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Review

Nootropics as Cognitive Enhancers: Pharmacological Properties and Therapeutic Use

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ABSTRACT

Nootropics, also known as "smart drugs" in modern times, are a group of medicinal substances that positively affect learning and memory. While these substances are more effective when significant impairment is present, they are frequently used by healthy individuals, particularly students, to increase intelligence and improve memory. This review provides a general overview of the most commonly used and well-known classic nootropics, as well as naturally derived botanical nootropics, and their use and procurement by students today.

Keywords: Botanicals, cognitive enhancers, drug use, neuroenhancement, non-medical drug use, smart drugs

Nootropics are defined as the expansion of the capacity of the mind by improving cognitive functions and enhancing internal and external information processing systems.[1] It can improve cognitive function in two ways: pharmacologically, with cognitive enhancer (CE) drugs or substances, or through mental and social activity by adopting a healthy lifestyle.[2,3]

Recently, nootropics, also known as "smart drugs," have become a heterogeneous group of chemicals used to improve cognitive functions.[4] For a compound to be classified as a nootropic, it must activate brain mechanisms without inducing subcortical, limbic, or reticular responses at the same time, thus compensating for neural activity deficiencies. Originally designed for use in geriatric psychiatry, nootropics are now used to enhance memory, increase learning performance, improve attention and concentration, and promote wakefulness and creativity in healthy individuals, particularly when cognitive functions are significantly impaired.[5,6]

Nootropics can sometimes be obtained by healthy individuals from prescribed or non-prescribed sources such as family and friends.[7] They come in two forms: natural and synthetic, with the majority of these substances being of natural origin. They are not prescription drugs and can be easily obtained as dietary supplements or herbal extracts.

The most common botanicals among nootropics are *Ginkgo biloba* (*G. biloba*), American ginseng, and *Bacopa monnieri* (*B. monnieri*). Synthetic forms are generally sold by prescription and are limited in availability. The incidence of side effects is low and those that do occur are usually mild. Long-term use of most nootropics requires patients to use them for an extended period of time.[8-10]

Healthy individuals have the highest rates of misuse of three neuroenhancers: methylphenidate, modafinil, and piracetam. Both modafinil and amphetamines have been used in many wars since the 1940s to keep soldiers awake.[11-13] Nowadays, they are mostly used by students to enhance academic performance and manage stress more easily. Additionally, people who work night shifts and athletes prefer these drugs.

CLASSIC NOOTROPIC COMPOUNDS

Deanol (2-dimethylethanolamine)

Deanol (DMAE) is a compound that is used

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as a nootropic and is believed to help improve concentration, memory, and cognitive performance. Its chemical name is 2-(dimethylamino)-ethanol. This compound is naturally present in the human brain and is often marketed as a natural dietary supplement. Many dietary supplements contain DMAE in the form of tartaric acid salt (bitartrate salt). This compound is particularly found in salmon and other shellfish. Deanol is a choline precursor that allows for the optimization of acetylcholine production, which is the primary neurotransmitter involved in learning and memory in the brain.[14,15] By supporting the functions of brain cells, it has a positive effect. Additionally, it is believed that deanol may widen blood vessels, increasing blood flow to the brain and allowing for more oxygen and nutrients to be delivered.

In a study conducted on rats, it was observed that it increased choline and acetylcholine extracellular levels in the prefrontal cortex of the brain *in vivo*. It was also observed to further improve spatial memory and reduce scopolamine-induced memory deficit.[16]

The recommended daily dose of DMAE bitartrate is 500-2000 mg.[17,18] It is contraindicated during pregnancy, lactation, and in patients with schizophrenia.[19]

Meclofenoxate

Another name for it is "centrophenoxine" and it consists of DMAE and ethyl ester of para-hydroxybenzoic acid. Meclofenoxate is used to help improve brain functions. It is well-absorbed when administered parenterally.

The nootropic effects of meclofenoxate are related to its ability to increase the production of phospholipids that help protect the structure of brain cells and enhance the flexibility of cell membranes. Additionally, it is believed that Meclofenoxate can improve memory and learning functions by increasing the amount of acetylcholine in the brain.[20]

In a study, oral administration of meclofenoxate to rats (100 mg/kg, daily for 37 days) significantly improved memory impairment and reduced neuronal damage, proinflammatory mediator levels, and oxidative stress to normal levels.[21-23] Another study conducted on elderly individuals showed that meclofenoxate increased mental alertness and improved long-term consolidation of new information in human memory.[24]

Meclofenoxate can be prescribed and the dosage is usually determined based on the individual's age, health status, and other factors. The daily dose should be between 500-2000 mg.[25] Meclofenoxate is considered safe and tolerable. Possible side effects are usually caused by overdose and include dizziness, restlessness, nausea, and headaches.[25-27]

Nicergoline

Nicergoline, also known as ergoloid mesylates, is a medication that works by increasing blood flow in various regions of the brain and body. Therefore, nicergoline is classified as a medication used in the treatment of cerebrovascular diseases.

Nicergoline works by increasing blood flow in the cerebral arteries, thus providing better nourishment of brain tissue with oxygen and nutrients.[28,29] This may help improve memory and cognitive function. Specifically, it is used for memory loss, decreased alertness, ability to concentrate, mood changes, dizziness, fatigue, and vestibular and cochlear disorders.[30,31] Additionally, nicergoline is used in the treatment of other medical conditions such as peripheral circulation disorders, migraines, and Raynaud's disease.

Studies have shown that nicergoline is an effective drug to prevent neural vulnerability due to experimental induction of nerve growth factor deficiency and it improves the function of cholinergic and catecholaminergic neurotransmitters *in vivo* in mice.[32-34] Additionally, many studies have shown that nicergoline increases arterial blood circulation, has antioxidant properties in vivo in rats, and supports metabolic activity.[35] Moreover, it has also been shown to have a therapeutic effect on cognitive function in mouse models of Alzheimer's disease.[36]

The daily dose of nicergoline should be between 30-60 mg.[31] Side effects are rarely observed and usually include nausea, dizziness, diarrhea, fainting, and headache.[37,38] Its use in pregnant women is not fully established, so it is not recommended during pregnancy or breastfeeding.

Piracetam

The chemical name of piracetam is 2-(2-oxo-pyrrolidin-1-yl)-acetamide. This medication was discovered in the late 1960s and has been used since then to help improve learning, memory, and cognitive functions. While it is not fully understood how it works, it is believed to act on brain neurotransmission through modulation of ion channels in the brain, leading to increased neuronal excitability in a non-specific manner.[39] As a result, it helps to improve memory, learning, concentration, attention, and other cognitive processes.

In a study conducted by Scheuer et al.[40], the effects of piracetam on active avoidance performance were investigated in young and aged rats, at a dose of 300 mg/kg/day for six weeks. Membrane fluidity and N-methyl-D-aspartate receptor and muscarinic cholinergic receptor densities were determined in the hippocampus, striatum, and cerebellum. Piracetam treatment improved active avoidance learning only in aged rats and increased membrane fluidity in all brain regions except for the cerebellum in aged animals. Additionally, this treatment was observed to increase muscarinic cholinergic receptor density in the hippocampus, but only in aged animals. Piracetam also works by increasing blood flow between nerve cells in the brain. This may help neurons in the brain receive better oxygen and nutrients.[41]

In addition to its metabolic effects on brain tissue, piracetam increases erythrocyte plasticity and therefore brain perfusion.[42] It has been clinically used for the prevention and treatment of cognitive and mental function impairments after trauma, as well as for improving learning and memory functions in developmental dyslexia in pediatric patients.[43]

The effective dose of piracetam for acute treatment is 4-8 g per day. The maintenance dose is usually around 2-4 g per day and is adjusted based on renal function. The effects of piracetam on the brain are generally slow and cumulative, meaning that its effects increase with regular use. Piracetam has excellent tolerability. Its side effects are mild and may include symptoms such as short-term memory loss, headache, sleep disturbances, increased libido, and stomach discomfort.[39][44] There is insufficient data on the use of piracetam during pregnancy and lactation.

Pyritinol

Pyritinol was synthesized in 1961 by combining two molecules of B6 vitamin (pyridoxine) through a disulfide bridge. It is a member of the piracetam family of nootropics and enhances their functions by affecting neurotransmitter systems in the brain. This compound crosses the blood-brain barrier and accumulates in gray matter, particularly in the hippocampus, cerebral nuclei, cerebellum, and cortex.[45]

In a study conducted by Martin et al.[46], older rats were given pyridoxine for two to three weeks, and it was found that it increased the concentration and release of endogenous acetylcholine and nucleic acid metabolism in the cortex and striatum. Additionally, it was observed that pyritinol also scavenged free oxygen radicals, thus serving as an antioxidant.[47]

The recommended minimum daily dose is 300 mg divided into three doses, but the amount taken should be 600 mg or more.[45,48] Common side effects include headaches, diarrhea, nausea, loss of appetite, and acute pancreatitis.[49-51]

BOTANICALS WITH NOOTROPIC EFFECTS

Some botanicals have become popular due to their nootropic properties. Some botanicals used as nootropics are *B. monnieri*, *G. biloba*, *Panax ginseng*, *Rhodiola rosea*, Ashwagandha, Siberian ginseng, and *Melissa officinalis* (*M. officinalis*). These botanicals with nootropic properties have many effects, including improving memory, learning, and mental quality, enhancing brain functions by increasing blood circulation, reducing stress, and improving concentration. There are many studies suggesting the potential benefits of these botanicals.

Bacopa monnieri

Bacopa monnieri (from the Scrophulariaceae family), also known as the water hyssop, is a small perennial plant that is native to marshy areas and has been used in medicine for centuries to improve memory and intelligence.[52] In Turkish, it is known as "lütuf otu" or "hint kurusu". The main phytochemical compounds believed to be associated with the pharmacological effects of *B. monnieri* are bacoside-A and bacoside-B. The two most extensively studied commercial extracts of *B. monnieri* for their beneficial effects on memory in clinical trials are KeenMind® and BacoMind™.[53]

In a randomized and placebo-controlled study, 46 healthy subjects aged 18 to 60 were given either a KeenMind® capsule (150mg CDRI 08 extract) or a placebo twice daily for 12 weeks to observe cognitive function.[54] According to this study, KeenMind® improved visual information processing speed and learning rate after 12 weeks. These findings suggest that the botanical extract may improve higher cognitive processes. Side effects included nausea, dry mouth, and muscle fatigue.

In a study using BacoMind™, 98 healthy participants aged 55 and older were given 300 mg of BacoMind™ or a placebo once a day after meals for 12 weeks to observe improvement in memory performance in healthy older adults.[55] As a result, it was concluded that this treatment improved the ability to retain information in memory. Thirteen volunteers dropped out of this study, nine of whom were due to side effects such as increased stool frequency and nausea.

Studies have also been conducted on *B. monnieri* extracts. In a study using another standardized extract of *B. monnieri* (Bacognize®), a logical memory test, finger tapping test, reaction time, and some other neuropsychological tasks were evaluated. A total of 60 medical students (aged 19-22) were given a placebo or 150 mg Bacognize® (standardized to 45% bacosides) twice a day for six weeks and were evaluated with a 15-day follow-up at weeks 0 and 6. Significant improvement was observed in two of the 10 neuropsychological tasks evaluated with backward digit span and logical memory after six weeks of treatment with *B. monnieri*. The authors concluded that *B. monnieri* might be beneficial for some components of memory with just six weeks of application.[56]

In animal experiments, a reproductive toxicity study was conducted on male rats fed with all doses of *B. monnieri* plant extract up to 80 mg/kg for 28 days. The study showed no difference in body weight, testis, epididymis, and seminal vesicle weights, but an increase in sperm viability and spermatogenic cell density was observed.[57]

Ginkgo Biloba

Ginkgo biloba L., also known as the "mağbet ağacı" in Turkey, is one of the unique and rare trees known today. The leaf extract of this tree is one of the most popular herbal supplements used to improve mood, and attention, and to have positive effects on circulation. *Ginkgo biloba* has been studied for a long time in dementia and Alzheimer's patients. Phytochemical compounds thought to be active in *G. biloba* extracts include flavonol glycosides, terpene lactones, and ginkgolic acids. One of the most common and well-studied standardized extracts of *G. biloba* is EGb 761®, which contains 24% flavonoids and 6% terpenes, including ginkgolides and bilobalide. Common doses of EGb 761® used in clinical trials are 120 mg per day or 240 mg per day (divided into two doses of 120 mg per day).[53][58]

Kaschel et al.[59], evaluated the effects of EGb 761® extract (240 mg/day) on memory performance compared to placebo in healthy middle-aged individuals (aged 45-56 years) with similar cognitive scores over a 6-week period. A randomized, placebo-controlled study with a 1:1 ratio was conducted to track improvement in the subjects' memory tests in recall and recognition tests and showed that the group treated with EGb 761® had better free recall amounts.

Studies have also examined clinical trials to determine whether *G. biloba* can improve cognitive function in healthy individuals. Mix et al.[60], investigated the effects of EGb 761® in elderly individuals without a history of neurocognitive impairment. 48 subjects between the ages of 55 and 86 participated in a randomized, placebo-controlled, double-blind study of a 6-week treatment with 180 mg of EGb 761® per day. Cognitive function outcomes included assessments of processing speed (e.g., Stroop Color and Word Test color naming task). Processing outcomes with EGb 761® were significant for the Stroop Color and Word Test and showed a trend toward positive results in other tasks evaluating the timed speed of the processing component. There was no significant difference in objective memory measurements evaluated using the Wechsler Memory Scale-Revised between the treatment and placebo groups.

Fewer studies have been conducted to determine whether EGb 761® has a positive effect on mood. Woelk et al.[61] conducted a randomized, double-blind, placebo-controlled study that included 107 participants with a generalized anxiety disorder or adjustment disorder with anxious mood. *Ginkgo biloba* has the potential to improve mood and alertness.

In an animal study, a *G. biloba* leaf extract was tested on mice and rats in a 105-week study. At the end of the study, there was an increase in liver tumors in male and female mice, thyroid tumors in male rats, and liver and thyroid tumors in female rats. Genotoxicity studies conducted with *G. biloba* extracts have produced questionable results, as reported in the National Toxicology Program's Technical Report. Previous three-month toxicity studies conducted by the same group in rats and mice showed that the liver and thyroid were target organs for toxicity.[62]

Melissa officinalis

Melissa officinalis or commonly known as "lemon balm," is a plant in the mint family. It is widely used for reducing mental stress and symptomatic treatment of gastrointestinal complaints from the past to the present. It has been studied in clinical trials for its effects on sleep, anxiety, and stress. Soltanpour et al.[63] conducted a randomized, placebo-controlled study to examine the effects of *M. officinalis* dried leaf powder on sleep quality and anxiety reduction. Eight hospitalized volunteers who had undergone coronary artery bypass surgery were given 500 mg capsules of *M. officinalis* dried leaf powder three

times a day (morning, noon, and before bed) for seven days. Sleep outcomes were evaluated using the St. Mary's Hospital Sleep Questionnaire. Significant improvements in anxiety scores were observed.

In another clinical trial, an iced tea beverage containing three grams of *M. officinalis* and natural fruit sweetener was found to be associated with lower anxiety and improved working memory at one and three hours after ingestion, indicating long-term anxiolytic potential. This effect was actually similar to that observed with benzodiazepines, but without the negative impairments on performance (e.g. psychomotor). Working memory performance was also significantly improved with the same treatment at 1-3 hours post-ingestion. At higher doses of *M. officinalis* (0.6g), only mathematical processing was improved within 1 hour, and psychomotor performance was significantly improved as evaluated by a tracking module. Interestingly, a 0.6g *M. officinalis i*ced tea beverage containing artificial sweeteners caused a higher level of anxiety three hours after ingestion, which the authors associated with the presence of artificial sweeteners.[64]

Panax ginseng

Asian ginseng, also known as *Panax ginseng*, is derived from the roots of plants in the *Panax* genus and has been used in traditional Chinese medicine for years. Ginseng is typically used as a supplement and can be found in capsule, powder, or tea form. It has energizing, cognitive-enhancing, physical performance-enhancing (including sexual performance), stress-reducing, adaptogenic, and antioxidant properties.[65]

In a study conducted by Churchill et al.[66], intraperitoneal injections of 0, 0.25, 2.5, and 5.0 mg/kg of ginsenoside Rb1 were administered to 80 chicks for five days. The group receiving 0.25 mg/kg injection had a significantly reduced number of errors during retention trials 24 and 72 hours after injection. However, animals receiving higher doses showed initial trends towards improvement, but performance deterioration was reported 72 hours after injection.

The daily dosage for a healthy adult is between 1-2 grams. It can be consumed in the form of tea, capsules, tablets, liquid extract, or powder. Possible side effects include insomnia, headaches, irritability, increased heart rate, stomach discomfort, diarrhea, constipation, and nosebleeds.[67,68]

ADVANTAGES AND DISADVANTAGES OF NATURAL AND SYNTHETIC NOOTROPICS

Natural nootropics contain compounds that occur naturally, as they are derived from natural sources such as plants. Therefore, they are considered to be healthier and have fewer side effects compared to synthetic compounds.[69] Long-term use of natural nootropics may be safer and less likely to cause addiction. However, the effects of natural nootropics may be less pronounced and less intense compared to synthetic ones. The effects of synthetic nootropics can be seen and felt more quickly. Additionally, the dosage of synthetic nootropics can be easily controlled and adjusted accurately.[70] However, synthetic nootropics may have more side effects compared to natural ones and are more likely to cause addiction. Therefore, long-term use of synthetic nootropics is less recommended. They may also be more expensive compared to natural alternatives.

THE USE OF NOOTROPICS AMONG YOUNG INDIVIDUALS

Almost everyone has dreamed of being smarter, thinking faster, performing better in exams, and having a better memory. Nowadays, nootropics that promise these benefits are frequently used by students, not only to achieve these desires but also to feel better motivationally, stay awake longer, and socialize more. Mixtures of CE, known as "academic doping," are on the rise and are used by healthy individuals looking to improve their cognitive performance, including students, academics, shift workers, and even chess players.[71,72]

Comprehensive reports focusing on the intake of CE to aid concentration and memory, among other things, have been found among healthy individuals, potentially allowing them to work longer hours or enhance their working memory performance.[73]

The use of CE among university students worldwide is becoming increasingly concerning. The misuse and lifetime prevalence of these substances ranges between 6% to 20%. In a survey conducted among university students in the United Kingdom and Ireland, the lifetime prevalence of modafinil, methylphenidate, and amphetamine use was found to be 6.2%, 5.9%, and 2%, respectively.[74] The lifetime prevalence of CE intake among university students in the United States is estimated to be between 5% and 43%.[75]

The use of nootropics, particularly in high-level universities and stressful and highly competitive fields such as medicine and pharmacy, is concerning. In a study, most of the data was obtained from the United States[76-78], followed by the United Kingdom[74], Australia[79,80] and Europe, including France[81,82] and Italy[83,84]. The most popular prescription CE's among those surveyed were modafinil, methylphenidate, and amphetamine salt combinations, with methylphenidate being the most popular among students.[85,86] In contrast, the most popular CE available for free was caffeine.[87] While there were no gender differences in the preference for methylphenidate as the most popular CE or any other CE, differences were observed in the motivation for use between genders.[88] Female students aimed to increase their motivation, concentration, alertness, academic performance, and socialization through CE use. In contrast, male students were primarily motivated to increase their study time and experiment. Similarly, a study conducted in Lithuania reported a point prevalence of 8.1% for CE's (modafinil, methylphenidate, and amphetamine) among medical students.[89]

The use of caffeine as a cognitive enhancer has also increased in popularity worldwide because caffeine is the most popular CE that can be obtained for free. It has been shown that caffeine and related products may be associated with the need to increase energy, stay awake, improve concentration, and meet social needs.[90] In a study that focused on the effects of the caffeine-containing plant *Paullinia cupana* (guarana) on cognition in young, healthy adults, improved levels were found in both reaction time and accuracy performance.[91] Guarana has also been reported to improve memory performance and increase levels of alertness.[92] However, the long-term use of high doses of guarana can also cause a range of side effects, such as nervousness, palpitations, and anxiety.[2][93] A study evaluated the prevalence of caffeinated beverage consumption among university students.[90] More than 98.5% of the participants in the study were shown to be caffeine consumers, with 31% reporting being caffeine-dependent. High doses of caffeine consumption can lead to a range of medical and psychiatric effects, typically including anxiety, panic attacks, sleep disorders, and cardiovascular problems.[94]

PROCUREMENT OF NOOTROPICS

In countries, the use of CE for non-medical indications is influenced by a range of factors such as legal, social, and ethical considerations. Some CE's are marketed online as "smart drugs," "study aids," or herbal supplements. Additionally, the sources of CE acquisition can be related to friends and family.[7][95] Studies have found that 75.5% of methylphenidate was obtained from friends on a university campus, while 64.3% of modafinil was obtained online.[74] Nowadays, purchasing drugs or substances from websites poses a risk to young people since the real content cannot be known. More than a third of websites selling modafinil have been found to promote the use of the drug, particularly for aiding in studying.[96] Guarana has also become popular as a legal alternative to prescription or illicit misuse of cognitive-enhancing drugs, with affordable online prices encouraging young users/students to purchase larger quantities for discounts and free shipping.[96,97]

In the United Kingdom, both methylphenidate and amphetamine compounds are class B controlled drugs.[98] This means they can only be obtained with a prescription, and the maximum amount given should not exceed 30 days (this can vary depending on the prescribing authority), and if this amount is exceeded, a personal import/export license is required to transport the drug within or outside of the United Kingdom.[96] Modafinil is only available by prescription in the UK, but it is not controlled under the Misuse of Drugs Act 1971 or subject to the Misuse of Drugs Regulations 2001; therefore, obtaining it without a prescription is illegal, but possessing the drug for personal use is not.[98]

Although caffeine is also a stimulant, its use is not associated with issues of purchase, affordability, availability, or legality.[99,100]

Most research articles report the use of prescription CE among university students. Therefore, the actual prevalence of prescription and non-prescription CE among university students is not fully understood, and more research is needed.

In conclusion, nootropics are a heterogeneous group of drugs that enhance cognitive function, particularly in cases where there is damage or degeneration, and are used as CE in healthy individuals. They are used as supportive therapy in acute, subacute, and chronic conditions of memory, consciousness, and learning disorders, as well as in patients with Alzheimer's disease, schizophrenia, hyperkinetic disorder, or senile dementia. Often, long-term use is necessary to observe their effects. Most nootropic substances have rare and typically mild side effects. These substances are of interest

to university students due to their potential to improve memory and thinking and their ease of availability. University students' attitudes toward CEs and their potential benefits are based on anecdotal and likely biased information obtained from media, the internet, and friends. The widespread and uncontrolled use of these drugs is concerning, as they are not recommended for individuals without any cognitive impairment, particularly with long-term use of their synthetic variants due to inadequate clinical data. The use of nootropics can be controversially reduced by emphasizing that the intake of CEs can pose a risk to safety, particularly for vulnerable individuals, if the awareness levels of students are increased. High doses can lead to dangerous results. Additionally, the use of herbal supplements with nootropic effects, which show very few side effects compared to synthetic nootropics and appear to be more reliable, should not be used during pregnancy or breastfeeding in any case. In numerous examples taken from the studies examined above, a botanical may show promising effects on attention or focus in healthy young individuals but has no significant effect on populations of elderly individuals with some cognitive impairment. Evaluating clinical trials with nootropic outcomes can be difficult due to the numerous types of tests used, which makes it difficult to compare studies. Differences in the types of tests used often vary depending on the geographic regions where studies are conducted. Future research on nootropics should focus on experiments with more diverse human groups based on age, health, gender, or weight.

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