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Review Article

Nootropics: Clinical and Analytical Toxicology Review of The Cognitive Enhancement Among Healthy Individuals

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ABSTRACT

The term nootropic refers to a group of substances that are used to treat deficits of cognition. Nootropic substances, or cognitive enhancers, have been used therapeutically for the treatment of certain diseases that affect cognition, memory, and mental function. Lately, the use of these substances has been growing widely among young and healthy individuals seeking cognitive enhancement. Some of these substances have been advertised as 'smart drugs' or 'legal highs.' The safety profile and benefit for those substances are not fully established and mostly are extrapolated from clinical therapeutic use. The wide availability, lack of regulation, and the increasing demand for those enhancers make it important to categorize them, recognize their mechanisms of actions and possible side effects that can be encountered.

In this review, we want to emphasize the importance of further studies and clinical trials for the benefit and safety profile of those dietary supplements.

Keywords: Toxicology; Drugs; Dietary; Caffeine; Nicotine; Amphetamine; Khat; Cathinone; Marjuiana; Cannabis; Designer drugs; Synthetic cathinones; Flakka; Synthetic Cannabinoids

INTRODUCTION

Nootropics drugs, or cognitive enhancers, are drugs that have been studied or used to improve and enhance deficits in cognition. Cognition (from the Latin word cognoscere "to know" or "to recognize") is the ability to process information that is acquired through learning and perception process. It involves language, memory, perception, creativity, problem-solving, and complex psychomotor functions [1]. The term nootropic (noos=mind; tropic=toward) was first coined by professor Giurgea when he first described his findings on piracetams as he described it to impact the higher brain integrative activity, and enhance its efficacy and compensate partially for its deficits [2]. His findings on piracetams did not fall under any known category of any psychotropic substances at the time [3]. The use of cognition enhancers to treat cognition deficits has been well known and long studied in the clinical settings, trying to demonstrate benefit in the elderly population with declining functions in memory and attention such as in Alzheimer's disease

Nootropics or cognitive performance enhancers category is not straight forward, and variable substances can fit under this classification. as there is no widely universal agreement or clear criteria to define these substances. It can be broadly classified as being used for therapeutic treatment in a clinical setting, or the use in healthy individuals for performance enhancement. Therapeutic studies, despite being numerous and promising, the evident results of benefits are still not absolute in treating and enhancing abilities in the deficit state. and it is even less evident in cognitive enhancers use among healthy populations [4-10]. Despite this lack of evidence, the demand and use are growing in the non-clinical setting by healthy individuals based mostly on extrapolations of the findings from the therapeutic studies [11]. The ease in obtaining them and the wide availability of these substances along with marketing advertisements of safety and its non-regulated nature as dietary supplements all have been contributing to the ever-growing demand on these substances. This uncontrolled use is dangerous because of the lack of evidence and the unknown nature of the safety profile and the proper dosing of these substances. The lack of regulatory bodies

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for these substances sold as dietary supplements leads to even further safety concerns on the components and purity of these compounds. The classification of these compounds is further complicated by its diversity. In this review, we suggest the following examples which are not meant by any means to be considered a complete or an exhaustive list as more and more substances are recognized every day. The selection of examples is based on most frequently resulted substances in searching the keywords "nootropic" "cognitive enhancers" and only including results among healthy individuals and excluding therapeutic studies. The main aim of this article is to review examples of misused substances that can have nootropic or cognition enhancement properties and to discuss their toxicities and adverse effects to be able in future studies to focus on the safety of their use.

CAFFEINE

Caffeine (1,3,7-trimethylxanthine) (Figure 1) is a plant-derived alkaloid and psycho-stimulant that is present in many products (coffee, cocoa beans, tea, kola nuts, soft drinks) [12-14]. Many dietary supplements and products contain caffeine in different quantities. Estimation of levels of caffeine in different types of food is published by the United States Department of Agriculture (USDA), but similar estimates are not available for caffeine found in various dietary supplements [15].

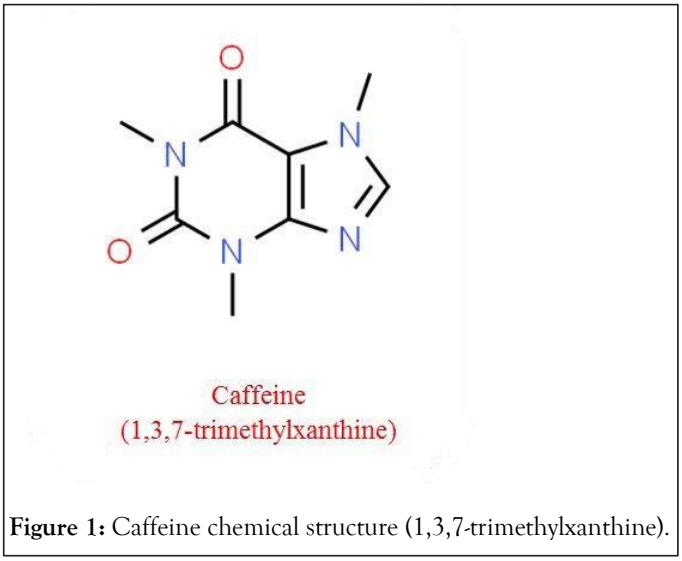

Figure 1: Caffeine chemical structure (1,3,7-trimethylxanthine).

Caffeine is the main methylxanthine found in coffee [16-19]. The main mechanism of action of methylxanthines is adenosine antagonism that leads to catecholamine release [20]. It has a very similar structure to adenosine and thus is able to bind to adenosine receptors inhibiting adenosine effects. since adenosine is well known to inhibit the Dopamine neurotransmitter release, this leads to a net effect of increased dopamine release leading to high Dopamine concentration in the brain [21]. This has an enhancement effect on improved alertness, attention, and reaction times [22]. Methylxanthine can also regulate intracellular calcium levels, modulate GABA receptors, and phosphodiesterase inhibition [23]. The estimated lethal oral dose is 150 mg/kg [20]. Products are sold, often from the internet as pure powdered caffeine, or found as a main or adulterant component in many dietary supplements and drug products [24]. Caffeine-containing supplements contain an estimated caffeine content of 50 mg to 500 mg per can or bottle [18]. Unregulated dietary supplements containing caffeine have the potential to cause significant harm due to the lack of appropriate dosing and instructions. One teaspoon of a pure caffeine powder could have the equivalent of "25 cups of coffee" [24].

Anhydrous caffeine, which is the powdered dehydrated form, can cause dosage confusion to the consumer. It is much more concentrated than the caffeine in the regular cup of coffee and is often used in supplements leading to accidental overdosing and deleterious effects [25-27].

In the sports world, caffeine supplements have always been advertised and tolerated due to the wellknown ergogenic effects on mental and physical endurance exercises [28,29]. It has a well-documented enhancement effect on the athlete's mental and physical performance during exhaustive exercises [30]. The prework out supplements and energy drinks are very appealing products for consumers of all ages. A 2013 report by the drug abuse warning network (DAWN) has found 20,783 Energy drink-related Emergency Department visit, 58% of those are Energy drink related alone and 42% related to other drugs involved as well (SAMHSA, Center for Behavioral Health Statistics and Quality n.d.). Many of the pre-workout supplement manufacturers do not disclose the exact amounts of its ingredients and labels often contain insufficient information about the specific doses per recommended serving size and does not take into account the fact that different sized individuals need variable serving sizes such as children versus adult and men versus women body habitus. Caffeine, Citrulline, Tyrosine, Creatine, Arginine, Beta-alanine, Taurine, and Vitamin B12 are few of the commonly found ingredients in variable amounts among the most known prework out brands [31,32]. Pre-workout supplements are not monitored by the Food and Drug Administration (FDA) and consistency of ingredients with those mentioned on the label is still the manufacturer's responsibility.

Stimulant effects of caffeine due to catecholamine release. It ranges from nausea, vomiting, tachycardia, hypertension, agitation, hallucination, seizures, cardiac arrhythmia, and myocardial infarction. Just like with other methylxanthines hypokalemia, hyponatremia, hyperglycemia, and rhabdomyolysis can be seen in moderate to severe cases. The majority of caffeine-related deaths are related to ventricular fibrillation [33-36]. In the literature search, 28 cases (29%) out of 92 described fatality case were accidental, the majority were related to over the counter supplements [37,38].

There are many analytical methods developed to analyse caffeine content in coffee products and beverages. high performance liquid chromatography (HPLC) is considered the method of choice by many researchers. However its use is limited by its high price, resources required and the high technical demand. Spectrophotometric use is reported to be also a preferred method of determination of caffeine content in coffee beans, beverages, products and tea leaves. UV-Vis spectrophotometry specifically is preferred because of its low cost, accuracy, reliability and reproducibility. one of the main limitations of

this method is its requirement for extraction of the caffeine from the aqueous solution of the coffee beans as direct determination of caffeine content is not feasible. Other analytical methods that can be used such as gas chromatography, liquid chromatography- tandem mass spectrometry and other spectroscopic techniques such as nuclear magnetic resonance spectroscopy, near infrared spectroscopy and fluorescence polarization immunoassays. One of the main important uses of spectrophotometric determination of caffeine in different beverages and products to estimate the content of caffeine and estimate its content especially in energy drinks and other sport related products.

NICOTINE

Nicotine (Figure 2) is another plant-derived alkaloid with stimulant properties [39,40]. Along with caffeine, nicotine is also considered the most widely used addictive xenobiotic (Dance 2016). It is related to coniine (from the poison hemlock) and to lobeline (from lobalia inflate, the Indian tobacco) [16]. It binds to the nicotinic acetylcholine receptor (nAChr) with high affinity [41]. These receptors are widely found throughout the central nervous system (CNS) [42]. The nicotinic alkaloids act as agonists on the (NAChr) by causing increase sodium ion influx through the channel. Activation of (nAChr) in the CNS directly stimulates neurotransmitter release [43]. There is a substantial body of literature focused on the effects of nicotine and CNS (nAChr)'s on cognition, motor, and behavioral systems [44-46].

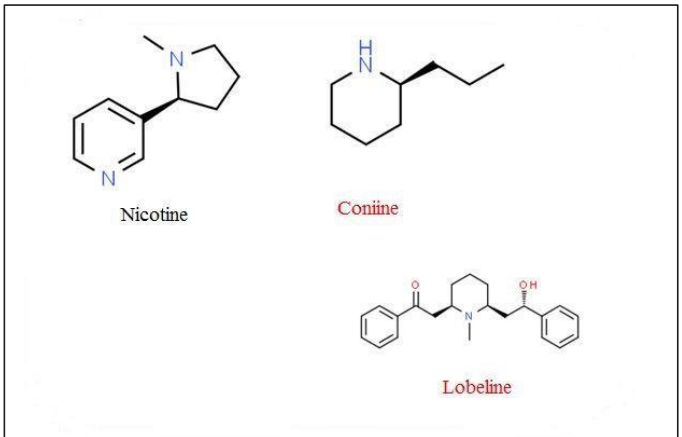

Figure 2: Nictoinic alkaloids, Nicotine, Coniine and Lobeline.

Nicotine mimics the effects of acetylcholine release by binding to postsynaptic (NaChr) [47-51]. The acute nicotine effects are related to enhanced neurotransmission in the cortico-basal ganglia-thalamic circuits, and possibly a combination of direct stimulation of the nAChRs, dopamine release, and monoamine oxidase (MAO) inhibition [52].

The toxicity of nicotine will vary between individuals depending on their habituation of nicotine effects. An estimated 40 to 60 mg of nicotine can be fatal [53,54]. A regular cigarette can contain from 13 up to 30 mg of nicotine; a cigarette butt can contain up to 5 mg of nicotine.

In children, ingestion of 1 mg/kg can induce toxicity

Liquid nicotine is another source of concern. Electronic cigarettes refill cartridge can contain up to 36 mg/mL (3.6 %). One drop of the solution may contain up to 1.8 mg of nicotine, which could produce significant symptoms in a young child [55-57].

When inhaled symptoms can manifest as early as within 60 seconds, chewing gum can take manifest within 30 minutes or less.

Symptoms are usually related to cholinergic excess such as diaphoresis, gastrointestinal upset, tachycardia, hypertension, and can progress to fasciculations, confusion, seizure, and cardiac dysrhythmias [58-66].

In children, accidental ingestion can be frequently encountered. In one study, it was found that only 18% became symptomatic [67,68]. Of those symptomatic, 39 % presented with vomiting. Lethargy, dysphagia, mydriasis, and diaphoresis were less encountered (childhood poisoning). More severe presentations have been reported in children, especially with chewing gum ingestion [69].

Even though nicotine is not considered a prescription drug, its effects are similar to smart drugs and are used by many individuals as a self- medicating therapy to reach a chemical boost, and hence the addiction and dependence issues follow what seems to be innocent behavior [44,70,71].

The principal source of nicotine is still tobacco products (cigarettes, cigars, pipe tobacco and chewing tobacco, E-cigarettes) but smoke cessation products containing nicotine (gums, transdermal patches, inhalers sprays, and pills) are an increasingly available source of nicotine.

Recently, the use of E-cigarette and vaping products have been increasingly recognized to be associated with lung injury. Tachycardia, tachypnea, fever, and progression to hypoxemic respiratory failure have been reported in multiple cases recently [72-74]. Although nicotine is usually the main component in these devices, many other substances such as aldehydes, glycerin, and propylene glycol, vitamin E acetate, and tetrahydrocannabinol (THC) are probably involved as well [75,76].

There are several published methods to measure the nicotine level especially in the e-liquid juices that are used in the popular E-cigarettes such as gas chromatography-mass spectrometry (GC-MS), gas chromatography with flame ionization detector (GC-FID) and liquid chromatography-mass spectrometry (LC-MS). Because of the limited availability of the GC, several HPLC methods have been described.

AMPHETAMINE

Amphetamines comprise a large class of compounds that are diverse. They can be considered pharmacological cognitive enhancers. These synthetic pharmaceutical stimulants are typically designed to mimic certain neurotransmitters and increase neural signaling molecules in the brain. Their efficacy for augmenting brain function and cognition in healthy subjects is controversial and not completely proven [13].

The parent compound (**α**–methylphenylethyl-amine) belongs to the family of phenylethylamines. Substitutions of the phenylethylamine backbone is possible in numerous ways which give to the diversity of the group [77].

The amphetamine group includes synthetic and natural compounds such as ephedrine and Cathinone [78]. Of the commonly abused substances that belong to the amphetamine group amphetamine (AMPH), methamphetamine (METH), and 3,4-methylenedioxymethamphetamine (MDMA) [79]. These substances have a powerful central nervous system stimulant effects and are commonly abused for their psycho-stimulant effects [80]. The amphetamine group is also used clinically in certain medical conditions, where it has been found to be beneficial in the treatment of Attention deficit hyperactivity disorder (ADHD), narcolepsy, and short term weight reduction therapy [81-84].

The main mechanism of action for Amphetamine and its analogs (Figure 3) is by increasing concentrations of catecholamines present at neuronal synapses, mainly dopamine and norepinephrine, by blocking their presynaptic uptake, blocking their vesicular storage, and by inhibiting the metabolism of catecholamines by monoamine oxidase [85-88].

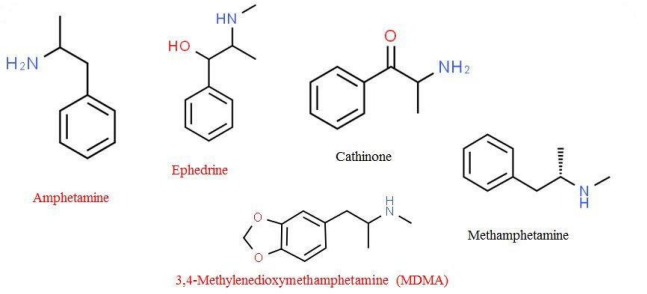

Figure 3: Amphetamine compound and its analogs.

The increased catecholamine levels and the sustained activation of the sympathetic nervous system is responsible for the sympathetic activation and the familiar "fight or flight" response [89]. Clinical effects of Amphetamine include tachycardia, hypertension, mydriasis, diaphoresis, hyperthermia, agitation, and seizures. These effects are all mediated by excess stimulation of the sympathetic nervous system and excess release of monoamine neurotransmitters (Serotonin, dopamine and norepinephrine) [16,90].

Methylphenidate (MPH), also known as Ritalin, is one of the commonly prescribed and studied stimulant drugs for the treatment of ADHD along with Adderall (Amphetamine-Dextroamphetamine).

The primary effect of Ritalin has increased arousal, but reported positive effects on cognition, behavior, and memory in healthy individuals has been controversial [91,92]. In Individuals without ADHD, the most established finding in studies evaluating the effects of stimulants on cognition is the stimulants positive effects on improving attention [93,94]. These substances have been listed by DEA as Schedule II controlled substances with high potential for abuse in 1970 to prevent the non-medicinal use of amphetamines [95]. Its use as an illicit drug emerged back in 1980 as the so-called designer amphetamines [96]. Amphetamine use is prevalent among college students for memory enhancement, test-taking ability, and study marathons [97,98]. In U.S. methylphenidate use in the period from 2001 to 2004 among college students averaged 5.0 % and 2.9 % among non-college emerging adults in the same period [99].

3,4-Methylenedioxymethamphetamine (MDMA) or also known as Ecstasy or Molly, is a psychoactive drug that has been initially introduced for therapeutic purposes, but nowadays, it has a very limited therapeutic role and is mostly used for recreational purposes [106]. It shares with its closely related amphetamine group the ability to block the reuptake of catecholamines by competitive inhibition, and the release of serotonin (5-hydroxytryptamine [5-HT]), but MDMA is known to have more recognized serotonergic effects [100-102]. Among its competitors, Amphetamine and hallucinogens, MDMA (Ecstasy) was found to give the most euphoria, open mind and happiness, and significantly more positive mood and intimacy effects compared to amphetamines [103-108].

Ephedra or Ma huang (traditional Chinese medicine) have been known and used commonly as a herbal supplement for weight loss and performance enhancement [109-111]. It acts as a sympathomimetic agonist and enhances the release of norepinephrine from the sympathetic neurons.

Using L-ephedrine it is easy to synthesize methamphetamine by reducing it to its pure D-methamphetamine, which is several times more active than its L form [112]. Despite being marketed as a safe herbal supplement, it was quickly noted that serious adverse events arise from ephedra use such as myocardial infarction, cardiac dysrhythmias, hepatotoxicity, cerebrovascular accidents, and seizures [110,113-115]. Ephedra-containing products were prohibited by the FDA in 2004 [116].

KHAT, CATHINONE

Khat is a well-known tree in Arabian countries, especially those around the red sea, such as Ethiopia. Kenya, Somalia, Tanzania, Malawi, Uganda, Zimbabwe [117]. But its presence and social use are much more prominent in Yemen. The known plant Catha edulis, contains around 40 alkaloids, the three main ones in the khat leaves are the cathines; -S-cathinone (S-a-aminopropriophenone), norpseudoephedrine and norephedrine [118-120]. This phenylpropylamines (Figure 4) composition is variable between the different country of origins of different plants [121]. When the fresh leaves are analyzed, Cathinone (benzylketoamphetamine), The β-keto analog of Amphetamine, is found to be the main active agent and the most potent psychoactive compound [118-220].

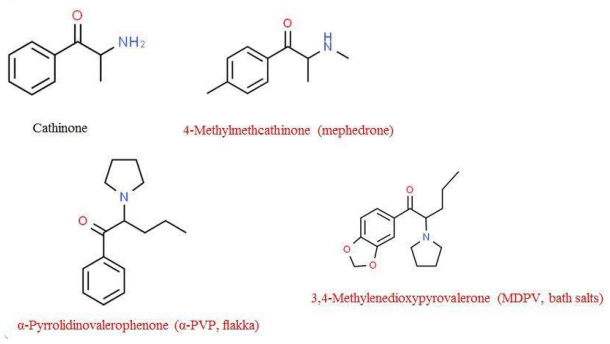

Figure 4: phenylpropylamine compounds (cathinones, Mephedrone, α-PVP and bath salts).

Cathinones, structurally and functionally, closely resemble amphetamines. The only difference is the presence of a carbonyl group in the cathinone alpha side chain [122]. This results in similar CNS stimulation and sympathomimetic effects such as tachycardia and hypertension. Khat is also reportedly related to altered sensorium and rhabdomyolysis [119]. Upon long term use, it can cause insomnia, exacerbate preexisting cardiovascular disorders can cause psycho-toxicity, depression, lethargy, and bad dreams [118]. Multiple reports have linked long term Khat use with oral carcinomas, hepatoxicity and ischemic cardiomyopathy [121].

Cathinone, the active ingredient, is considered a Schedule I substance by the DEA of the United States, even though khat is considered legal in East Africa and many European countries [95,117].

Because of its CNS effects, more interest was growing on psychoactive compounds synthesized from cathinone derivatives for medicinal (legal) use. But this have quickly escalated to illicit use and wide availability in "headshops" and "smart drugs" stores and emergency related visits to synthetic cathinones, have increased tremendously [123]. The term "designer drugs" have been used more commonly to describe any chemical analog related to preexisting psychoactive substances and will be discussed further in the sections below [124].

There are approximately 30 known cathinone derivatives. To detect certain psychoactive substances including cathinones, the use of immunoenzymatic assays, most common one is enzyme-linked immunosorbent assay (ELISA) is used as a screening technique in biological samples. It is considered non specific as it have cross reactions with other substances such as MDPV and butylone. for the analytical techniques for specific cathinone determination, different sophisticated techniques and sensitive instrumentation to detect and quantify cathinone, methcathinone and ephedrine, HPLC and GS-MS are the most widely used techniques in forensic toxicology.

MARJUIANA, CANNABIS

Cannabis sativa plant have been cultivated and used in traditional and herbal medicine for thousands of years. The main component known and heavily researched, Δ9-tetrahydrocannabinol (THC) (Figure 5), have had many potential medicinal benefits and have been a long subject of controversy over the years. many other active cannabinoids contained in the cannabis plant and its effects is yet to be researched an described [125]. Numerous studies have examined the acute and chronic effects of cannabis on cognition [126,127].

Figure 5: Δ9-tetrahydrocannabinol (THC) and aminoalkylindole JWH-018.

The cannabinoid receptors (CB1) which were found to be abundant in the central nervous system are thought to be mostly related to parts in the brain controlling the movement, memory, and complex thinking processes [128].

Ultra-high-performance supercritical fluid chromatography (UHPSFC) have been developed as a novel method that does not require derivatization nor decarboxylation as the GC method, and is able to discriminate reliably different cannabinoids in complex matrices.

DESIGNER DRUGS

Those are the drugs that are synthetically synthesized as a substitute for stimulant drugs such as cocaine—Ampethamine, MDMA, Khat, etc. They are usually chemically related to an existing psychoactive drug [129]. The new substances are synthesized in a way to give equal or more potency than the original ones, and also to be able to avoid the drug laws [130]. Because of its constant modification, it is difficult for both Users and healthcare professionals to recognize patterns of acute or chronic toxicity associated with an individual class of NPS [131,132].

The New psychoactive substances (NPS) have been overwhelming the street drug market, where they are rapidly spreading and continuously modified and provided by manufacturers and suppliers who are completely anonymized as illegal networks on the internet (darknet) [133,134].

SYNTHETIC CATHINONES

The methyl derivative of Cathinone (methacathinone) have been chemically synthesized and abused as a comparable potent alternative to MDMA [135].

N-methylcathinone (ephedrone), 4-methylmethcathinone (mephedrone, 4-MMC) are of the more prototypical synthetic cathinone derivative. α-pyrrolidinovalerophenone (α-PVP, flakka) and 3,4-methylenedioxypyrovalerone (MDPV, bath salts) are few of the publicized new psychoactive substances (NPS) in the street drug market [136].

FLAKKA

Flakka (alpha-pyrrolidinovalerophenone, α-PVP) is one of the NPS that is chemically closely related to the primary alkaloid (Cathinone). It exerts the same effects as other cathinones as a potent inhibitor of the dopamine and norepinephrine transporters.

The aggression and psychosis-like state (agitated delirium) that have been much more frequently seen with α-PVP (Flakka) abuse, and drug induced hyperthermia have been frequently reported leading to the point of cardiovascular collapse and death [137-139].

GC–MS have been commonly used for the identification of α - PVP, and LC–MS-MS for the quantitative analysis of targets compounds because of the thermal degradation during GC–MS.

SYNTHETIC CANNABINOIDS

In 1980 professor John Huffman developed the first synthetic cannabinoid, aminoalkylindole JWH-018 as part of his researches [140] (Figure 6)). Today, hundreds of synthetic cannabinoids with variable chemical structures related to the original compound have been developed and is marketed in the illicit drug market as a herbal blend [141].

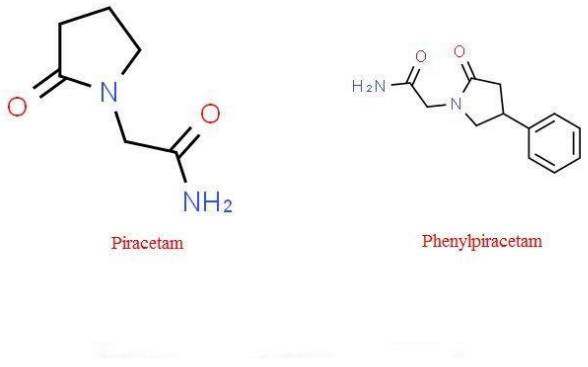

Figure 6: Piracetam (2-oxo-1-pyrrolidine acetamide) and its analogue Phenylpiracetam.

It can be found with different names such as “spice” or “K2” and can be found in many formulations such as capsules, powders, tablets and liquid formulations that can be smoked by a pipe or a joint or can be vaped using electronic cigarettes [142,143]. (THC) is thought to have a partial agonist effect on CB1 cannabinoid receptors, and synthetic cannabinoids is thought to exert its effects by full potent agonist effects that is four times higher affinity to CB1 cannabinoid receptors, and ten times higher affinity to CB2 cannabinoid receptors

PIRACETAM AND PHENYLPIRACETAM

Piracetam (2-oxo-1-pyrrolidine acetamide) is a cyclic gamma-aminobutyric acid (GABA) derivative [144-150]. It was discovered first when trying to create a hypnotic agent where it failed to show any hypnotic or GABA-ergic effects, but it was noted to facilitate learning and retrieval of acquired information in animal studies.

Open-label or non-controlled studies in animals and humans looked at clinical indications related to cognition, epilepsy, memory, ischemia, neurodegenerative diseases and anxiety.

Interest has grown lately into studying the clinical effects of Phenylpiracetam and Levetiracetam specially in concern with epilepsy and seizures Phenylpiracetam (phenotropil or Carphedon) (Figure 5) available in Russia mainly as a prescription drug. In Phenylpiracetam the addition of the phenyl group causes changes in the pharmacokinetic properties of Piracetam [151-167].

CDP-CHOLINE

CDP-choline, also named citicoline is a natural precursor of phospholipid phosphatidylcholine. It is an essential nutrient to supply choline for the formation of acetylcholine [168]. Clinical studies have focused on the potential benefit of CDP-choline to be used in treatment of neurological diagnoses and recovery in chronic rehabilitation and stroke-related diseases [169].

Based on the few clinical studies, CDP-choline use was extrapolated for use in the healthy population by nootropic enthusiasts. It is being distributed and sold as a safe and effective supplement that improves memory, focus and enhances cognition. Its availability is broad and widely unregulated.

HERBAL COGNITIVE ENHANCERS

Other than the previously mentioned Ma-huang and khat, there are multiple ancient herbs that have been known and cultivated among different traditional herbal medicine practitioners. Despite the proposed potential benefits to improve brain abilities, improve memory, and enhance the intellect, herbal dietary supplements benefits and safety profiles remain subjective for further studies [170].

BETEL NUT

Betel quid/ Areca nut use has been commonly cultivated and socially acceptable in South and Southeast Asia and the Asia Pacific region for a long time [171-174]. It is chewed or tucked into the cheek for its mildly stimulant effect [175]. The arecoline is the main cholinergic alkaloid in the betel nut. It acts as an agonist in the nicotinic and muscarinic receptors as an acetylcholinesterase inhibitor and a CNS stimulant because of the competitive inhibition of gamma-hydroxybutyric acid (GABA) causing euphoria and agitation Arecaidine, the second main alkaloid in the betel nut, is the hydrolyzed product of arecoline. Its side effects are related to its pharmacological effects: tachycardia, hypotension, diaphoresis, dyspnea, dizziness and chest discomfort can be expected, along with cholinergic toxicity in naïve first time or frequent heavy use [117,175]. Chronic long use has been linked to oral leukoplakia, oral squamous cell carcinomas, and submucous fibrosis [176-179]. The four main important alkaloids found in Areca catechu are arecoline, arecaidine, guavacoline and guavacine. The volatile alkaloids have been separated by gas chromatography-mass spectrometry, but the method required extensive sample

preparation prior to analysis. Capillary zone electrophoresis (CZE) with rapid separation and high efficiency.

YOHIMBINE

Pausinystalia Yohimbe is traditionally used in the African regions as an aphrodisiac, for treatment of cough and fever. The main chemical constituents in this plant are Yohimbine alkaloids (Figure 7) and its isomers. It is frequently found in weight loss and muscle building herbal combinations. It has also been known to be sold to the public as a sexual enhancement herb [33,180].

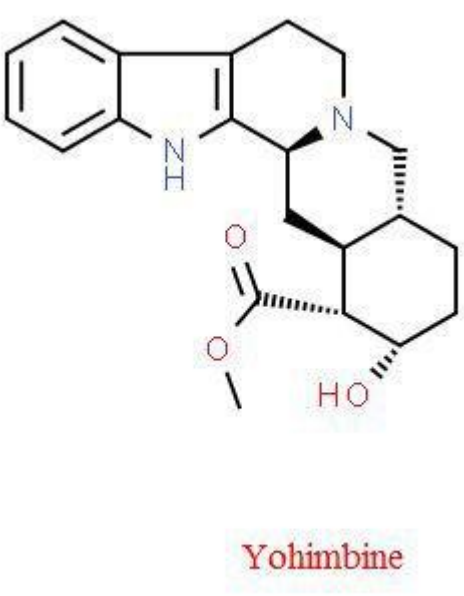

Figure 7: Yohimbine alkaloid.

It can be purchased in the form of powder, tea or tablets in combination with other herbs. It is a selective alpha 2-adrenergic receptor antagonist, and increases the release of norepinephrine as a sympathetic stimulant [181,182]. CNS excitation is common along with tachycardia, hypertension, mydriasis, nausea and diaphoresis. Few case reports have been described for yohimbine toxicity as an increased overdose presenting with sympathetic overstimulation, with one case presenting as an acute dissociative reaction [183]. Its effect is not completely established but it is thought to have increased side effects if taken with other drugs such as antidepressants or selective serotonin reuptake inhibitors [184]. High performance thin layer chromatography (HPTLC) have been the most used and validated in qualitative detection and separation of a mixture of alkaloids including yohimbine from different species belonging to family *Apocynaceae*.

GUARANA

Guarana (*Paullinia cupana*), is a species of a climbing plant that is native to Brazil, Guyana, Venezuela, Ecuador, and Peru. It was used in some Amazonian traditional medicines. Guarana seed is reported to contain 2.5–6% caff eine. A cup of guarana beverage contains what is equal to twice the amount of canine in a cup of coffee. Though caffeine was found to be the major component in guarana, other alkaloids were found below 0.3% theobromine (3,7-dimethylxanthine) and theophylline (1,3-dimethylxanthine) [185-187]. Guarana is lately added on many energy and focus stimulating drinks. It has been linked to improved alertness, enhanced memory, mood and performance. Other than caffeine-related stimulation and overdose no conclusive research is completely provided about acute or chronic toxicity of guarana.

BACOPA MONNIERA

It is an important plant that is commonly used in Āyurvedac medicine. It has been observed to promote memory and intellect, enhancing life-span, and providing nourishment. *Bacopa monniera* extract contains Bacoside A and Bacoside B which are steroidal saponins [47,188]. In two studies, Bacopa monnieri supplementation was thought to be associated with improvement in cognitive performance, delayed recall memory and improved attention [189,190]. The safety of pharmacological doses of isolated bacosides has been tested in healthy human volunteers and demonstrated it was well tolerated with no side effects experienced by the volunteers after 4 weeks of administration [191,192].

GINKGO BILOBA

The Ginko tree (*Ginko Biloba*), is a tree that is native to China and other parts in Asia. Even though it was well known and described in the traditional Chinese medicine, A special extract from the leaves of *Ginko Biloba* (EGB761) has been known and studied by the western medicine, especially in Europe [193-198]. Many studies have been interested to look at the safety and efficacy of *Ginko Biloba* supplements on the cognitive performance and function in demented patients, and or normal healthy individuals. The results have not been consistent as some showed benefit where others did not [199,200].

GINSENG

The use of Ginseng has been established in the Chinese traditional medicine thousands of years ago. The main two widely available ginseng types are *Panax Ginseng*, which is grown mainly in China and South Korea. And the Panax quinquefolius (American Ginseng) which is grown in United States and Canada. Most of the clinical trials referring to Ginseng are referring to the Chinese (*Panax Ginseng*) The most common bioactive compounds in p.ginseng are the glycosylated steroidal saponins (ginsenosides) and gintonin [201-203]. Ginseng have been long considered to be a substance that can improve cognitive skills and physical performance. Multiple studies tried to study its effect on fatigue, and it seems to have a modest effect with relatively no side effects [204].

Most methods used for analytical analysis for Ginseng are separation-based tools, including TLC, HPTLC, HPLC, UPLC, GC, MS, capillary electrophoresis (CE), and counter current chromatogra- phy (CCC)2. More recently, UPLC has emerged as a powerful tool in many analytical laboratories to profile

phytochemicals in plant extracts because it provides high resolution and high accessibility to MS [205-207].

CONCLUSION

Cognitive enhancers use has been growing widely because of ease to obtain and the false sense of safety of its use. While the above mentioned list of substances by no mean is exhaustive, but we think it can provide a quick review and reminder for clinicians to keep a high index of suspicion when presented with cases of ingestions or overdoses and to be vigilant in obtaining history not only about pharmaceuticals or illegal substances but also about what is considered to be harmless dietary supplements.

This review aims to urge the awareness of these substances, mechanism of actions, side effects and toxicological profiles. An emphasis on the lack of studies and the need for more epidemiological, pharmacological and toxicological trials is needed, to better understand, spread awareness and establish a reasonable safety profile and control for its use.

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