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Review Article

A REVIEW ON NATURAL MEMORY ENHANCERS (NOOTROPICS)

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ABSTRACT

Nootropics also referred to as smart drugs, memory enhancers, neuro enhancers, cognitive enhancers, and intelligence enhancers, are drugs, supplements, nutraceuticals, and functional foods that purportedly improve mental functions such as cognition, memory, intelligence, motivation, attention, and concentration. Nootropics are thought to work by altering the availability of the brain's supply of neurochemicals (neurotransmitters, enzymes, and hormones), by improving the brain's oxygen supply, or by stimulating nerve growth. Drugs considered cognitive enhancers include dietary products and supplements, racetams, stimulants, dopaminergics, cholinergics, GABA blockers, glutamate activators, serotonergics and hormones, etc. however not all are healthy or safe to use but they can still have mental benefits. The safest types of cognitive enhancers consist of herbal drugs and are available in supplement form, which mostly contain vitamins, fatty acids, antioxidants, amino acids, minerals, etc and other herbal ingredients. Vitamins are involved in brain development and in adult brain function. Omega-3 influences both communication between cells and cell function. Antioxidants help to retain the mental abilities longer, keep the brain younger and protect it from oxidative damage. Amino acids help to produce the catecholamines and create alertness. Hormones increase neurogenesis and improve both memory encoding and recall. Iron helps create hemoglobin, which transports oxygen to the brain. Creatinine protects ATP during transport. Lipoic acid improves oxygen usage and antioxidant recycling, improving memory and Germanium increases oxygen supply to the brain. Herbs and herbal products which have been found useful in improving cognitive ability include *Bacopa monniera*, *Ginkgo biloba*, *Siberian ginseng*, *Rhodiola rosea*, *Brahmi rasayana*, *Lycoris radiata*, *Sutherlandia frutescens*, *Mucuna pruriens*, *Butea frondosa*, *St John's Wort*, *Arecholine*, Royle's Jelly, Caffeine, *Curcumin* and so on. The mechanism of action is different for different drugs. These drugs are used primarily to treat people with cognitive difficulties as in Alzheimer's disease, Parkinson's disease and Attention-deficit hyperactivity disorder (ADHD).

Keywords: Brain, Memory enhancers, Herbs, Intelligence.

INTRODUCTION

The brain is the center of the nervous system which controls memory, thought, reason judgment, consciousness and emotion. Supporting the brain health is vital for ensuring a successful regulation and coordination of body activities. There are a variety of nutritional supplements that are useful in preserving the health of brain¹.

The natural system of medicine is exploring tremendous benefits from the herbs which are used in various aspects and one of the aspects include brain function with includes improving memory, improving alertness, improving intelligence, improving mental performance etc.

Cognitive enhancers are drugs, supplements, nutraceuticals, and functional foods that enhance attentional control and memory. Nootropics are cognitive enhancers that are neuroprotective or extremely nontoxic. Nootropics (pron.: /noʊ.əˈtrɒpɪks/ *noh-ə-TROP-iks*), also referred to as smart drugs, memory enhancers, neuro enhancers, cognitive enhancers, and intelligence enhancers, are drugs, supplements, nutraceuticals, and functional foods that purportedly improve mental functions such as cognition, memory, intelligence, motivation, attention, and concentration^{2,3}.

Various mechanisms by which nootropics acts are as follows:

1. Increasing circulation to the brain.

2. Providing precursors to neurotransmitters (chemical messengers in the brain).
3. Improving neuron function.
4. Preventing free radical and oxidative damage to brain cells.
5. Providing usable energy to the brain and so on.

Cognitive enhancers generally include:

1) Dietary Sources and Supplements:

Dietary sources and supplements increase glucose levels in the brain and hence influence memory, learning, concentration and decision-making. Lack of these leads to a negative effect on the brain. Examples- Vitamins, Omega-3, Iron, Antioxidants, Amino acids, Caffeine⁴.

2) Racetams:

Their mechanisms of action are not fully understood, however, piracetam and aniracetam are known to act as positive allosteric modulators of AMPA receptors. They also appear to modulate acetylcholinergic systems⁵. Although aniracetam and nebracetam show affinity for muscarinic receptors, only nefiracetam shows it at the nanomolar range. Racetams have been called "pharmacologically safe" drugs⁶. Nefiracetam, however, shows much more serious health risks to males. Other examples includes: Pramiracetam, Oxiracetam, Aniracetam, Nebracetam⁷.

3) Stimulants:

They are often seen as smart drugs, but may be more accurately termed productivity enhancers. These typically improve concentration and a few areas of cognitive performance, but only while the drug is still in the blood. Some scientists recommend widespread use of stimulants such as methylphenidate and amphetamines by the general population to increase brain power^{8,9}.

Examples-

1. Amphetamines:

- a. Amphetamine - adrenergic, dopaminergic
- b. Lisdexamfetamine - dextroamphetamine (prodrug)
- c. Methamphetamine- adrenergic, dopaminergic

2. Adrenergics:

- a. Atomoxetine- norepinephrine reuptake inhibitor (approved for ADHD)
- b. Reboxetine- Norepinephrine reuptake inhibitor; approved in Europe or clinical depression but may also be used off-label to treat ADHD
- c. Synephrine (found in Bitter orange)- agonist at α_1 adrenergic receptors

3. Cholinergics: Arecoline, Nicotine

4. Eugeroics: Adrafinil, Armodafinil, Modafinil

5. Xanthines: Caffeine, Paraxanthine, Theobromine, Theophylline¹⁰

4) Dopaminergics:

These are substances that affect the neurotransmitter dopamine or the components of the nervous system that use dopamine. Attributable effects of dopamine are enhancement of attention, alertness, and antioxidant activity⁶. Dopamine is the primary activity of stimulants like methylphenidate (Ritalin) or amphetamine. Dopaminergic nootropics include following classes:

1. Metabolic precursors- raise levels

- a. L-Phenylalanine—purported cognitive improvement
- b. L-Tyrosine (or N-Acetyl-L-Tyrosine, more bioavailable form)—purported cognitive improvement
- c. L-DOPA (L-3,4-dihydroxyphenylalanine)- precursor to catecholamines (dopamine); neurotoxic effects documented^{11,12,13}.
- d. Biopterin—a rare vitamin (coenzyme) that is synthesized in the pineal gland & crucial to the biosynthesis of dopamine
- e. Pyridoxal-phosphate (or PLP, pyridoxal-5'-phosphate, P5P, active form of Vitamin B6)- plays a role in the conversion of L-DOPA into dopamine (via the enzyme aromatic L-amino acid decarboxylase)

1. Reuptake inhibitors- stabilize/improve levels

- a. Amineptine- mild stimulant
- b. Methylphenidate- stimulant approved for ADHD; strong DAT inhibition.
- c. Bupropion- atypical antidepressant; moderate DAT inhibition

2. MAO-B inhibitors- prevent breakdown

- a. Selegiline- Mild stimulant; irreversible
- b. Rasagiline- Mild stimulant; irreversible
- c. *Rhodiola rosea*- Adaptogenic herb; reversible¹⁴

3. Dopamine agonists

- a. Ropinirole- agonist at D2, D3, and D4 receptors
- b. Pramipexole- agonist at D2, D3 and D4 receptors

4. Others

- a. Mucuna pruriens- natural source of L-DOPA
- b. Modafinil—purported dopaminergic activity
- c. Citicoline¹⁵(aka: cytidine diphosphate-choline (CDP-Choline) & cytidine 5'-diphosphocholine)—studies suggest CDP-choline supplements increase dopamine receptor densities, and suggest that CDP-choline supplementation can ameliorate memory impairment caused by environmental conditions.

5) Memory Enhancers:

a) Cholinergics: They affect the neurotransmitter acetylcholine or the components of the nervous system that use acetylcholine which is a facilitator of memory formation. Cognitive functions in the brain are improved by increasing the availability of this neurotransmitter. Cholinergic nootropics include acetylcholine precursors and cofactors, and acetylcholinesterase inhibitors etc: Examples-

1. Precursors

- a. Choline- precursor of acetylcholine and phosphatidylcholine
- b. DMAE- precursor of acetylcholine
- c. Meclofenoxate- probable precursor of acetylcholine, approved for Dementia and Alzheimer's,
- d. Alpha-GPC- thought to be the only cholinergic that delivers choline to the brain across the Blood-brain barrier; sold under its chemical name

2. Cofactors

- a. Acetylcarnitine—amino acid that functions in acetylcholine production by donating the acetyl portion to the acetylcholine molecule
- b. Vitamin B₅—cofactor in the conversion of choline into acetylcholine

3. **Acetylcholinesterase inhibitors**
Galantamine, *Lycoris radiata*, Huperzine A, Donepezil, Rosemary, Sage, Cannabis¹⁶

4. **Reuptake inhibitors and enhancers**
Coluracetam, Ginsenosides Source

5. **Agonists**
Ispronidine, Nicotine, Arecoline⁶

b) GABA Blockers: The GABA_A $\alpha 5$ receptor site has recently displayed memory improvements when inverse agonized.

Example: $\alpha 5$ inverse agonist- $\alpha 5$ IA and $\alpha 5$ partial inverse agonist- Suritazole

c) Glutamate Activators: The significant memory improvement and possible alertness enhancement has been seen when AMPA transmitter and the AMPA receptors are agonized. The drug class for AMPA system modulation is called Ampakines.

Examples- IDRA-21, CX-717, LY-503,430⁶.

d) cAMP: Cyclic adenosine monophosphate is a secondary messenger that, if increased, has shown memory improvements. One common method is by decreasing the activity of phosphodiesterase-4, an enzyme that breaks down cAMP. Typical effects include wakefulness and memory enhancement. Examples- Propentofylline, Rolipram, Mesembrine⁶.

e) Others: The prefrontal cortex and the locus coeruleus are concentrated heavily with $\alpha 2A$ receptors. They have the potential to improve attention abilities via modulating post-synaptic $\alpha 2A$ receptors in the prefrontal cortex. Examples- Guanfacine¹⁷.

6) Serotonergics:

These substances work by affecting the neurotransmitter serotonin or the components of the nervous system that use serotonin. Examples-

1. **Serotonin precursors and cofactors:** 5-HTP, Tryptophan, Pyridoxal-phosphate¹⁸
2. **Serotonin reuptake inhibitors:** SSRIs, *Scelietium tortuosum*, *Hypericum perforatum*
3. **MAO-A inhibitors:** Resveratrol¹⁹, Curcumin²⁰, Piperine²¹, Harmal²², *Rhodiola rosea*¹⁴
4. **Reuptake enhancers:** Tianeptine⁶.

7) Anti-depression, Adaptogenic (Antistress) and Mood stabilization agents:

Stress, depression, and depressed mood negatively affect cognitive performance. Thus, counteracting and preventing depression and stress may be an effective cognition strategy. Examples- Anxiolytics, Beta blockers, Adafenoxate, Valerian, *Butea frondosa*, Gotu Kola

GABA transaminase inhibitors: Lemon balm

MAOI: Passion flower, *Rhodiola rosea*

SSRI: St John's Wort

Adaptogens: Siberian Ginseng, Tea, Foti

Anti-inflammatory: *Sutherlandia frutescens*⁶.

8) Blood flow and Metabolic function enhancers:

Brain function is dependent on many basic processes such as the usage of ATP, removal of waste and intake of new materials. Improving blood flow or altering these processes can benefit brain function. Examples- Blessed thistle,

Coenzyme Q-10, Creatine, Lipoic acid, Pyritinol, Picamilon, Ginkgo Biloba, Vinpocetine⁶.

9) Nerve growth stimulators and Brain cell protecting agents:

Nerves are necessary to the foundation of brain communication and their degeneracy, under performance, or lacking can have disastrous results on brain functions. Antioxidants are frequently used to prevent oxidative stress, but do not improve brain function if that is their only activity. Examples- Idebenone, Melatonin, Glutathione, Inositol, Phosphatidylserine, Lion's Mane Mushroom, SAM-e (s-Adenosyl methionine), Dopamine enhancers⁶.

10) Direct Hormones:

These hormones have activity not necessarily attributable to another specific chemical interaction, but they have shown effectiveness. Examples- Vasopressin, Pregnenolone, Orexin⁶.

11) Secondary Enhancers:

These are substances which by themselves may not improve brain function, but may have benefits for those lacking them (in the case of hormones) or may alter the balance of neurotransmitters. Examples: Dehydroepiandrosterone (DHEA)⁶.

12) Unknown Enhancement:

Other agents purported to have cognitive effects but whose mechanisms have not yet been established or have clinically significant effects include, *Bacopa monniera*, *Brahmi rasayana*, Fipexide, Gerovital-H3, Sulbutiamine, Royal jelly, Curcumin⁶. These agents are considered and used as cognitive enhancers and have mental benefits, but all of them are not healthy or safe to use. Many of them are extremely effective at treating serious mental issues but they also are associated with a number of side effects. The safest types of cognitive enhancers are made up of natural ingredients, available in supplement form. Usually these supplements mostly contain vitamins and herbal ingredients²³.

The important natural and herbal cognitive enhancers include:

1) Amino acids and Proteins

Adult brains use amino acids, which are typically found in protein rich food, for the production of enzymes that transport molecules, structural material and neurotransmitters, along with other essential molecules. Eating high protein but low calorie meals increases alertness and attentiveness, although too much protein can have a negative effect as well²⁴. Some of the amino acids found beneficial in cognitive enhancement include;

A) L-cysteine: The form of L-cysteine used in cognition enhancement is N-acetyl L-cysteine. The amino acid cysteine shows strong scientific evidence in the production and biosynthesis of Brain-Derived Neurotrophic Factor (BDNF). BDNF facilitates the growth of new neurons, as well as, protect existing neurons from neuronal death. BDNF protein has also shown to be particularly important for long-term memory in the hippocampus region of the brain. N-acetyl-L-cysteine (NAC) is a more stable form of the amino acid L-cysteine and is the most effective way to boost glutathione (an exceptional antioxidant) levels in the body. NAC is a more

stable form of L-cysteine because it has an acetyl group (CH₃CO) attached. It has all the properties of L-cysteine but is more water soluble and said to be more bioavailable than L-cysteine. N-acetyl-L-cysteine (NAC) provides powerful immune support and packs a powerful anti-toxin potential. Its ability to neutralize cell and DNA damaging free radicals can help slow down what many scientists point to as a key factor in the aging process²⁵.

B) L-carnitine: The form of L-carnitine used in cognition enhancement is acetyl L-carnitine. It is a stabilized naturally occurring and more absorbable form of the amino acid L-carnitine and plays an important role in protecting and supporting brain and muscle function²⁵. It is well known as a beneficial nutrient for the cardiovascular system, especially due to its ability to strengthen the heart and reduce cholesterol and triglycerides. It facilitates the entry of fats into the mitochondria of cells to be burned for energy. The acetyl form of L-carnitine possesses these attributes as well as additional effects on mental functions²⁶. It is involved in aspects of neuronal metabolism because its molecular structure resembles the neurotransmitter acetylcholine. Supplementing with acetyl L-carnitine may improve acetylcholine production and stimulation of protein and membrane phospholipid synthesis²⁶. It has also been shown to reverse age-related memory loss, successfully treat depression in the elderly, improve blood flow to the brain and even to successfully treat symptoms of Alzheimer's disease. Although most effective in elderly patients, it also improves mental performance and reflex speed in young, healthy adults as well. It does not have a high risk of side effects or toxicity²⁶.

C) L-phenylalanine: It increases mental energy and helps to produce the neurotransmitters Dopamine, Norepinephrine and Epinephrine. It promotes a healthy mood and assists with the neurological processes of learning and memory²⁵.

D) L-glutamine: It is another example of an amino acid with substantial benefits to mental functioning. Glutamic acid (a stimulatory neurotransmitter) can be used as an energy source by the brain. Glutamic acid, which is sometimes called a 'brain food', is derived from dietary L-glutamine. The conversion of glutamine to glutamic acid is made in the brain itself after successfully passing the blood-brain barrier. Aside from generally providing an energy source for the brain to function at a higher level, glutamic acid is thought to play a role in mental alertness and perhaps even memory enhancement. Evidence shows that glutamic acid does not readily pass through the blood-brain barrier, while glutamine passes through very easily and vitamin-B6 is needed for its utilization²⁶.

E) L-tryptophan: It is an important amino acid especially found in the proteins contained in dairy products. It helps to improve decision-making, stabilizes mood and influences the cognitive process, specifically learning and memory. Foods high in carbohydrates, which do not contain tryptophan, help to push tryptophan into the brain by triggering the release of insulin. Insulin stimulates muscles to take up competing amino acids. Even calcium, which typically comes in many protein-rich foods, helps regulate nerve impulse transmission²⁴. It is a precursor of two important neurotransmitters (Acetylcholine

and Serotonin). Acetylcholine is essential in memory formation and maintenance. It is found in egg yolks and organ meats. Creation and utilization of Acetylcholine is crucial to memory. Serotonin helps with sleep regulation and reduction of anxiety. It is manufactured from tryptophan. Major Food Sources of tryptophan are cottage cheese, milk, meat, fish, turkey, bananas, dried dates, peanuts, all protein rich foods²⁷.

F) L-tyrosine: It is an essential amino acid which supports brain function. It helps to produce the catecholamines (Dopamine, Norepinephrine and Epinephrine), hormones which are depleted by stress, excessive work and certain drugs. By replenishing catecholamines, mental energy levels are enhanced and a feeling of contentment often occurs. L-tyrosine boosts neurotransmitter production in the brain thereby helping to create alertness. It is converted in the body into other key biologic compounds, including L-dopa, CoQ10, thyroid hormones and melanin. The form of L-tyrosine used in cognition is N-acetyl L-tyrosine (an acetylated derivative of the essential amino acid L-tyrosine). Ordinary L-tyrosine is less stable and insoluble in water, which may result in reduced bioavailability. N-acetyl-Ltyrosine Ltyrosine, which is converted in the body to L-tyrosine, is 20 times as soluble in water as L-tyrosine itself. For this reason, it serves as an efficient supplement for raising tyrosine levels in the body, since un-dissolved substances are not absorbed from the digestive tract. Acetylation enhances the solubility and stability making it a more rapidly absorbed and bioavailable form of the amino acid L-tyrosine which is less prone to urinary excretion²⁵.

2) Antioxidants

They have been found to be very beneficial to brain functioning in many ways. The most common effect of antioxidants on the brain is their protection against oxidative damage. Vegetables(leafy green or cruciferous vegetables), most likely due to their vitamin-E, folate and antioxidant content, help people to retain their mental abilities longer, keeping their brain younger²⁸.

a) Alpha Lipoic Acid (ALA): It is an extremely potent and strong antioxidant that helps neutralize cell-damaging free radicals in both the watersoluble and fat soluble compartments in the cell and enhances the activity of antioxidant vitamin-B and vitamin-C. It is an extremely versatile nutrient that is both water and fat soluble, which gives it the ability to function in almost any part of the body. It is also a key component in the metabolic process, and can help decrease fat storage in your body by directing calories into energy production. It improves the action of insulin, which increases glucose, amino acid and nutrient uptake in brain cells, thus acting to improve memory²⁵.

b) Anthocyanins, Flavonoids, Tannins, Phenolic acids and Stilbenoids:

Anthocyanins found in blueberries and blackberries, enter the brain and improve cognitive function. Blackberry juice and its main anthocyanin component, cyaniding-3-O-glucoside has a protective effect against free radical-mediated endothelial dysfunction and vascular failure. Blackberries, like blueberries exert their protective effects directly through alterations in cell signaling to improve or increase neuronal communication,

calcium-buffering ability, neuroprotective stress shock proteins, plasticity and stress signaling pathways. Berries are a great antioxidant food source, and happen to be high in flavonoids, condensed and hydrolysable tannins, phenolic acids, stilbenoids, and cyanidin-3-O-glucoside, which have the highest oxygen radical absorbance capacity among anthocyanins. Blackberries are high in antiproliferative, antioxidant and anti-inflammatory activities, making them a great food for the brain. The blueberry diet improves spatial working memory²⁹.

c) Polyphenolics: They are also known as phenols. They are present in fruits and vegetables and help in brain functioning. They positively affect brain signaling to enhance neural communication. They also help to get rid of free radicals. The darker colored fruits and vegetables tend to be high in phenolics, therefore possessing large antioxidant and anti-inflammatory activity. At high levels, these effects retard and reverse elements of brain aging, such as Dopamine decrease and other cognitive deficits. Blackberry supplemented diet has been reported to be effective in reversing age related deficits and neural function and helps improve motor performance²⁹.

c) Isoflavones: They are a plant derived class of phytoestrogens and play an important role in cognition enhancement. They are richest in soy products, but can also be found in foods such as legumes. Isoflavones protect the brain from cognitive decline. Soy protein helps to reduce cholesterol, which influence how the brain works³⁰.

3) Dimethylaminoethanol (DMAE)

It is a natural nutrient substance which has been shown to increase the production of acetylcholine. It occurs naturally in certain types of seafood's. When supplemented in higher doses, it has been found to enhance memory and learning capabilities. It has been shown to improve mood and sleep patterns and appears to provide a mild stimulant effect which does not cause a noticeable 'let down' if one stops taking it. Although DMAE is generally considered very safe, excessive dosage can cause headaches, tenseness and insomnia. Manic-depressive individuals should avoid supplemental use of DMAE²⁶.

4) Glucose

Glucose is essential for the proper functioning of brain. The constant supply of glucose to the brain operates it properly. Optimal brainpower is reached when blood glucose is stable. Simple sugars can spike blood glucose and their glucose supply does not last long, so they should be avoided. Too high blood glucose can also inhibit mental function. It is best to replace simple sugars with complex carbohydrates found in fiber rich food, starchy whole grains, protein, legumes or vegetables, which take longer to be broken down and therefore, do not spike blood glucose. Eating regularly and snacking can help maintain glucose supply to the brain. Since the brain cannot store carbohydrates, a constant supply of glucose is therefore needed. Without it, one loses the ability to concentrate. If one is low on glucose supply due to fasting, the brain is forced to get its energy from metabolizing ketones, which come from the breakdown of body fat, and cognitive function worsens, since it requires synthesis of special enzymes which take longer to metabolize. Glucose is broken

down to become an important element in brain cell function, as well as being important in the creation of a neurotransmitter called acetylcholine. This chemical is particularly linked to memory, and it is no accident that extra glucose is linked to an increase in memory and learning ability³¹.

5) Hormones

a) Dehydroepiandrosterone (DHEA):

It is a steroid hormone produced naturally by the adrenal gland, and is the most abundant steroid found in the human blood stream. It has a significant cognitive enhancement effect³². It improves brain cell activity and enhances memory. It helps to maintain the brain cells ability to store and retrieve information in short-term memory³³. DHEA levels naturally decline, as one gets older, and there is strong reason to think that DHEA supplements may extend life span and make one more youthful³². It is involved in protecting brain neurons from senility-associated degenerative conditions like Alzheimer's disease. Not only does the neuronal degenerative condition occur most frequently at the time of lowest DHEA levels, but also brain tissue contains more DHEA than is found in the bloodstream. Very low concentrations of DHEA are found to increase the number of neurons, their ability to establish contacts, and their differentiation. DHEA also enhances long-term memory.

b) Vasopressin:

It is a brain hormone that is released by the pituitary gland. It improves attention, concentration, memory retention, and recall (both short-term and long-term). It facilitates more effective learning by helping to "imprint" new information in the memory centers of the brain, a function which cannot be achieved without the action of vasopressin. Cocaine, LSD, Amphetamines, Ritalin and Cylert (Pemoline) cause a release of vasopressin. Frequent use of these drugs can deplete levels of vasopressin with a result of making one slow and doxy. Alcohol and Marijuana, however, inhibit the release of vasopressin. It is very useful in situation where there is a large amount of new information to learn. It increases the ability to memorize and recall specific factual information. Vasopressin usually produces the following side effects: runny nose, nasal congestion, itch or irritation of the nasal passages, headache, abdominal cramps, and increased bowel movements. Vasopressin has not been proven safe for use during pregnancy. It usually comes in a nasal spray bottle and produces a noticeable effect within seconds²⁷.

c) Pregnenolone:

It is a naturally occurring steroid hormone and the most powerful intelligence enhancing agent ever. Pregnenolone helps in balancing overall hormone levels and have benefits in enhancing memory³⁴. It is converted into DHEA in the body and helps to maintain the brain cells ability to store and retrieve information in short-term memory and to improve memory retention³³.

6) Iron

It is also necessary for a fully functioning brain and for staying mentally sharp. It helps create hemoglobin, an iron containing protein in red blood cells, which transports oxygen to the brain. Oxygen in the brain is vital, since it helps to metabolize glucose. If a child does not receive enough iron, it can impair

brain development and lead to deficits in speech, math, and reading. Women of reproductive age need the most iron, and therefore may be more likely to end up with a deficiency. Persons with sufficient iron in their blood perform better on cognitive tests than those who are iron deficient¹⁰.

7) Omega-3 Fatty acids

A) Docosahexaenoic acid (DHA):

It is a long chain omega-3 fatty acid that is present in high concentrations in the central nervous system. Fish oil contains both eicosapentaenoic acid (EPA) and DHA. It increases the learning power of an individual³⁵.

B) α -linolenic acid:

It has a strong influence on the brain. It influences both communication between cells and cell function. It appears to make receptors on the cell membranes that are more sensitive to serotonin, a neurotransmitter, which helps give people a "happy" feeling. It has also been linked to help in retaining brain functions. When eaten during pregnancy it helps to produce a more intelligent child. Increasing the content of α -linolenic acid in the diet has been shown to lower risk of depression, much better than depression medication. It can be found in cold-water fish, such as salmon, as well as almonds, avocados, walnuts and flaxseed. Fish oils in particular are components of nerve cell membranes and myelin, which help to keep blood vessels in the brain healthy. Fish oil reduces the degree of brain damage experienced in cerebral stroke³⁶. Long-chain omega-3 appear to be more favorable in the brain, compared to the medium lengths, which are found in plants; however the human body is able to make its own long-chain omega-3's when plants containing medium length omega-3's are consumed³⁷.

8) Phospholipid Derivatives

a) Phosphatidyl choline:

It is a component of the phospholipid known as lecithin and is needed in order to make another vital stimulatory neurotransmitter called Acetylcholine. Acetylcholine plays a major role in many functions of the brain such as memory and learning abilities as well as alertness. In addition to these properties, Acetylcholine is needed for proper nerve and muscle control throughout the body. Although the basic form of choline can be used to make acetylcholine, phosphatidyl choline is more efficient in this purpose. The B-vitamin pantothenic acid is needed for the conversion of phosphatidyl choline into Acetylcholine. Phosphatidyl choline is very safe, but those suffering with manic depression should avoid large amounts²⁶.

b) Phosphatidylserine:

It is a nutrient phospholipid found in brain cell membranes and is involved in enhancement of mental abilities in both young and old. Phosphatidylserine is a powerful cognitive enhancer and its benefits include long-term memory retrieval. It is an important neurochemical for learning, cognition, concentration, mood and other mental functions. Memory enhancement and improvement of learning abilities have been shown with administration of phosphatidylserine in healthy, normal adults. In the elderly, it has been reported to reverse depression and symptoms of Alzheimer's disease, besides leading to a general increase in mental capabilities. A few

actions of phosphatidylserine appear to account for these benefits. It increases the number of Acetylcholine receptors in the brain thus increasing memory as well as alertness and learning. It also enhances glucose metabolism (the brain's main energy source), and acts as a 'detergent' which helps prevent adverse changes in the constitution of cell membranes and lipids. Even in very high doses the only occasional side effect reported was mild nausea, however it is noted that it should not be combined with prescribed anti-coagulants²⁶.

9) Vitamins

The B group of vitamins is vital in cognitive function, but not all of them play a role in brain function. Vitamins which have a significant influence in brain function include:

a) Vitamin-B1 (Thiamine):

It aids in nerve cell function and helps the body to convert food, specifically carbohydrates, into glucose. Glucose is what the brain uses as an energy source, making it a very critical need for the brain³⁸. It has a profound effect on the brain and helps in the production of Acetylcholine and GABA. Vitamin-B1 also helps to alleviate pain in the legs and feet because of its ability to regulate circulation³⁹. Foods containing vitamin-B1 include whole grains, rice, wheat germ, bran and organ meats³⁸.

b) Vitamin-B12 (Cyanocobalamine / Methylcobalamine):

There are two types of vitamin-B12, cyanocobalamine and methylcobalamine. Both of them are used to make neurotransmitters. One of their primary functions is the formation of blood cells. They also maintain the nervous system by helping to metabolize fatty acids, which are essential for the maintenance of myelin that surrounds nerves³⁸. Without Vitamin-B12 or with not enough of it, the ability to focus, and think analytically is reduced or even completely diminished³⁹. Vitamin-B12 is originally synthesized by bacteria only. There are no dietary plant sources for it except Spirulina. In addition to including vitamin-B in one's diet, there are factors that can play a role in the uptake and use of vitamin-B. It is usually found in meat or fish products³⁸. Soy and soy based products are a depletory of this essential vitamin³⁹.

c) Vitamin-B3 (Niacinamide):

It leads to the production of NADH coenzyme 1, for optimal functioning of the brain. It is used for medical conditions such as schizophrenia, anxiety and against HIV³⁹.

d) Folic acid:

It is a type of B-vitamin that has a multiple effect on the human body and is very much required for brain functions. Without it dementia problems occur. Elderly people require higher amounts to maintain cognitive abilities as well as memory retention³⁹.

e) Choline:

It is also a B-vitamin as well and produces acetylcholine throughout the body that sends and receives signals from the brain and thus is utilized in memory and cognitive abilities. Eggs are a good source of choline³⁹.

10) Amla (*Emblica Officinalis*)

Emblica officinalis, the Indian gooseberry, or amla, is a deciduous tree of the Phyllanthaceae family. It is known for its edible fruit of the same name. Anwala churna is an ayurvedic

preparation of amla which possesses memory enhancing action and has been proved to be a useful remedy in the management of Alzheimer's disease. This memory enhancing activity of amla has been attributed to its property of reducing brain cholinesterase activity and total cholesterol levels⁴⁰.

11) Brahmi (*Bacopa monniera*)

It is an ayurvedic herb and has long been used as a cognitive enhancer. It keeps the brain safe from free radical damage and stimulates improved learning and cognitive function. Its medicinal properties are derived from the two main alkaloids present ³n ³t – brahmine and herpestine. It stimulates improved learning and cognitive function. Taken on a regular basis, it helps to increase the concentration and improves memory and retention capacity. Regular use of the brahmi oil is effective in treating mental imbalances, emotional disturbances and in the prevention and cures of geriatric mental problems such as amnesia and Alzheimer's disease. It is used commonly used as a brain tonic. It has a drawback also; an excess of brahmi prevents the oxidation of fats in the bloodstream, making them to accumulate in the blood and increasing the risk of cardiovascular disorders⁴¹.

12) Guggul (*Commiphora wightii*)

Commiphora wightii (Guggal, Guggul or Mukul myrrh tree) is a flowering plant in the family Burseraceae. It is a shrub or small tree, reaching a maximum height of 4 m, with thin papery bark. Guggul produces a resinous sap known as gum guggul. The extract of this gum, called gugulipid has been used in Ayurvedic medicine for nearly 3,000 years in India. The active ingredient in the extract is the steroid guggulsterone, which acts as an antagonist of the farnesoid X receptor. Gugulipid has significant protective affect against streptozotocin-induced memory deficits model of dementia that can be attributed to anti-oxidant and anti-AChE activity of gugulipid which suggest gugulipid as a potential anti-dementia drug⁴².

13) Caffeine (*Kola vera*)

There are many mixed opinions about caffeine and the effects that it has on the brain. Caffeine helps in increasing cognitive function but also has some negative effects. It reaches its highest concentration in the blood and brain within 30–40 minutes after consumption and has an elimination half-life of 4 to 6 hours and has been shown to increase alertness and performance. Children and adults who consume low doses of caffeine show increased alertness, yet a higher dose is needed to improve performance. Caffeinated beverages help improve short-term concentration and facilitate learning, as well as memory. Caffeine dilates the blood vessels in the brain, if consumed in small amounts. Negative effects of caffeine are not seen if it is consumed 6 hours or more apart and in appropriate doses. Such regular consumption may also enhance the neuro-protective actions of adenosine. Adenosine is a nucleoside that contains adenine as its base. Caffeine has also been shown to have more of an effect on improving cognitive performance and sustaining attention in older adults. Chronic pretreatment of caffeine has shown to reduce ischaemic brain damage, in addition to reducing the risk of Parkinson's disease. Depression, stress and anxiety may be lessened with caffeine. Beverages that contain caffeine

typically have antioxidants as well, which have show to have a strong association with improving brain cognition⁴³.

14) Ginger (*Zingiber officinale*)

Zingiber Officinale (Zingiberaceae) rhizomes posses potent memory enhancement in scopolamine induced memory impairment by significantly increasing whole brain acetyl cholinesterase inhibition activity. *Zingiber Officinale* significantly improves learning and memory. Its major active constituents are gingerin, gingerol, shogaol and zingerone. A scientific study has demonstrated beneficial effect of ginger rhizome to protect against focal cerebral ischemia. The cognitive enhancing effect and neuroprotective effect of Ginger is partly due to its antioxidant activity⁴⁴.

15) Coconut Milk Powder (*Cocos nucifera*)

Coconut Oil and the medium chain fatty triglycerides (MCTs) are effective in slowing cognitive decline. Medium chain triglycerides (MCTs) and ketone bodies help the brain better utilize oxygen and metabolize glucose²⁵.

16) Curcumin (*Curcuma longa*)

Curcuminoids present in curcumin have the ability to improve mental function and act as neuroprotectors. Curcumin also acts as a powerful antioxidant²⁵.

17) Cinnamon (*Cinnamomum zeylanicum*)

Cinnamon is an exceptional source of antioxidants. Cinnamon contains phytochemicals that assist the brain in metabolizing glucose- an essential form of energy for mental functions²⁵.

18) Ginkgo (*Ginkgo biloba*)

The leaves of this plant are known for increasing blood flow to the brain and greater amounts of oxygen to the tissues. This herb improves brain glucose metabolism while affecting levels of amine neurotransmitter substances in the brain. An extract of ginkgo containing 24% flavone glycosides (the herb's active flavonoids) has been found to enhance mental functioning both in the young and old. There are several mechanisms by which ginkgo exert its beneficial effect on mental functioning. Ginkgo is known to improve circulation to the brain. It appears to initiate vasodilatation (opening of the blood vessels) in the capillaries, which accounts for the increased blood flow and thus an increased level of oxygen and nutrients to the brain cells. Ginkgo extracts enhance nerve transmission in the brain and improve the production and usage of neurotransmitters within the brain. Ginkgo components are known to act as powerful antioxidants in the brain, thereby scavenging free radicals which otherwise would cause premature death of cells. In addition, ginkgo biloba promotes the more efficient metabolism of glucose, the brain's major source of energy. The result of these actions means an improvement in the performance of the brain. *Ginkgo biloba* has shown preventive action in corticosterone induced neuronal atrophy and cell death in the hippocampus⁴⁵.

19) Golden Rose / Golden Root (*Rhodiola rosea*)

It is a plant and is found to be effective for improving mood and alleviating depression. It improves physical and mental performance and reduces fatigue. *Rhodiola rosea's* effects are potentially mediated by changes in serotonin and dopamine levels due to monoamine oxidase inhibition and its influence on opioid peptides such as beta-endorphins. It is included among a class of plant derivatives called adaptogens, which

differ from chemical stimulants, such as nicotine, and do not have the same physiological effects⁴⁶.

20) Gotu Kola (*Centella asiatica*)

This plant mentioned in Indian literature has been described to possess CNS effects such as stimulatory-nervine tonic, rejuvenant, sedative, tranquilizer and intelligence promoting property. This herb reduces adrenal corticosterone blood levels during stress and is useful for cognitive and nervous disorders as well as vascular problems in the brain⁴⁷.

21) Green Tea (*Camellia sinensis*)

Green tea extract contains high levels of polyphenols (a bioflavonoid) and is a superb source of EGCG (an antioxidant hundreds of times more powerful than vitamin E in fighting free radicals). Consumption of green tea is associated with a lower prevalence of cognitive impairment. Green tea also contains trace amounts of theanine which is a unique amino acid. Theanine converts in the brain into GABA, the neurochemical involved in inhibiting over active mental activities, such as stress, anxiety, worrying, and nervousness. Unlike herbs, theanine protects & enhances cognition, without causing sleepy or drowsiness. It causes instant relaxation due to its potent effects on raising GABA. Unlike the supplement GABA, it passes through the blood brain barrier readily and has superior GABA raising effects^{25,27}.

22) Guduchi (*Tinospora cordifolia*)

It is an herbaceous vine of the family Menispermaceae indigenous to the tropical areas of India, Myanmar and Sri Lanka. Guduchi has been shown to enhance cognition (learning and memory) in normal rats and reverse cyclosporine-induced memory deficit. Alcoholic and aqueous extracts of *Tinospora cordifolia* have been shown to produce a decrease in learning scores in Hebb William maze and retention memory, indicating enhancement of learning and memory⁴⁷.

23) Liquorice (*Glycyrrhiza glabra*)

Liquorice or licorice is the root of *Glycyrrhiza glabra*. The roots and rhizomes of *Glycyrrhiza glabra* (Fabaceae) is an efficient brain tonic, it increases the circulation into the CNS and balances the sugar levels in the blood. Liquorice has been reported to improve learning and memory on scopolamine induced dementia. The main constituent of *Glycyrrhiza glabra* is glycyrrhizin. The protective effect of liquorice may be attributed to its antioxidant property which results in reduced brain damage and improved neuronal function and hence enhancing memory⁴⁸.

24) Lycopodium saururus (*Huperzia saururus*)

It is fern (Lycopodiaceae) reported in Argentinean popular medicine as a memory enhancing agent. Chemical studies have shown that the main constituents of the species are Lycopodium alkaloids: Huperzine A and B. It is used mainly as aphrodisiac. *Huperzia saururus* has been reported to produce marked increase in the hippocampal synaptic plasticity⁴⁹.

25) Maca (*Lipidium meyenii*)

Lipidium meyenii (Brassicaceae) known commonly as maca, is an herbaceous biennial plant or annual plant native to the high Andes of Peru and Bolivia. It has showed beneficial improvement on memory and learning. Aqueous and

hydroalcoholic extracts of Black Maca have significantly ameliorated the scopolamine-induced memory impairment in mice⁵⁰.

26) Magnolia Bark (*Magnolia officinalis*)

Magnolia officinalis (commonly called Houpu Magnolia or Magnolia-bark) is a species of Magnolia native to the mountains and valleys of China at altitudes of 300-1500 m. It is a deciduous tree growing to 20m in height. The bark is thick and brown but does not fissure. Magnolol, honokiol, and obovatol are well-known bioactive constituents of the bark of Magnolia and have been used as traditional Chinese medicines for the treatment of neurosis, anxiety, and stroke. A study has suggested that the ethanol extract of *Magnolia officinalis* and its major ingredient, 4-O-methylhonokiol, may be useful for the prevention of the development or progression of Alzheimer's disease⁵¹.

27) Sesame (*Sesamum indicum*)

Sesame is a flowering plant in the genus Sesamum. It is widely naturalized in tropical regions around the world and is cultivated for its edible seeds, which grow in pods. Sesaminol glycosides are one of the most abundant lignan glycosides found in sesame seeds. Dietary sesaminol has showed a protective effect against Abeta-induced learning and memory deficits in passive avoidance and the Morris water maze test⁵².

28) Red Spider Lilly (*Lycoris radiata*)

It is an herb and contains galantamine alkaloid as an active ingredient. It is used for the treatment of mild to moderate Alzheimer's disease and various other memory impairments, particularly those of vascular origin. Galantamine is a competitive and reversible cholinesterase inhibitor. It reduces the action of AChE and therefore tends to increase the concentration of acetylcholine in the brain. When used with choline bitartrate or alpha- GPC, it can dramatically increase one's odds of becoming lucid and increases memory consolidation during dreaming. Along with other cholinergics or acetylcholinesterase inhibitors such as Huperzine A, galantamine also has been used as a brain enhancer to enhance memory in brain-damaged adults⁵³.

29) Shankpushpi (*Evolvulus alsinoides*)

Evolvulus alsinoides (Convolvulaceae) is used as nootropic or brain tonic in traditional systems of medicines. In the Ayurvedic system of medicine, the whole herb of 'Shankpushpi' has been employed clinically for centuries for its memory potentiating, anxiolytic and tranquilizing properties. Ethanolic, aqueous and ethyl acetate extracts of *Evolvulus alsinoides* have been seen to improve learning and memory in rats⁵⁴.

30) Siberian Ginseng (*Eleutherococcus senticosus*)

This herb has an anti-stress effect by exerting antioxidant and steroid metabolism activity on the hypothalamus-pituitary-adrenal endocrine function. It stimulates activity in the brain to cause a more economical release of body energy, resulting in increased work output⁵⁵.

31) Spanish Sage (*Salvia lavandulaefolia*)

Salvia Lavandulaefolia (Lamiaceae) and other salvia species are prominent for their reputed beneficial effects on memory disorders, depression and cerebral ischemia. Anti cholinesterase activity (Nicolette Perry et al., 1996) helps the

supplementation of Ach. *Salvia* majorly contains essential oils, l, 8-cineole, linalool, α - and β -pinene, carvacrol, luteolin⁵⁶.

32) *St John's Wort (Hypericum perforatum)*

It is a perennial plant with extensive, creeping rhizomes. It is a highly valued herb that has been used in healing for more than two thousand years. It shows MAOI activity, treats mild depression and helps to elevate mood and restore mental balance is common for many people⁵⁷.

33) Vinpocetine

It is a derivative of vincamine (a phytonootropic from periwinkle) and a less potent mental stimulant than vincamine. Vinpocetine is the preferred nootropic for enhancing blood flow to the brain, eyes and ears. Its effects on cerebral blood flow far exceed all other cognitive enhancers. It enhances brain metabolism by increasing glucose utilization, blood & oxygen flow. It boosts mental energy & cerebral circulation, stimulates the locus coeruleus (specialized neurons involved in information processing, attention, cortical/ behavioral arousal, learning and memory), inhibits platelet aggregation (reduces abnormal blood clots) and has a significant antioxidant effect²⁷.

34) Sweet Flag (*Acorus calamus*)

Acorus calamus, commonly known as Sweet Flag or Calamus and erroneously as 'rush' or 'sedges', is a plant from the Acoraceae family, in the genus *Acorus*. It is a tall perennial wetland monocot with scented leaves and more strongly scented rhizomes. It has been used in traditional Chinese and Indian prescriptions for its beneficial effects on memory disorder, learning performance, lipid peroxide content, and anti-aging and anticholinergic activity. Pharmacological studies have revealed that *Acorus* rhizome and its constituents, particularly α - and β -asarone, possess a wide range of pharmacological activities such as sedative, CNS depressant, behavior modifying, anticonvulsant, acetylcholinesterase inhibitory, memory enhancing, antiinflammatory, antioxidant, antispasmodic, cardiovascular, hypolipidemic, immunosuppressive, cytoprotective, antidiarrheal, antimicrobial, anthelmintic, insecticidal, aduicticidal, diuretic, antioxidant, genotoxic, and mutagenic activities⁴⁴.

35) Yerba mate (*Ilex paraguayensis*)

Mate tea has been reported to have hypocholesteremic, hepatoprotective and central nervous system stimulant activity. The mate tea leaves contain two active principles: polyphenols (chlorogenic acid) and xanthenes (caffeine, theophylline and theobromine). The *Ilex* leaves are reported memory enhancing activity on dementia on different models⁵⁸.

36) Royal Jelly

Increases brain cell growth and diversity, only demonstrated in-vitro, improbable in-vivo (it has been reported to stimulate the growth of glial cells and neural stem cells in the brain^{59,60}).

CONCLUSION

Nootropics can increase mental awareness, concentration, quickness, intelligence and so on. Many different drugs are classified as cognitive enhancers or nootropics so it is important to find the right one for ones condition. Symptoms of some serious health conditions such as Alzheimer disease,

Parkinsonism disease or may be ADHD can even be treated with the use of certain cognitive enhancers.

The choice of nootropics can be made by seeking advice from either doctor or physician relevant to the pattern of disease and also there is a need to speak with experts to find how they can help one deal with any mental problem.

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