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Physiological concept of memory and herbs used as memory stimulant

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Abstract
Memory is most important and complex feature of brain which makes the development of human being and animals. In the field of neurosciences, the major discovery in past two decades is the elucidation of behavioral, neurobiological and cellular basis of learning and memory process. Accordingly, effect of wide variety of pharmacological agents on brain lesions or cognitive behavior have been studied and most validly interpreted as "enhancement or impairment" of learning and memory processes. In traditional practices of medicine, numerous Herbs have been used to treat cognitive disorders, including neurodegenerative disease such as Alzheimer's disease (AD) and other memory related disorders. An ethno pharmacological approach has provided leads to identifying potential new drugs from plant sources. There are numerous drugs available in western medicine that have been directly isolated from plants, or derived from templates of compounds from plants sources. For example, some alkaloids from plant source have been investigated for their potential in AD therapy, and now in clinical use (e.g. galantamine from *Galanthus nivalis* is used in the United Kingdom). Various other plant species have shown favorable effects in AD, or pharmacological activities indicating the potential for use in AD Therapy. This review is focus on understanding the physiological concept of memory and commonly used herbs as memory stimulant in the ancient India system of medicine.

Keywords: Memory, herbal, drugs, ayurvedic, psychotropic, Alzheimer

Introduction
Physiologically, memories are caused by change in the sensitivity of synaptic transmission between neurons as a result of previous neural activity. These changes in turn cause new pathways or facilitated pathways to develop for transmission of signals through the neural circuits of the brain. The new or facilitated pathways are called memory traces. They are important because once the traces are established; they can be activated by the thinking mind to reproduce the memories (Guyton A. C., 2004) [14].
A characteristic of animal and particularly of human is the ability to alter behavior on the basis of experience. Learning is acquisition of the information that makes this possible and Memory is the retention and storage of that information (Tortora G. J., 2003) [37].

Types of Memory
From the physiological point of view, memory is appropriately divided into explicit memory and implicit form.

Explicit memory, which is also called Declarative or Recognition memory, is associated with consciousness or at least awareness and is dependent for its retention on hippocampus and other parts of medial temporal lobes of the brain. It is divided into:-

- Memory of events-episodic memory and
- The Memory of words, rules and language- semantic memory

Implicit memory does not involve awareness and is also called Nondeclarative or Reflexive memory, its retention does not involve processing in the hippocampus, at least most instances and it includes, among other things, skill, habits and conditioned reflexes. Implicit memory includes skills and habits which one acquired and become unconscious & automatic. It also includes priming, which is facilitation of recognition of worth or object by prior exposures to them. The Implicit memory can be divided into:-

- **Nonassociative learning:** The organism learns about a single stimulus, and
- **Associative learning:** In which the organism learns about the relation of one stimulus to another.

Habituation is a classical example on non-associative learning which is the simplest form of learning, in which a natural stimulus is repeated many times where as Sensitization is in a sense the opposite reaction. A classical example of associative learning is a Conditional reflex, which is a reflex response to a stimulus that previously elicited little or no response, acquired by repeatedly pairing the stimulus with another stimulus that normally does produce the response.

Explicit Memory and many forms of Implicit Memory involve:-

- **Short-term memory,** which lasts seconds to hour, during which processing in the hippocampus and elsewhere lays down long-term changes in synaptic strength, and
- **Long-term memory,** which stores memory for the years and sometimes for life.

  During short-term memory, the memory traces are subjected to disruption by trauma and various drugs, whereas long-term memory traces are remarkably resistant to disruption.
- **Working Memory,** is a form of short-term memory that keeps information available, usually for very short period while the individual plans action based on it.

  Encoding explicit Memory Encoding explicit Memory involves working memory in the frontal lobes and unique processing in hippocampus.

Working memory: Working memory keeps incoming information available for a short time while deciding what to do with it. It is that form of memory which permits us, for example, looks up a telephone number, while we pick up the telephone and dial the number. It consists of what has been called a central executive located in the prefrontal cortex and two "rehearsal system", a verbal system for retaining verbal memories, and a parallel Visuospatial system for retaining visual and spatial aspect of objects. The executive steers information into these rehearsal systems. Working memory areas are connected to the hippocampus portions of the medial temporal cortex. In humans, bilateral destruction of the ventral hippocampus or Alzheimer's disease and similar disease processes that destroy its CAI neurons cause striking defects in short term memory. Humans with such destruction have intact working memory and remote memory. Their implicit processes are generally intact. They perform adequately in terms of conscious memory as long as they concentrate on what they are doing. They are capable of new learning and retain old prelesion memories, but they cannot from new long term memories. The connection of the hippocampus to the diencephalons is also involved in memory. Some alcoholics with brain damage develop impairment of recent memory, and the memory loss correlates well with the presence of pathologic changes in the mamillary bodies, which have extensive efferent connection to the hippocampus via the fornix. The amygdala is closely associated with the hippocampus and is concerned with encoding emotional memories.

Long-term Memory While the encoding process for short-term explicit memory involves the hippocampus, long-term memories are stored in various parts of the neocortex. Apparently, the various parts of the memories-visual, olfactory, auditory, etc.-are located in the cortical regions concerned with these functions, and the pieces are tied together by long-term changes in the strength of transmission at relevant synaptic junction so that all the components are brought to consciousness when the memory is recalled. Once long-term memories have been established, they can be recalled or accessed by long a large number of different associations.

Molecular Basis of Memory

The key to memory is alteration in the strength of selected synaptic connections. In all but the simplest of cases, the alteration involves protein synthesis and activation of genes. This occurs during the change from short-term working memory to long term memory. In animals, acquisition of long-term responses is prevented if, within five minutes after each training session, the animals are anesthetized, given electroshock, subjected to hypothermia, or given drugs, antibodies, or oligonucleotides that block the synthesis of proteins. If these interventions are performed four hours after the training sessions, there is no effect on acquisition.

The human counterpart of this phenomenon is the loss of memory for the events immediately preceding brain concussion and electroshock therapy (Retrograde amnesia). This amnesia encompasses longer periods then it does in experimental animals, sometimes many days but remote memories remain intact.

The biochemical events involves in habituation is due to a decrease in Ca^{2+} in sensory endings that mediate the response to a particular stimulus, and in sensitization is due to prolongation of action potential in these ending with resultant increase in intracellular Ca^{2+} that facilities release of neurotransmitter by exocytosis. (Gagnong W. F., 1999) [12].

In Indian context various herbs and herbal formulations are used as memory stimulant and memory enhancer from long back which is recommended in ancient literature of ayurveda like Charak samhita, Sushurt samita etc. Some of commonly used herbs for momory enhacement are Brahmi, Sankhapuspi, Jatamansi, Vaca, Ashwagandha etc. (Chopra, R. N., 1958) [7].

Brahmi (*Bacopa monnieri*)

Drug consists of the dried whole plant, preferably leafs and stems of *Bacopa monnieri*, Fam. Scrophulariaceae. It is distributed throughout India in all plain districts. The main active constituent is saponin glycosides i.e. triterpenoids and Bacoside A&B. (The Ayurvedic Pharmacopoeia of India Part-I, Vol-II Ist edition, 2003)

Brahmi is an Indian medicinal plant, has been described as possessing central nervous system activity, such as improving intelligence. Alcoholic extact increase the learning performance of rates and the activity is attributed to saponin mixture. The triterpenoid saponins and their bacosides are responsible for Bacopa's ability to enhance nerve impulse transmission. The bacosides aid in repair of damaged neurons by enhancing kinase activity, neuronal synthesis, and restoration of synaptic activity, and ultimately nerve impulse transmission. (Singh, H. K. *et al*., 1997) [34].

The bacosides of Brahmi have antioxidant activity in the hippocampus, frontal cortex, and striatum. (Bhattacharya, S. K *et al*., 2000) [5]. The clinical studies in adults shows that drug shows cognitive-enhancing effects on chronic administration (Nathan, P. J. *et al*., 2001) [24].

To investigate effect of Brahmi (Bacopa monnieri) on human memory seventy-six adults aged between 40 and 65 years took part in a double-blind randomized, placebo control study in which various memory functions were tested and levels of anxiety measured. The results show a significant effect of the Bacopa monnieri on a test for the retention of new information. Follow-up tests showed that the rate of learning was unaffected, suggesting that *Bacopa monniera* decreases the rate of forgetting of newly acquired information. Tasks

assessing attention, verbal and visual short-term memory and the retrieval of pre-experimental knowledge were unaffected. (Ganguly, D. K. *et al*., 2002) [11].

The adaptogenic property of a standardized extract of *Bacopa monniera* against acute (AS) and chronic stress (CS) models in rats shows similar effects (Rai, D. *et al*., 2003) [30].

The Brahmi rasayana (The Ayurvedic formulation of Brahmi) also Improves Learning and Memory in mice was proven in animal study in which BR (100 and 200 mg/kg) was administered for eight successive days to both young and aged mice and elevated plus maze, and passive-avoidance paradigm were employed to evaluate learning and memory parameters. (Joshi, H. *et al*., 2006) [16].

Sankhapuspi *(Convolvulus pluricaulis)*

The drug consist of whole plant of *Convolvulus pluricaulis* Fam. Convolvulaceae, a prostrate, sub-erect, spreading, hairy, perennial herb with a woody root stock, found throughout country. Mainly it contains alkaloids. (The Ayurvedic Pharmacopoeia of India Part-I, Vol-II Ist edition, 2003)

Sankhapuspi is an indigenous plant commonly mentioned in Ayurveda, as a rasayana which is mainly advocated for use in mental stimulation and rejuvenation therapy. It is a brain tonic and sovereign remedy in bowel complaints especially dysentery. The plant is reported to be a prominent memory improving drug. It is used as a psycho stimulant and tranquilizer. It is reported to reduce mental tension. The ethanolic extract of the plant reduces total serum cholesterol, triglycerides, phospholipids and nonesterfied fatty-acid. (Barar, F. S.*et al*., 1996) [3].

The water-soluble fraction of sankhapuspi has effect on pithed frog heart and on isolated rabbit intestinal loop. It also decreased the heart rate and force of cardiac arrest in diastole. (Kulkarni, 1993) [23]. Clinically sankhapuspi is used in various herbal formulation for immeory improvement like it constitutes one of the ingredients of the herbal psychotropic preparation BR-I 6A (Mentate) useful in the management of nervous disorders.

Jatamansi *(Nardostachys jatamansi)*

The drug consists of dried rhizome of *Nardostachys jatamansi* Fam. Valerianaceae. It is distributed in the alpine Himalayas from Kumaon to Sikkim and Bhutan, at an altitude of 3,000-5,000 m. the drug is bitter and pungent in taste with highly aromatic odor. The major active constituents are Essentail oil valeranone (Jatamansone), a sesquiterpenoid. (The Ayurvedic Pharmacopoeia of India Part-I, Vol-III Ist edition, 2003).

Jatamansi have a significant role in insomnia. The study proves that composite herbal drugs containing N. jatamansi as one of the ingredients provide relief from insomnia and irritability in humans. (Bhattacharya, 1994) [4].

Jatamansi have the memory enhancing effects in Healthy Volunteers. Which is proven by work on psychotropic activity of jatamasi in human volunteers (Persson, J. *et al*., 2004) [27].

Ashawagandha (*Withania somnifera*)

The drug consists of dried roots of *Withania somnifera* fam. Solanaceae. The plant is widely distributed in north-west India from plains to mountain regions of Himachal. Roots are bitter and acrid in taste with characteristic odour. The major active constituents are alkaloids i.e. isopelletierine, anaferine, cuseohygrine, anahygrine and steroidal lactones i.e. withanolides, withaferins and saponins. Ashawagandha is classified as Rasayana (tonic) in ayurvedic medicine system and recommend as nervine tonic (The Ayurvedic Pharmacopoeia of India Part-I, Vol-III Ist edition, 2003; Mishra *et al*., 2000) [22].

Ashwagandha root extract shows the neurotropic effect in naive and amnesic mice (Dhuley, J. N., 2001) [10]. The withanoside IV (a constituent of Ashwagandha; the root of Withania somnifera) induced neurite outgrowth in cultured rat cortical neurons. The study suggest that orally administrated withanoside IV may ameliorate neuronal dysfunction in Alzheimer's disease and that the active principle after metabolism is sominone (Kuboyama, T *et al*., 2006) [18].

Withania somnifera root extract are useful drug for treatment of drug induced dyskinesia which is one of the major side effects of long-term neuroleptic treatment. (Naidu, P.S. *et al*., 2006) [23]. Ashawagandha is effective in increasing the stamina (physical endurance) and preventing stress induced gastric ulcer, carbon tetrachloride (CCl_4) induced hepatotoxicity and mortality and have similar anti-stress activity in rats (Archana, R., 1999) [2].

Ashawagandha have potent anti-oxidant, anti-peroxidative and free radical quenching properties in various diseased conditions which may be helpful in protecting the neuronal injury in Parkinson's disease (Ahmad, M *et al*., 2005) [1]. Withanolide A (WL-A), isolated from root of Withania somnifera could regenerate neurites and reconstruct synapses in severely damaged neurons and the effect of WL-A on memory-deficient mice showing neuronal atrophy and synaptic loss in the brain (Kuboyama, T. *et al*., 2005) [17].

Vaca *(Acorus Calamus)*

The drug consists of dried rhizome of *Acorus calamus* Fam. Arceae, A semiaquatic herb, wild or cultivated throughout the country ascending up to 1800m in the Himalayas. The drug is bitter and pungent in taste with aromatic odour mainly contains volatile oils (Eugenol and Asarone) and a bitter principle Acrorine and Tannin. (The Ayurvedic Pharmacopoeia of India Part-I, Vol-II Ist edition, 2003)

Acorus calamus used in traditional Korean medicine for improvement of memory and cognition in old age, which is tested for cholinesterase inhibitory properties using the Ellman colorimetric method (Mandal S., 1991, Panchal, G. M., 1989) [21, 25].

Brahmmanduki (*Centella asiatica*)

It consists of dried whole plant of *Centella asiatica* family Apiaceae found throughout India. Plant contains saponins glycosides, brahmoside, brahminoside, sasiaticoside, tannins, ascorbic acid (Kumar, 2003) [20]. Ancient literature describes the use of plant in epilepsy, neurological disorders and as memory stimulant (Siddiqui, B. *et al*., 2007) [33]. Fresh leaf extract of *Centella asiatica* enhanced learning ability and memory retention power in wistar rats (Rao, M. K., *et al*., 2007) [31]. Plant is also used in depression, rheumatism, mental weakness, abdominal pain, and epilepsy (Gohil, K., *et al*., 2010) [13].

Rose Root (*Rhodiola rosea*)

Rose root or Golden root is used in traditional medicine systems of Europe due to its adaptogenic properties. It is a perennial flowering plant of *Rhodiola rosea* Family Crassulaceae found in high latitude and altitude regions. The roots and rhizome are rich in polyphenols, salidroside, tyrosol and other primary bioactive compounds. Plant is reported to have anti-depressant, anti-oxidant, antifatique, adaptogenic, anticancer activities. It also have neurogenerative activities by stimulation of central nervous

system (Petkov V. D. *et al*., 1986) [28]. The components of *Rhodiola rosea* increase blood permeability of blood brain barrier to biochemicals which are involved in memory like 5-HT. The plant stimulates secretion of epinephrine, dopamine, serotonin and nicotinic cholinergic effects which are components of memory. It seems to have beneficial effect on ascending memory (Darbinyan V. *et al*., 2000) [9].

Rosemary (*Rosmarinus officinalis*)

Rosemary oil is used as memory enhancer. It contains essential oil of *Rosmarinus officinalis* Family Labiatae prepared by distillation of flowering top of leafy twigs of rosemary plant. Plant is evergreen shrub and native of Europe having several therapeutic applications in folk medicine in curing or managing a wide range of diseases like depression (Evans, W.C., 2002) [38]. The oil stimulates nervous system under sympathetic control resulting in better concentration and improved learning capacity. The oil reduces acetylcholinesterase release. Speed of learning, quality of memory, and secondary memory factors were improved by volatile oil of rosemary. The extract of R. officinalis produced an antidepressant like effect, which is mediated by an interaction with the monoaminergic system (Daniele G. M., 2009) [8]. Rosemary diterpenes have been shown to inhibit neuronal cell death (Solomon H., 2016) [35].

The plant Kingdom is abundant in species that act as memory stimulant to animal nervous system. Some plants investigated for psychotropic activity are as follows (Chopra, R. N., 1958, Chaudhry, R. D., 2004, Principe, P.P., 1989, Tyler et at. 1981) [6, 29, 7, 39]:

Table 1: List of herbs used as memory stimulant

Sr. No.	Plant Name	Botanical Name	Family	Part use	Active constituents
1.	Aagustia	*Sesbania grandiflora*	Fabaceae	Leaf and seed	Tannins
2.	Akarkara	*Anacyclus pyrethrum*	Asteraceae	Root	Pirathrin,Volatile oils
3.	Amarbail	*Cuscuta reflexa*	Cuscutaceae	Whole plant	cuscutin, amarbelin, β-sitosterol
4.	Ashwagandh	*Withania somnifera*	Solanaceae	Roots	alkaloids i.e. isopelletierine, steroidal lactones i.e. withanolides, withaferins and saponins
5.	Baahmmanduki	*Centella asiatica/ Hydrocotyle asiatica*	Umbelliferae	Whole plant	saponin glycosides i.e. brahmoside, brahminoside, brahmic acid
6.	Bahera	*Termininalia bellirica*	Commelinaceae	Fruit	Tennins
7.	Brahmi	*Bacopa monnieri*	Scrophulariaceae	Dried whole plant	saponin glycosides, triterpenoids and Bacoside A&B
8.	Calamus/Sweet Flag/Vaca	*Acorus calamus*	Araceae	Rhizome	volatile oils, sesquiterpenes and asarone
9.	Common snowdrop	*Galantus nivalis*	Amaryllidaceae	Bulbs and Flowers	Alkaloid, Galantamine
10.	Danipola	*Canscora decussata*	Gentianaceae	Whole plant	Alkaloids and Triterenes
11.	Ginseng	*Panax quniquefolium*	Araliaceae	Roots	Saponins, Ginsenosides
12.	Jatamansi	*Nardostachys jatamansi*	Valerianaceae	Rhizome	Essentail oil
13.	Malakanguni	*Celastrus peniculatus*	Celastraceae	Seed, leaves and oil	Seed contains oil, tannin and alkaloids
14.	Rose Root	*Rhodiola rosea*	Crassulaceae	Roots	Phenols, rosavin, rosin, Flavonoids
15.	Sankhapuspi	*Convolvulus pluricaulis*	Convolvulaceae	whole plant	Alkaloids
16.	Shankhahuli	*Evolvulu alsionoides*	Convolvulaceae	Whole plant	Alkaloids, Shankhapushpin, evolvine

Conclusion

A Search for novel pharmacotherapy from medicinal plants for psychiatric illnesses has progressed significantly in the past decade. This is reflected in the large number of herbal preparations for which psychotherapeutic potential has been evaluated in a variety of animal models. Many herbs reviewed were classified as anxiolytic, antidepressant, narcoleptic, anti-dementia, or anti-substance abuse herbs. A considerable number of herbal constituents whose behavioral effects and pharmacological actions have been well characterized may be good candidates for further investigations that may ultimately result in clinical use. Ancient Indian systems of medicine (Ayurveda) have classified various herbs for memory stimulation and psychotropic activity. On the basis of this literature and other animal studies a large portion of the herbal extracts and herbal mixtures are investigated for their psychotropic effectiveness.

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