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Review Article

Natural Remedies for Improving Learning and Memory-Review

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Abstract

Dementia is a syndrome usually occurs in Alzheimer's disease (AD) and vascular dementia (VD) due to disease in brain. It associate's the impairment of memory, thinking, learning disability, orientation and judgement. Memory is perhaps the most vital of all aspects that differentiates human beings from other animals. However, memory can become faulty due to several reasons, and in that case the person is not able to make full use of his or her potentials. Cognitive enhancers are drugs, supplements, nutraceuticals and functional foods that are purported to improve mental functions such as cognition, memory, intelligence, motivation, attention and concentration. Drugs considered cognitive enhancers include dietary products and supplements, racetams, stimulants, dopaminergics, cholinergics, GABA blockers, glutamate activators, serotonergics and hormones, etc. Not all of them are healthy or safe to use but they can still have mental benefits. In recent year's research on medicinal plants have been studied for nootropic activity. *Bacopa monnieri* (Brahmi), *Evolvulus alsinoides* (Shankpushpi), *Tinospora cordifolia* (*Guduchi*), *Acorus calamus* (Bach) etc., are used as a memory enhancer drugs. The abstract refers to several plants with their activity. The main aim of this article is to give up the data reviews on plants with nootropic properties.

1. INTRODUCTION

Memory is the ability of an individual to record sensory stimuli, events, information etc., retain them over a short or long period of time and recall the same at a later date when needed¹. Learning is the process of acquiring knowledge about the world and memory could be considered as the retention of the acquired knowledge, which can be retrieved as and when, required. Memory function is vulnerable to a variety of pathologic processes including neurodegenerative diseases, strokes, tumors, head trauma, hypoxia, cardiac surgery, malnutrition, attention-deficit disorder, depression, anxiety and the side effects of medication, and normal ageing¹. Memory disorders can range from mild to severe and can be progressive (neurodegenerative disease) or immediate (brain injury). Almost all are linked with some damage to neuroanatomical structures, either in part or full, which hinders acquisition (learning), consolidation (storage of labile stable memory), and retrieval (recall)³. A large number of studies have shown that the cholinergic system plays an important role in learning and memory. Moreover, a loss of cholinergic neurons and reduced choline-acetyltransferase activity in the cerebral cortex and hippocampus are consistent with findings in Alzheimer's disease (AD)⁴. In fact, reduced cholinergic activity in the brains of individuals with AD provides the rationale for the development of acetyl cholinesterase (AChE) inhibitors to treat the dementia associated with AD. The commonly prescribed AChE inhibitors, such as Donepezil®, Rivastigmine, and Galantamine were developed on this basis⁴. As memory involves many interwoven brain functions, there are several different types of memories and virtually any type of brain damage can result in one or other type of memory loss⁵. Cognition enhancers are medications and natural supplements that

are used to improve the function of various human cognitive abilities such as cognition, memory, intelligence, motivation, attention and concentration when they have become impaired in some manner. Sometimes referred to as nootropics, or smart drugs, the cognition enhancers may be used to combat health conditions that interfere with the process of learning, motor control and the maintenance of a healthy emotional state. They are mostly used for enhancing mental concentration and increasing memory capabilities and are available in various items such as prescription medication, supplements and functional foods⁶. Through the ages, many medicinal herbs have been used to improve memory and cognitive function and to treat neurodegenerative diseases in traditional medicine⁷. Pharmacological effects of some plants have also been reported⁸. Ayurveda, the Indian system of medicine, is gaining greater attention and popularity in many parts of the world. The disease preventive and health promotive approach of ayurveda, which takes into consideration the whole body, mind and spirit while dealing with the maintenance of health promotions, now enjoys increasing acceptability⁹.

2. SCIENTIFIC DOCUMENTATION OF HERBS

In traditional practices of medicine, numerous plants have been used to treat cognitive disorders, including neurodegenerative diseases such as Alzheimer's disease (AD) and other memory related disorders. Various studies been undergone to identifying potential new drugs from plant sources, including those for memory disorders. There are numerous drugs available in market that have been isolated from plants, e.g. alkaloids from plant sources have been investigated for their potential in AD therapy, and are now in clinical use. Usually herbal preparations are well tolerated but they may have harmful side-effects, including interactions with pharmaceuticals. Herbal medicines, such as *Ginkgo Biloba*, *Bacopa monnieri* (Brahmi), *Shankpushpi* etc. has been found to increase memory power¹⁰.

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2.1. GLYCYRRHIZA GLABRA (FABACEAE)

The roots and rhizomes of *Glycyrrhiza Glabra* (*Fabaceae*) is an efficient brain tonic, it increases the circulation into the CNS system and balances the sugar levels in the blood¹¹. Significant action on memory enhancing activity in dementia disorder¹². Liquorice shows significantly improved learning and memory on scopolamine induced dementia. The main constituent of *Glycyrrhiza Glabra* is glycyrrhizin. The roots have anti ulcer, expectorant, diuretic, laxative, sedative, antipyretic¹³, anti microbial and anxiolytic activities¹⁴. Oxygen free radicals and other products of oxidative metabolism have been shown to neurotoxic¹⁵. The protective effect of liquorice extract may be attributed to its antioxidant property by virtue of which susceptible brain cells get to less oxidative stress resulting in reduced brain damage and improved neuronal function thereby enhancing the memory¹².

2.2. CAESALPINIA CRISTA LINN. (CAESALPINIACEAE)

Caesalpinia crista (Lin.) synonym: *Caesalpinia bonduc* (L.) Roxb.), *Caesalpinia bonducella* belongs to family Caesalpinaceae and is commonly known as kat-takaranja in Hindi and sagargota in Marathi. It is prickly shrub found throughout the hotter regions of India and Srilanka¹⁵.

The seeds of the plant contain bonducin, proteins, saponin, starch, sucrose, an enzyme, two phyosterols namely sitosterol and heptasane, fattyacids such as palmitic acid, stearic acid, lognocer, oleic, linolenic acid. The seed kernals of the plant contain furanoditerpenes- α -caesalpin, β -caesalpin, γ -caesalpin, δ -caesalpin, ϵ -caesalpin, and F-caesalpin¹⁶.

In India, various parts of this plant has been used in various therapeutic uses like adaptogenic¹⁷, antimicrobial, antiproliferative, antidiabetic¹⁸, anti-filarial, contractility on uterus, hepatoprotective, antitumor, and antioxidant activities¹⁹. Ethanol extract of dried seed kernel of *Caesalpinia crista* Lin. enhances learning and memory activity, impairment induced by scopolamine and these effects are mediated in part by inhibition of AChE activity in the brain.

2.3. GINKGO BILOBA (GINKGOACEAE)

Ginkgo Biloba (*Ginkgoaceae*) is also known as maiden hair tree, kew tree, ginkyo, yinhing. The herb shows memory enhancing action by increase the supply of oxygen, and helps the body to eliminate free radicals thereby improving memory¹¹. More recently, an in vitro study indicated that Ginkgo extract had an anti amyloid aggregation effect²¹. G. biloba extract has also been reported to increase transthyretin RNA levels in mouse hippocampus; transthyretin is part of the mechanism for beta amyloid transport and this mechanism may also protect against amyloid deposition in brain²².

The main medicinal constituents are found in the ginkgo leaf. These include flavonoids and several terpene trilactones unique to ginkgo (ginkgolides and bilobalide). The 3 major flavonoids of ginkgo are quercetin, kaempferol, and isorhamnetine. About 40 minor flavonoids also have been identified and include catechins, dehydrocatechins (proanthocyanidins), and flavones (eg, ginkgetin, amentoflavone, bilobetin, sciadopitysin). The major terpene molecules unique to ginkgo are ginkgolides A, B, C, J, and M and bilobalide²³.

Ginkgo biloba can improve behavioral adaptation despite adverse environmental events, as shown in rats taught reward versus punishment (stress) testing to obtain drinking water. This supports clinical use of ginkgo to treat cognitive impairment in the elderly Population²³.

2.4. CENTELLA ASIATICA (UMBELLIFERAE)

Centella asiatica (L) Urban (Umbelliferae/Apiaceae family) is commonly known as Mandukparni. It is a perennial creeping herb, widely cultivated as a vegetable or spice in India. Since ancient times, it has been used as a memory enhancing, strength promoting, wound healing, immune booster, anti-anxiety, anti-epilepsy and anti-stress substance. This plant is also found to improve short-term memory and learning. *Centella asiatica* has also shown a protective effect against oxidative damage caused by lead acetate induced neurotoxicity²⁴.

Centella Asiatica herbal formulation as a brain tonic, cognition, recalling of thoughts and as an antioxidant capable of treating amnesia and having property for improving memory²⁵. Treatment

with *C. asiatica* extract during the early postnatal developmental stages, when the higher brain centers are maturing, can produce long lasting beneficial effects on the mouse brain. Beneficial effects on cognitive functions are probably mediated through their effect on cholinergic system and by influencing the neuronal morphology. Extract of *C. asiatica* (whole plant) has also been reported to increase the endogenous antioxidant enzymes in the rat brain²⁶.

2.5. TINOSPORA CORDIFOLIA (MENISPERMACEAE)

Tinospora cordifolia (Willd.) Miers ex Hook.F. & Thoms. (family: Menispermaceae) commonly known, as "Amrita" or "Guduchi" is an important drug of Indian System of Medicines (ISM) and used in medicines since times immemorial²⁷. It is distributed throughout the tropical Indian subcontinent and China, ascending to an altitude of 300 m. In Hindi, the plant is commonly known as *Giloe*²⁸.

A large number of chemicals have been isolated from *T. cordifolia*, belonging to different classes such as alkaloids, diterpenoid lactones, glycosides, steroids, sesquiterpenoid, phenolics, aliphatic compounds and polysaccharides. Leaves of this plant are rich in protein (11.2%), calcium and phosphorus²⁹. Four new clerodane furano diterpene glucosides (amritosides A, B, C and D) have been isolated as their acetates from stems. *Tinospora cordifolia* has been extensively studied and reported to have potent immunostimulant action. *T. cordifolia* is claimed to be useful in treating leprosy, fever, asthma, anorexia, jaundice, gout, skin infections, diabetes, chronic diarrhea, dysentery, etc.³⁰. 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 memory³¹.

2.6. ZINGIBER OFFICINALE (ZINGIBERACCAE)

Ginger, or *Zingiber officinale*, a plant in the family of *Zingiberaceae*, has longterm been used as both a spice and as a medicine in Asian, Indian, and Arabian folklore. The rhizomes of *Zingiber officinale* exhibit a wide range of pharmacological properties including antilipidemia, antiemetic, anti-inflammation, and antiarthritis. According to Arabian folklore, ginger has been claimed to improve memory. Moreover, it has also been traditionally used as an ingredient for cognitive enhancement³².

Zingiber Officinale significantly improves learning and memory³³. 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 activity³⁴.

Zingiber officinale was previously reported to enhance the level of norepinephrine, epinephrine, dopamine and serotonin contents in the cerebral cortex and hippocampus. Moreover, this plant extract and its active component, 6-gingerol, also inhibited the cholinesterase activity which in turn increased acetylcholine (ACh)³⁸.

2.7. BACOPA MONNIERA (SCROPHULARIACEAE)

Bacopa monniera, a member of the scrophulariaceae family³⁵. It is known as *Brahmi*, *Nir-brahmi* in Sanskrit, *Brihmi-sak*, *Jalanimba* in Bangali, *Brahmi* in Hindi³⁶.

The *Bacopa monniera* (BM) is a creeping, glabrous, succulent herb, rooting at nodes whose habitats include wetlands and muddy shores. Stem 10-30 cm long, 1-2 mm thick, soft, glabrous; branches ascending. Leaves 0.6-2.5 cm long and 3-8 mm broad, sessile^{37,38}. The compounds responsible for the memory enhancing effects of *Bacopa monniera* are triterpenoid saponins called "Bacosides"³⁹.

The major chemical entity shown to be responsible for the memory-facilitating action of *Bacopa monniera*, Bacosides A, was assigned as 3-(α Larabinopyranosyl)-O- β -D-glucopyranoside-10, 20-dihydroxy-16-keto-dammar-24-ene. Three new saponin have been isolated from the *Bacopa monniera* designated as bacosides III, IV, V with structures 3-O α -L- arabinofuranosyl-(1 \rightarrow 2)- β -D-glucopyranosyljujubogenin, 3-O β -D-glucopyranosyl (1 \rightarrow 3)- α -Larabinopyranosyljujubogenin, 3-O β -D-glucopyranosyl-(1 \rightarrow 3)- α ⁴⁰. *Bacopa monniera* is used in following conditions Memory enhancing activity, Antispasmodic activity, Anticholinesterase activity, Neuroprotective role, Antioxidant activity, Antidepressant properties, Bronchovasodilatory activity, Antiulcerogenic activity, Antibacterial activity, Anticancer activity, Antileishmanial properties⁴¹.

2.8. ILEX PARAGUARIENSIS (AQUIFOLIACEAE)

Ilex Paraguariensis Yebra mate tea (mate) leaves (Aquifoliaceae) is a dioecious evergreen tree, which can grow to an elevation of up to 8–15 m. The 8 cm long olive-green leaves are perennial, alternate, coriaceous, obovate with slightly crenate dentate margins and obtuse apex, and have a wedge shaped base. The petioles are up to 15 mm long. The flowering stage occurs during spring season, producing small, unisexual flowers which have 4 white petals. In some tropical or subtropical species, the number of petals may be 5, 6 or 7⁴². *Ilex paraguariensis* green (non-roasted) extracts contain purine alkaloids (methyl xanthines), flavonoids, vitamins such as vitamin A, B complex, C and E, tannins, chlorogenic acid and its Derivatives, and numerous triterpene saponins derived from ursolic acid, known as matesaponins^{43,44,45}. The *ilexes* leaves are reported memory enhancing activity on dementia on different models are spontaneous locomotor activity, social recognition task and inhibitory avoidance task methods⁴⁶.

2.9. HUPERZIA SQRURUS (LYCOPODIACEAE)

Huperzia saururus (Lam) Trevis. (=Lycopodium saururus Lam., =Urostachis saururus (Lam.) Herter) (Lycopodiaceae) is known in Argentina under the names of “cola de quirquincho”, “pijiyay” or “pijiyay”. *Huperzia saururus* named as “cola de quirquincho” is used mainly as an aphrodisiac⁴⁷. Its habitat spreads from the northwest region of the country to the sierras of the center (Cordoba) and south of Buenos Aires. It has also been found in other South American and African countries⁴⁸. *Huperzia squarurus* mainly contain two major constituents hyperzine A and B are lycopodium alkaloids among the compounds with known activity on memory and learning⁴⁹. Huperzine A has been investigated for memory improvement and for the treatment of Alzheimer's disease and myasthenia gravis⁵⁰.

2.10. EVOLVULUS ALSINOIDES L. (CONVOLVULACEAE)

Evolvulus alsinoides (EA) is an important plant that has been well documented in Ayurveda for its therapeutic values. EA (Linn) (Family: Convolvulaceae) commonly known as *Shankhpushpi* is found throughout India ascending to 6000 ft in the Himalayas. It is well known for its therapeutic effect on brain disorders like insanity, epilepsy, memory enhancement and nervous debility in Indian Ayurvedic system of medicine⁵¹. *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 ‘Shankhpushpi’ 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 rats⁵².

Evolvulus Alsinoides L contains alkaloids betaine, sankhpushpine and evolvine, scopoletin, scopolin, umbelliferone, 6-methoxy-7-O-β-glucopyranoside coumarin queretene-3-o-β glucopyrenoside are reported⁴⁹. *Evolvulus Alsinoides* L possesses antibacterial and anthelmintic⁵⁴.

2.11. ACORUS CALAMUS (ARACEAE)

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 rhizomes⁵⁵. *Acorus Calamus* contains majorly α-and β-asarone. The rhizomes of *Acorus Calamus* are used in loss of memory given in combination with other drugs like *Centella Asiatica*, *Bacopa Monniera* and *Rauwolfia Serpentina*⁵⁶. *Acorus Calamus* also shows anti inflammatory, antioxidant, anti spasmodic, hypolipidemic, immunosuppressive, cytoprotective, antidiarrheal, antimicrobial and anthelmintic activities⁵⁷.

2.12. COMMIPHORA WHIGHITTI (BURSERACEAE)

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. The active ingredient in the extract is the steroid guggulsterone, which acts as an antagonist of the farnesoid X receptor⁵⁸. The guggulipid shows potential cognitive enhancer for improvement memory in scopolamine induced memory deficits⁵⁹. The *commiphora whighitti* acting on impairment in learning and memory and decreased choline acetyltransferase levels in hippocampus⁵⁹.

2.13. EMBLICA OFFICINALIS (EUPHORBIACEAE)

Emblica officinalis, The Indian gooseberry, or amla. It is known for its edible fruit of the same name⁶⁰. *Emblica Officinalis* (Euphorbiaceae) possesses memory enhancing action on improvement in memory in scopolamine and diazepam induced memory deficits. *Emblica Officinalis* inhibits the AChE activity. Amla contains major active constituents of vit-C, phyllembin. Due to vit-C the amla possesses the beneficial effects such as, memory improving property, cholesterol lowering property and anti cholinesterase activity²². Amla churna produced a dose-dependent improvement in memory of young and aged rats. It reversed the amnesia induced by scopolamine and diazepam. Amla churna may prove to be a useful remedy for the management of Alzheimer's disease due to its multifarious beneficial effects such as memory improvement and reversal of memory deficits⁶⁰.

2.14. SALVIA LAVANDULAEFOLIA (LAMINACEAE)

Salvia Lavandulaefolia (Spansih sage) (Laminaceae) and other *salvia* special are prominent for their reputed beneficial effects on memory disorders, depression and cerebral ischemia, anti cholinesterase activity⁶². *Salvia* majorly contains essential oils, 1, 8-cineole, linalool, α-and β-pinene, carvacrol, luteolin. *Salvia Lavandulaefolia* has been reported to be antioxidant⁶¹. *Salvia Lavandulaefolia* inhibit the acetylcholinesterase and improvement of memory in dementia⁶².

2.15. FOENICULUM VULGARE (UMBELLIFERAE)

Foeniculum vulgare Linn. Extract used as a nootropic and anticholinesterase agent in mice. *F. vulgare* extract increased step-down latency and acetylcholinesterase inhibition in mice significantly. *F. vulgare* is employed in treatment of cognitive disorders such as dementia and Alzheimer's disease⁶³.

2.16. MAGNOLIA OFFICINALIS (MAGNOLIACEAE)

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 stroke⁶⁴. Magnolol and honokiol exhibited an AChE inhibitory property, in rat spleen microsomes and human polymorpho nuclear leukocytes⁶⁵. *Magnolia Officinalis* shows memory enhancing property by using water maze and step down avoidance methods⁶⁶.

2.17. LEPIDIUM MEYENII (BRASSICACEAE)

Lepidium 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 mice⁶⁷. *Lepidium Meyanii* acting on cholinergic dysfunction mainly neurotransmitter (ACh) related to memory and learning⁶⁸. Black maca (0.5 and 2.0 g/kg) decreased brain malondialdehyde (MDA) levels marker of oxidative stress and acetylcholinesterase (Ache) levels in ovariectomized mice whereas no differences were observe in monoamine oxidase (MAO) levels⁶⁹.

2.18. ROSA ALBA (ROSACEAE)

Rosa Alba (Rosaceae) posses memory enhancing property. *Rosa alba* produces symptomatic improvement in learning and memory. *Rosa Alba* might proven to be a useful memory restorative agent in the treatment of cognitive disorders. *Rosa alba* reported the effects on cognitive functions learning and memory by using elevated plus-maze and passive-avoidance test. *Rosa alba* inhibits cholinesterase and improves the memory power⁷⁰. *Rosa Alba* also used in leprosy, biliousness burning sensation, appetite, cold, headache, bronchitis, ophthalmia, rheumatism and its perfume is a tonic for the brain and the heart⁷¹.

2.19. THESPESIA POPULNE (MALVACEAE)

Thespesia populnea (Malvaceae) is a large tree found in the tropical regions and coastal forests of India. Various parts of *T. populnea* are found to possess useful medicinal properties, such as antifertility, antibacterial, and anti-inflammatory. The learning and memory parameters were assessed using elevated plus maze and

passive avoidance paradigm. It showed significant improvement in memory of young and aged mice. *T. populnea* bark possessed a powerful memory enhancing activity in mice. Since diminished cholinergic transmission and increased cholesterol levels appear to be responsible for development of amyloid plaques and dementia in Alzheimer patients⁷².

2.20. SESAMUM INDICUM (PEDALIACEAE)

Sesamum Indicum is annual herb family (Pedaliaceae). 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 test⁷³. *Sesamum Indicum* contains major active constituent's protein, carbohydrates, vitamins, (Thiamine, Niacin), riboflavin, nicotinic acid, pantothenic acid and ascorbic acid. Sesame oil is rich in oleic and linolic acids. The main sesame lignans are sesamin and sesamol which are found in sesame oil⁷⁴. sesame oil having the antioxidant activity⁷³. Sesamum seeds are considered emollient, diuretic, lactagogue and nourishing tonic, emmenagogue and cough. Powdered seeds are used in amenorrhoea and dysmenorrhoea⁷⁵.

3. CONCLUSION

The review focuses on several natural memory enhancing agents acting on dementia. Dementia is a syndrome usually occurs with impairment in memory, thinking, orientation and judgement. In majority of the studies, the underlying mechanism was found to be anti acetylcholinesterase activity and free radical scavenging activity with the facilitation of the cholinergic transmission. The typical scientific approach for selecting plants to investigate for the treatment of these disorders is relatively rational method to develop more acceptable and better substitute to the present pharmacotherapy. The collection of herbal plants showing the nootropic activity were tabulated from the various journals and were reported above as we can conclude that herbal plants are very rich source of substance which are responsible of increasing nootropic activity.

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