Coffea robusta*/*arabica*), tea (*Camellia sinensis*), cocoa (*Theobroma cacao*), guarana (*Paullinia cupana*), yerba mate (*Ilex paraguariensis*) and kola nut (*Cola nitida*/*acuminata*) [33, 34].

In the United States it has been estimated that the overall caffeine consumption in adult population is 4mg/kg per day [35]. The mechanism of action of caffeine is nonselective inhibition of adenosine receptors and phosphodiesterase which increase the level of dopamine, nor epinephrine and serotonin and cause CNS stimulation [33, 36]. Caffeine increases the attention, reduces fatigue and improves mental alertness, it has been observed that it may reduce the metabolic syndromes such as obesity and reduce symptoms of Parkinson's disease [37, 38]. Caffeine generally does not have major adverse effects when consumed on daily basis(less than equal to 400 mg/day or 6.5 mg/kg/day for a 70 kg-adult) [37]. Toxicity due to caffeine is rare, the lethal dose is 150-200mg/kg or 10to 20gm/day [37].

Following plants are used as CNS Stimulants due to its caffeine content:

2.1.3 Tea (*Camellia sinensis*)

Tea is commonly used beverage after water. Tea is associated with a reduced risk of stroke and depression and improved metabolic profiles; it decreases glucose levels, lipids, weight, and blood pressure [39]. The caffeine content in the tea leaves varies from 3 mg/g to 30mg/g which would in a cup of tea containing between 7.5 mg and 75 mg of tea leaves [39]. Different parts of the tea plant contain different quantities of caffeine such as Leaf buds (tips) and younger leaves have high amount of caffeine than mature and older leaves [40]. Heavy consumption of tea as high intake of caffeine may cause insomnia, anxiety, restlessness and tachycardia [38].

2.1.4 Coffee (*Coffea robusta*/*arabica*)

Coffee is the third most commonly consumed beverage in the western country for main source of caffeine [33, 39]. The chemical composition of the Coffee by the presence of caffeine is about 1.45% in C. arabica and 2.38% in *C. robusta* (*C. canephora*) [41, 42]. Patient should not take high dose of caffeine as it may cause anxiety and insomnia [38]. Besides CNS stimulant property of the coffee Giulia Runti also observed that Arabica coffee extract shows antibacterial activity against *Staphylococcus epidermidis* and *Enterococcus faecalis* as well as [43] high caffeine intake may increase the calcium and magnesium urinary excretion which can affect the bone health in women [39].

2.1.5 Cocoa (*Theobroma cacao*)

Cocoa, also known as Cacao, is derived from the seeds of the *Theobroma cacao* L. tree and it is commonly used as an ingredient in food products, such as chocolate [44]. Cocoa consist of cocoa butter, minerals, methylxanthines (theobromine 1% to 4% and caffeine 0.07% to 0.36%), and polyphenols [45]. The flavonoid present in it produces neuromodulatory and neuroprotective actions. The two mechanisms by which the flavanols are acting: 1) direct interactions and cellular cascades, yielding expression of neuroprotective and neuromodulatory proteins and promote neurogenesis, improve neuronal function, 2) Increase the blood flow in brain and sensory systems [46]. Therefore it has been used for enhanced cognition, protection against insulin resistance, and anti-inflammatory properties [47]. Consumption of cocoa has been shown to prevent depression due to the conversion of cocoa-derived tryptophan into serotonin in one animal study [45]. Cocoa is well tolerated but sometimes it may cause the allergic skin reaction, increased urination, increased heart rate and constipation [48].

2.1.6 Cola Nut (*Cola nitida*/*acuminata*)

Cola species are from Western Africa. Caffeine and theobromine are two important constituents of kola nuts [49]. Cola nuts are cultivated from seeds of *Cola nitida* and *Cola acuminata* [38]. Caffeine content in herbal extract of Cola nut is1.5% to 3.8% [49]. It can be used for relieving physical and mental fatigue, depression, weight reduction and migraine. It is also used as flavouring agent in food industry [49, 50]. It should not be given in pregnancy because its gastrointestinal irritation side effect [49].

2.1.7 Guarana (*Paullinia cupana*)

The origin of the Guarana plant is central Amazonian Basin and it is ubiquitous ingredient in Brazilian soft drinks [31]. CNS stimulant property of the Guarana is due to presence of caffeine which consists of 2.5–5% of the extract's dry weight, although other purine alkaloids such as theophylline and theobromine are also present in smaller quantities [51]. The

psychoactive property of the guarana is also attributed to a high content of both saponins and tannins [52]. Guarana is rarely taken alone it gives in combination with Ginseng because it relieves the physical or psychological stressors [53, 54]. It has been reported that psychiatric adverse effects are observed such as anxiety, restlessness, and irritability associated with guarana containing energy drinks [38].

2.1.8 Yerba Mate (*Ilex paraguariensis*)

Yerba mate consists of dried leaves of *Ilex paraguariensis* belonging to family Aquifoliaceae. It is commonly used in southern Latin American countries, such as southern Brazil, Argentina, Paraguay, and Uruguay, as a source of caffeine and for its medicinal properties [38]. It is commercially available in United States in form of packed tea bags, oral capsules and also used in food and dietary supplement industries [55, 12]. Caffeine is in high concentration (1% to 2% of dry weight) which is responsible for CNS stimulation [55] [38]. Chronic consumption may cause development of oral, esophageal, lung, bladder and kidney cancer [55, 56, 38].

2.2 Psychoanaleptics

2.2.1 Ephedra

MA huang also known as an Ephedra has been known in China from ancient times. *Ephedra sinica* is the most common source of ephedra [57]. It consists of ephedrine and pseudoephedrine and possesses the CNS Stimulant activity similar to amphetamines [58]. Ephedrine acts centrally and enhances the release and inhibits reuptake of Noradrenaline and Adrenaline which decreases food intake and promotes satiety via hypothalamic centers controlling appetite [59, 60]. Ephedrine increases energy expenditure which helps in weight reduction. Its thermogenic effect is due to stimulation of β receptors [60, 61]. In 2004, the FDA banned the sale of ephedra-containing dietary supplements in the United States. The FDA found these supplements to have an unreasonable risk of injury or illness [62].

2.2.2 Khat

Khat is CNS stimulant which consists of the leaves or young shoots of *Catha edulis*. The plant is mainly cultivated in East Africa and the Arabian Peninsula [63]. Khat contains many different types of chemical constituents. Cathinone, the major alkaloid found in khat and a structural analog of Amphetamine, is responsible for most of khat's psychoactive properties [64, 65]. Cathinone and Amphetamine may have similar effect on metabolism and appetite suppression [63]. Although no change in ghrelin or Peptide YY secretion, habitual users decrease feeling of hunger and increase the feeling of fullness [66].

2.2.3 St. John's wort

St. John's wort is the common name for *Hypericum perforatum*, a yellow flowered perennial herb native to Europe, West Asia, and North America [67]. Recent research suggests the effectiveness of this herb in treating other ailments, including cancer, inflammation-related disorders, and bacterial and viral diseases, and as an antioxidant and neuroprotective agent [68]. Hypericin is an active constituent of St. John's wort which act as antidepressant [69]. Monoamine oxidase is an enzyme which is involved in degradation of amine neurotransmitters. Studies determine that the hypericin has the potential to inhibit MAO and further increase the level of neurotransmitters [70, 71].

2.3 Cognition Enhancers

2.3.1 Ginkgo

It consists of dried leaves of Chinese tree *Ginkgo biloba* which have been cultivated from thousand years for its medicinal property [72]. It is used in treatment of vertigo, short term memory loss, lack of attention. It is also used for cerebral vascular disorders [72]. Bryn Williams observed that extract of ginkgo directly interact with the glutamatergic system and acts as a cognitive enhancer in human subjects experiencing dementia [73]. Ginkgo biloba has radical scavenger activity as well as it acts as a neuroprotective by inhibiting amyloid-β neurotoxicity and protect against hypoxic challenges and increased oxidative stress [74, 75].

2.3.2 Gotu Kola

It is a herb of *Centella asiatica*, psychoactive medicinal plant. The active constituents of *Centella asiatica* are triterpenoid glycosides including asiaticoside, madecassoside, Asiatic acid and madecassic acid [76]. Nora E gray *et al* observed that plant extract increases the mitochondrial respiration and antioxidant genes in presence of or absence of amyloid β exposure [77]. This mechanism of action is related to Alzheimer's disease and also other conditions where mitochondrial dysfunction and oxidative stress are observed. Glutamate can induce neuronal degeneration by over-stimulation of NMDA receptors. Asiatic acid also reduces H_2O_2 induced cell death and reduce the intracellular free radical concentration. In invitro studies triterpene asiatic acid and its derivatives have been shown reducing glutamate-induced excitotoxicity and protect cortical neurons [78]. Centella extract (100, 200 and 300 mg/kg) showed dose dependent protective effect against cognitive deficits and oxidative stress in rats and improve the retention of memory [79].

2.3.3 Ginseng

It consists of dried roots of *Panax ginseng* and it has been used in Asia from past 2000 years especially in China, Korea, and Japan. Studies have been shown that ginseng extract is beneficial in treatment of Alzheimer's disease as a cognitive enhancer [80]. Active constituents of ginseng prevent amyloid β formation and prevent the spatial memory impairment in rats [81]. It also inhibits advanced glycation end products (AGE) by reducing its formation [82]. Red ginseng water extract (0.3–3 mg/mL) blocks reactive oxygen species (ROS) generation and neuronal apoptosis which was stimulated by glutamate, *N*-methyl-$_D$-aspartate, or β-amyloid in rat cortical cells and prevent the neuronal diseases [83].

3. Clinical trials

Sr. No.	Herbal Plant	Participants	Intervention	Conclusion	Reference
1	Caffeine	Volunteers(10females and 9 males aged61-79; 66 ± 2 years)	Pre and 60 minutes post ingestion	Enhance functional performance, manual dexterity and readiness to invest effort in apparently healthy older adults	Duncan MJ *et al*., 2014 [84]

2	Ephedra	One hundred and twenty-five otherwise healthy obese women (body mass index > or =25 kg/m2) were recruited and randomly assigned to three groups: ephedra group (n = 41), evodia group (n = 45) and placebo group (n = 39).	ephedra extract in capsules (pseudo-ephedrine 31.52 mg) or evodia extract in capsules (evodiamine 6.75 mg, rutaecarpine 0.66 mg) or placebo capsules as well as participating in a low-calorie diet for 8 weeks	Ephedra and evodia were proven to be safe for short-term use in the herbal form and ephedra combined with a low calorie diet was effective in reducing BMI.	Kim HJ *et al*., 2008 [85]
3	Khat	Six habitual khat chewers	For a period of 3h,chewed either khat leaves or lettuce	Chewing khat significantly decreased subjective feelings of hunger and increased fullness, anorexigenic effect of khat is due to cathinone.	Murray CD *et al*., 2008 [66]
4	Hypericum	one hundred thirty-five patients (57% women; mean age, 37.3 +/- 11.0) were randomized to double-blind treatment and were included in the intent-to-treat analyses.	12 weeks of double-blind treatment with LI-160 St John's wort extract (900 mg/d), fluoxetine (20 mg/d), or placebo.	John's wort was significantly more effective than fluoxetine and showed a trend toward superiority over placebo for antidepressant efficacy.	Fava M *et al*., 2005 [86]
5	Ginkgo	a randomized, double-blind, placebo-controlled trial	daily doses of 480 mg EGb 761, 240 mg EGb 761 or placebo for 4 weeks	It was safe and well tolerated and may have particular value in elderly patients with anxiety related to cognitive decline	Woelk H *et al*., 2007 [81]
6	Gotukola	Thirty-three participants (18 male and 15 female; average age 33 yrs)	Centella asiatica (CA) in a fixed dose regime (500 mg/capsule, twice daily, after meal)	CA further significantly improved the willingness for adjustment and cognition and may be used as a promising anxiolytic agent	Jana U *et al*., 2010 [87]
7	Ginseng	30 participants	200 and 400 mg	Reduced reaction time on 3-back reaction time at 400 mg, but increase in reaction time with 200 mg Increased 3-back sensitivity index scores with 400 mg, but decreased with 200 mg Improved self-reported mood levels	Reay *et al.* (2009) [88]

4. Novel Approaches for Herbal CNS Stimulants

Sr No.	Active Constituent	Formulation	Route of Administration	References
1	Ginkgoflavin	Phytosome	subcutaneous	Vandana SP *et al*., 2008 [89]
2	Ginsenosides	Phytosome	oral	Bhattacharya, 2009 [90]
3	Ginkgo flavonoids	Nanoparticle	oral	Shimada, 2012 [91]
4	Theasinesis	Phytosome	oral	Kidd PM, 2009 [92]
5	Ginseng, Guarana	Fast Dissolving Oral Films	oral	Anand V *et al*., 2007 [93]
6	Ginseng	Nanoparticle	oral	Wang F *et al*., 2010 [94]

5. Herbal CNS stimulants in research

5.1 Alpinia galanga

It consists of dried rhizomes of *Alpinia galanga* L. (*Zingiberaceae*).It is primarily used in cooking [95, 76]. The herb is widely distributed in various parts of India and Southeast Asia. The CNS stimulant activity of plant has been observed by crude methanolic extract as well as ethyl acetate fraction of *A. galanga* using various pharmacological tests. The significant activity shown by methanolic and ethyl acetate extract of *A. galanga* on mice using actophotometry and rotarod test. An increase in locomotor activity with mice treated with the methanolic extract and ethyl acetate fraction of the rhizome of *A galanga* in concentration of 250 and 500 mg/kg. CNS stimulants increase the motor coordination which increase the time spend by mice on rotarod. Both methanolic extract and ethyl acetate fraction of *A. galanga* significantly increases in gripping time at a dose of 500 mg/kg [96].

5.2 Cucurbita Maxima

Cucurbita maxima is a short lived shrub which belongs to family *Cucurbitaceae* [97]. Seeds are traditionally used as a bitter tonic, oil obtained used in debility nervous disorders, can be used in treatment of depression [98, 99]. This study was carried out using swiss albino mice to evaluate the CNS stimulant activity [100]. Caffeine was used as a reference drug [101, 100]. The crude extract showed significant CNS stimulant activity in comparison to control group and results were comparable to the activity shown by reference drug [100].

5.3 Rhinacanthus nasutus

The studies were done to observe the effect of *Rhinacanthus nasutus (R. nasutus)* leaf extract on impaired glucose and lipid metabolism in obese mice [102, 103]. High-fat diet (HFD) and abnormal lipid metabolism leads to obesity which can impair the insulin signalling by inhibiting the release of glucose from the liver and its uptake by the fat and muscle cells [103, 104] Obesity was induced in mice by feeding a high-fat diet (60 kcal% fat) for 12 weeks. Obese mice were administered with the water extract of R. nasutus leaves at 250 and 500 mg/kg per day for the next six weeks after first six weeks of diet [103]. The liver and adipose tissues are removed for histopathological examination and protein expression study. The blood glucose, lipid profiles, insulin, leptin, and adiponectin levels were measured [103]. After 6 weeks of treatment it was found that water extract of *R. nasutus* reduces increased lipid concentrations in their serum and liver tissues in obese mice [103]. The present studies reported that *R. nasutus* extract is improving the impaired glucose and lipid

metabolism in high-fat diet-induced obesity in mice via stimulating the insulin sensitivity in the liver and adipose tissues [103].

Herbal CNS stimulants are much safer than synthetic drugs therefore use of herbal products is increasing for prevention of diseases and therapeutic purposes.

6. Conclusion

The synthetic drugs are more costly, having narrow margin of safety and more side effects as compared to herbal CNS stimulants which are having wide margin of safety, cheaper and having mild side effects than synthetic drugs, so more research is going on herbal drugs in CNS disorders. Except the drug Cocaine, Khat (abusive drug) all other drugs such as caffeine, Ephedra having wide margin of safety and having less side effects as compared to amphetamine and methylphenidate.

Extensive research is going on for novel approaches and targeting of herbal CNS stimulants. Many problems related to research, production and application need to be solved. Suitable carrier should be developed which can reduce the toxicity of the drug as well as increase the pharmacological activity of the drug. Herbal drugs have enormous therapeutic potential which should be explored through some value added drug delivery systems.

7. References

1. David J Heal, Sharon L Smith. CNS stimulants, Neuropharmacology. 2014; 87:1-3.
2. Tripathi KD. CNS Stimulants and Cognition Enhancers, Essentials of Medical Pharmacology, Fifth Edition, 2003, 435.
3. 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.
4. Burton Angrist, Central Nervous System Stimulants: Historical Aspects and Clinical Effects, Handbook of Psychopharmacology, 2010; 11:99-165.
5. Stimulant Wikipedia. https://en.wikipedia.org/wiki/Stimulant. 2016.
6. Silverstone T. Appetite suppressants—a review. Drugs. 1992; 43(6):820-36.
7. Stotz Gabriele. Woggon Brigitte. Angst, Jules, Psychostimulants in the therapy of treatment-resistant depression Review of the literature and findings from a retrospective study in 65 depressed patients. Dialogues in Clinical Neuroscience. 1999; 1(3):165-174.
8. Stewart Jonathan W, Deliyannides Deborah A, McGrath Patrick J. How treatable is refractory depression. Journal of Affective Disorders. 2014; 167:148-152.
9. Dell'Osso Bernardo, Ketter Terence A, Cremaschi Laura, Spagnolin Gregorio, Altamura A. Carlo Assessing the roles of stimulants/stimulant-like drugs and dopamine-agonists in the treatment of bipolar depression. Current Psychiatry Reports. 2013; 15(8):378.
10. Corp Stephanie A, Gitlin Michael J, Altshuler Lori L. A review of the use of stimulants and stimulant alternatives in treating bipolar depression and major depressive disorder. The Journal of Clinical Psychiatry. 2014; 75(9):1010-1018.
11. Husain A, Virmani OP, Popli SP, Misra LN, Gupta MM, Srivastava GN, Abraham Z, Singh AK, Dictionary of Indian medicinal plants (CIMAP, Lucknow). 1992.
12. Bracesco N, Sanchez AG, Contreras V, Menini T, Gugliucci A. Recent Advances on Ilex paraguariensis Research: Mini Review, Journal of Ethnopharmacology. 2011; 136:378-384.
13. The US. Weight Loss and Diet Control Market. 9th edition. Tampa, FL: Marketdata Enterprises, 2007.
14. 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.
15. Barnes PM, Powell-Griner E, McFann K, Nahin RL, editors, Complementary and Alternative Medicine Use Among Adults, United States, Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, 2004.
16. Ernst E. Second thoughts about safety of St. John's wort. (erratum in Lancet 2000;355:580). Lancet 1999; 354:2014-6.
17. AltCareDex System. Thomson Reuters (HealthCare) Inc. Available at: http://www.thomsonhc.com. Accessed. 2008.
18. 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.
19. Ara Tachjian MD *et al*, Use of Herbal Products and Potential Interactions in Patients With Cardiovascular Diseases. Journal of the American College of Cardiology. 2010; 55(6).
20. Siegel RK. Ginseng abuse syndrome: problems with the panacea. JAMA. 1979; 241:1614-5.
21. Cartmell LW, Aufderheide AC, Springfield AC, Weems C, Arriaza B. The frequency and antiquity of prehistoric coca-leaf-chewing practices in northern Chile: radioimmunoassay of a cocaine metabolite in human-mummy hair. Latin American Antiquity, 1991; 2:260-268.
22. Indriati E, Buikstra JE. Coca chewing in prehistoric coastal Peru: dental evidence. American Journal of Physical Anthropology. 2001; 114:242-257.
23. Colzato LS, van den Wildenberg WP, Hommel B. Reduced spontaneous eye blink rates in recreational cocaine users: evidence for dopaminergic hypoactivity. 2008, PLoS ONE 3:e3461.
24. Billman GE. Mechanisms responsible for the cardiotoxic effects of cocaineFederation of American Societies for Experimental Biology, 1990; 4:2469-2475.
25. Rump AF, Theisohn M, Klaus W. The pathophysiology of cocaine cardiotoxicity, Forensic Science International. 1995; 71:103-115.
26. Lasoń W. Neurochemical and pharmacological aspects of cocaine-induced seizures, Polish journal of pharmacology. 2001; 53:57-60.
27. O'Brien CP, Drug addiction and drug abuse, in Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th ed (Brunton LL, Lazo JS, and Parker KL eds), The McGraw-Hill Companies, New York. 2006.
28. Kloner RA, Hale S, Alker K, Rezkalla S. The effects of acute and chronic cocaine use on the heart, Circulation. 1992; 85:407-419.
29. Tamrazi B, Almast J. your brain on drugs: imaging of drug-related changes in the central nervous system, Radiographics, 2012; 32:701-719.
30. 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.

31. Henman AR. Guarana (Paullinia cupana var Sorbilis): ecological and social perspective on an economic plant of the central Amazon Basin. Journal of Ethnopharmacology. 1982; 6:311-38.
32. Nehlig A *et al*. , Caffeine and the central nervous system: mechanisms of action, biochemical, metabolic and psychostimulant effects, Brain Research Brain Research Reviews, 1992; 17(2):139-70.
33. Hechman, MA, Weil J, Mejia EG. Caffeine (1, 3, 7-Trimethylxanthine) in Foods: A Comprehensive Review on Consumption, Functionality, Safety, and Regulatory Matters. Journal of Food Science, 2010; 75:R77-R87.
34. Smith BD, White T, Shapiro R. The Arousal Drug of Choice: Sources and Consumption of Caffeine, in Caffeine and Activation Theory: Effects on Health and Behavior (Smith BD, Gupta U, Gupta BS, editors, eds, ed) CRC Press, Boca Raton. 2007, 9-42.
35. 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-R151.
36. DRUGDEX System Micromedex 2.0. Caffeine.http://www.micromedexsolutions.com.proxy.libraries.rutgers.edu/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/10955F/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/BEFE12/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/evidencexpert.IntermediateToFullDocumentLink/docId/1291/contentSetId/31/title/CAFFEINE/servicesTitle/CAFFEINE. 2014.
37. 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-R151.
38. Caitlin E McCarthy *et al*., Anxiety-Inducing Dietary Supplements: A Review of Herbs and Other Supplements with Anxiogenic Properties, Pharmacology & Pharmacy. 2014; 5:966-981.
39. Bhatti SK, O'Keefe JH, Lavie CJ. Coffee and Tea: Perks for Health and Longevity? Current Opinion in Clinical Nutrition and Metabolic Care. 2013; 16:688-697.
40. Wu Y, Wu Z, Butko P *et al*., Amyloid-β-induced pathological behaviors are suppressed by Ginkgo biloba extract EGB 761 and ginkgolides in transgenic Caenorhabditis elegans," Journal of Neuroscience. 2006; 26(50):13102-13113.
41. Bicho NC, Lidon FC, Ramalho JC, Leitao AE. Quality assessment of Arabica and Robusta green and roasted coffees - A review Emirates Journal of Food and Agriculture, 2013; 25:945-950.
42. Oxana Babova *et al*., Chemical partitioning and antioxidant capacity of green coffee (Coffea arabica and Coffea canephora) of different geographical origin, Phytochemistry. 2016; 123:33-39.
43. Giulia Runti *et al*., Arabica coffee extract shows antibacterial activity against Staphylococcus epidermidis and Enterococcus faecalis and low toxicity towards a human cell line, LWT - Food Science and Technology, 2015; 62(1):108-114.
44. Ellam S, Williamson G. Cocoa and Human Health. Annual Review of Nutrition, 2013; 33:105-128.
45. De Araujo QR, Gattward JN, Almoosawi S, Silva MDC, Dantas PA, Araujo Jr QR. Cacao and Human Health: From Head to Foot—A Review. Critical Reviews in Food Science and Nutrition, In Press. 2013.
46. Alexander N Sokolov *et al*., Chocolate and the brain: Neurobiological impact of cocoa flavanols on cognition and behavior, Neuroscience & Biobehavioral Reviews, 2013; 37(10, 2):2445-2453.
47. Latif R. Health Benefits of Cocoa. Current Opinion in Clinical Nutrition and Metabolic Care, 2013; 16:669-674.
48. Natural Medicine Comprehensives Database (US) Cocoa Full Monograph. 2013.
49. Burdock GA, Carabin IG, Crincoli CM. Safety Assessment of Kola Nut Extract as a Food Ingredient. Food and Chemical Toxicology. 2009; 47:1725-1732.
50. Natrual Medicine Comprehensive Database (US) Cola Nut Full Monograph. 2013.
51. Warrier PK, Nambiar VPK, Ramankutty C. Indian medicinal plants (Orient Longman Ltd., Madras) 1993-95, 1-5.
52. Espinola EB, Dias RF, Mattei R, Carlini EA. Pharmacological activity of Guaranan (Paullinia cupana Mart) in laboratory animals, Journal of Ethnopharmacology, 1997; 55:223-9.
53. Mattei R, Dias RF, Espínola EB, Carlini EA, Barros SBM. Guarana (Paullinia cupana): toxic behavioral effects in laboratory animals and anti oxidant activity *in vitro*. Journal of Ethnopharmacology. 1998; 60:111-116.
54. Brekhman II, Dardymov IV. New substances of plant origin which increase nonspecific resistance Annual Review of Pharmacology and Toxicology. 1969; 9:419-30.
55. Henderer JD, Rapuano CJ. Ocular pharmacology, in Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th ed (Brunton LL, Lazo JS, and Parker KL eds), The McGraw-Hill Companies, New York, 2006.
56. Natural Medicine Comprehensives Database (US) Mate Full Monograph. 2013.
57. Soni MG, Carabin IG, Griffiths JC, Burdick GA. Safety of Ephedra: Lessons Learned. Toxicology Letters, 2004; 150:97-110.
58. Glennon RA, Young R. (+) Amphetamine-stimulus generalization to an herbal ephedrine product, Pharmacology Biochemistry and Behavior, 2000; 65:655-8.
59. Astrup A, Breum L, Toubro S. Pharmacological and clinical studies of ephedrine and other thermogenic agonists,Obesity Research & Clinical Practice, 1995; 3(Suppl 4):537S-40S.
60. Carek PJ, Dickerson LM. Current concepts in the pharmacological management of obesity. Drugs. 1999; 57:883-904.
61. Dulloo AG. Ephedrine, xanthines and prostaglandin-inhibitors: actions and interactions in the stimulation of thermogenesis. "International journal of obesity and related metabolic disorders. 1993; 17(Suppl 1):S35-40.
62. Food and Drug Administration Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk. Federal Register, 2004; 69:6787-6854.
63. Andrine M Lemieux *et al*., Khat use and appetite: An overview and comparison of amphetamine, khat and cathinone. Journal of Ethnopharmacology. 2015; 160:78-85.
64. United Nations, Etude sur la composition chimique du khat: Recherche sur la fraction phenylalkylamine. In: Nations, U. (Ed.). 1975.
65. Szendrei K. The chemistry of khat, Bullet in on Narcotics, 1980; 32:5-35.
66. Murray CD, LeRoux CW, Emmanuel AV, Halket JM, Przyborowska AM, Kamm MA *et al*., The effect of

Khat(Catha edulis)as an appetite suppressant is independent of ghrelin and PYY secretion. Appetite, 2008; 51:747-750.
67. Linde K. St. John's Wort—An Overview. Forschende Komplementärmedizin, 2009; 16:146-155.
68. Klemow KM, Bartlow A, Crawford J *et al*. Medical Attributes of St. John's Wort (Hypericum perforatum) In: Benzie IFF, Wachtel-Galor S, editors. Herbal Medicine: Biomolecular and Clinical Aspects, 2011 2nd edition. Boca Raton (FL): CRC Press/Taylor & Francis; Chapter 11.
69. DerMarderosian A, Beutler J. The Natural Review of Products. St. Louis, MO: Facts and Comparisons. 2002.
70. Suzuki O, Oya M, Bladt S, Wagner H. Inhibition of monoamine oxidase by hypericin, Planta Medica, 1984; 2:272.
71. Chavez ML, Chavez PI. Saint John's wort, Hospital Pharmacy Journal. 1997; 32(12):1621-32.
72. Clostre F. Ginkgo biloba extract (EGb 761). State of knowledge in the dawn of the year 2000, Annales Pharmaceutiques Françaises. 1999; (57 Suppl 1):1S8-88.
73. Bryn Williams *et al*., Age-related effects of Ginkgo biloba extract on synaptic plasticity and excitability**,** Neurobiology of Aging**,** 2004; 25(7):955-962.
74. 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.
75. Kampkötter T, Pielarski R, Rohrig *et al*., The Ginkgo biloba extract EGb761 reduces stress sensitivity, ROS accumulation and expression of catalase and glutathione S-transferase 4 in Caenorhabditis elegans," Pharmacological Research. 2007; 55(2):139-147.
76. 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.
77. Gray N *et al*., Caffeoylquinic Acids in Centella asiatica Protect against Amyloid-β Toxicity, Journal of Alzheimer's Disease, 2014; 40:359-373.
78. Mook-Jung *et al*., Protective effects of asiaticoside derivatives against beta-amyloid neurotoxicity. Journal of Neuroscience Research. 1999; 58:417-425.
79. Kumar MHV *et al*., Effect of *Centella asiatica* on cognition and oxidative stress in an intracerebroventricular streptozotocin model of Alzheimer's disease in rats, Clinical and Experimental Pharmacology and Physiology, 2003; 30:336-342.
80. Song XY *et al*., Ginsenoside Rg1 attenuates okadaic acid induced spatial memory impairment by the GSK3β/tau signaling pathway and the Aβ formation prevention in rats, European Journal of Pharmacology. 2013; 710:29-38.
81. 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 of Psychiatric Research. 2007; 41(6):472-80.
82. Quan HY *et al*., Korean red ginseng extract alleviates advanced glycation end product-mediated renal injury, Journal of Ginseng Research. 2013; 37:187-193.
83. Kim S *et al*., Korean red ginseng extract exhibits neuroprotective effects through inhibition of apoptotic cell death, Biological and Pharmaceutical Bulletin, 2014; 37:938-946.
84. Duncan MJ *et al*., The effect of caffeine ingestion on functional performance in older adults. Journal of Nutrition, Health and Aging, 2014; 18(10):883-887.
85. 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 of Acupuncture & Meridian Studies, 2008; 1(2):128-38.
86. Fava M *et al*., A Double-blind, randomized trial of St John's wort, fluoxetine, and placebo in major depressive disorder. Journal of Clinical Psychopharmacology. 2005; 25(5):441-7.
87. Jana U *et al*., A clinical study on the management of generalized anxiety disorder with Centella asiatica, Nepal Medical College journal. 2010; 12(1):8-11.
88. Reay JL, Scholey AB, Milne A, Fenwick J, Kennedy DO. *Panax ginseng* has no effect on indices of glucose regulation following acute or chronic ingestion in healthy volunteers, British Journal of Nutrition. 2009; 101:1673-1678.
89. Vandana SP, Suresh RN. Phytosomes, Experimental and Toxicologic Pathology, 2008; 60:397-404.
90. Bhattacharya S. fast dissolving films, Pharma Times. 2009; 41(3):9-12.
91. Shimada S, Composition comprising nanoparticle Ginkgo biloba extract with the effect of brain function activation, US 8105637 B2, 2012, 424-489.
92. Kidd PM, Bioavailability and Activity of Phytosome Complexes from Botanical Polyphenols: The Silymarin, Curcumin, Green Tea, and Grape Seed Extracts. Alternative Medicine Review, 2009; 14(3):226-246.
93. Anand V, Kataria M, Kukkar V, Saharan V, Choudhury PK. The latest trends in the taste assessment of pharmaceuticals, Drug Discovery Today. 2007; 12:257-265.
94. Wang F, Zhou L, Gu F. Characterization of anticancer hypocrellin A encapsulated with silica nanoparticles, Journal of Thermal Analysis and Calorimetry, 2010; 80:213-18.
95. Weckerle CS, Stutz MA, Baumann TW. Purine alkaloids in Paullinia. Phytochemistry. 2003; 64:735-42.
96. Sayan Saha, Sugato Banerjee. Central nervous system stimulant actions of *Alpinia galanga* (L.) rhizome: A preliminary study, Indian Journal of Experimental Biology. 2013; 51:828-832.
97. Huang Chang Chih, Shiah I Shin, Chen Hsing-Kang, Mao Wei-Chung, Yeh Yi Wei. Adjunctive use of methylphenidate in the treatment of psychotic unipolar depression. Clinical Neuropharmacology. 2008; 31(4):245-247.
98. Eagles JM. Treatment of depression with pumpkin seeds. British Journal of Psychiatry. 1990; 157:937-938.
99. MUNTEAN Edward *et al*., Cucurbita Maxima DUCH. As A Medicinal Plant, Hop and medicinal plants, 2013; 1-2(41-42).
100. 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.
101. Payal R Dande, Vikram S Talekar, Chakraborthy GS. Evaluation of crude saponins extract from seeds of *Sesbania sesban* for topical anti-inflammatory activity, International Journal of Research in Pharmaceutical Sciences. 2010; 1(3):296-299.
102. Lee B, Shao J. Adiponectin and energy homeostasis, Reviews in Endocrine and Metabolic Disorders. 2014; 15:149-56.

103. Supaporn Wannasiri *et al*., Rhinacanthus nasutus leaf improves metabolic abnormalities in high-fat diet-induced obese mice, Asian Pacific Journal of Tropical Biomedicine, 2016; 6(1):1-7.
104. Snel M, Jonker JT, Schoones J, Lamb H, de Roos A, Pijl H *et al*. Ectopic fat and insulin resistance: pathophysiology and effect of diet and lifestyle interventions, International Journal of Endocrinology. 2012.