

APPLICABILITY OF EXPLORING UNCONVENTIONAL COGNITIVE ENHANCERS THROUGH EVIDENCE BASED SCIENTIFIC STUDIES – A REVIEW

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ABSTRACT

Cognitive dysfunction is a growing problem of present era, which is mainly due to the Lifestyle modification. Pharmacotherapy is an essential part of disease management pertaining to Nervous system, which requires plant derived molecules. Medhya Rasayana is exclusively meant for increasing intellect or medha, consist four plants like *Mandukaparni* (*Centella asiatica*), *Yashtimadhu* (*Glycyrrhiza glabra*), *Guduchi* (*Tinospora cordifolia*) and *Shankhapushpi* (*Convolvulus pluricaulis*). More Cognitive enhancers in the name of *Smritikara dravya* have been added to the classical literature time to time during *Nighantu* period as well as in folk practices. In this review, an attempt has been made to describe Conventional & unconventionally used natural Cognitive Enhancers with respect to their pharmacology on central nervous system.

KEYWORDS: *Medhya*, Cognition, Neuro-transmitters, Nootropics.

INTRODUCTION

Ayurveda describes *Smriti*, *Medha* and *Vaksiddhi* as the utility of *Rasayana Chikitsa*^[1]. *Medha* and *Prajna* are mainly related with cognition and hence Cognitive enhancers have attained significance in the present circumstances due to increased prevalence of cognitive dysfunction. Cognition is defined as a process of acquiring knowledge & understanding through thoughts, experience & senses. It encompasses processes such as knowledge, attention, learning, memory, judgement, evaluation, reasoning and problem solving. Cognitive dysfunction is a condition in which there will be loss of intellectual functions such as thinking, remembering & reasoning of sufficient severity to interfere with daily functioning^[2]. Patients with

Cognitive Dysfunction have trouble with verbal recall, basic arithmetic & concentration. In India around 13 to 14% of all School going children suffer from learning disorders^[3].

Usage of synthetic cognitive enhancers in children is questionable. More of Nutraceutical products are also prescribed such as proteins, vitamins, omega fatty acids and so on. *Medhya Rasayanam*, a part of *Rasayanachikitsa* deals with improving and preventing intellect and cognitive dysfunctions respectively. Though *purvavaya* (childhood) and *madhyavaya* (early adulthood) is appropriate to start with *Rasayanachikitsa*^[1], exact age of *Medhya rasayanam prayoga* and its activity is ambiguous. *Medhya rasayanam* drugs

described in *Charaka Chikitsa rasayanadhikara* are used conventionally to improve learning and memory process^[4]. Explorations during late Samhita period, Nighantu period, Modern era and also through folk medicine lead to addition of more medicinal plants to Ayurveda Pharmacopoeia. Several herbs have been described in Ayurvedic literature to promote learning, memory and intelligence.

Deforestation and increased demand for Cognitive enhancers have led to decreased availability and supply of herbs, which necessitates new and unknown herbs to be brought in to practice based on evidences. Cognitive enhancers are said to modulate neuronal impulses through neuro-transmitter mechanism either by enhancing or supporting CNS functions. Such medicinal plants which are proven through evidence based scientific studies & practices are listed in this review article along with their possible modus operands.

In Ayurveda, the word *Medhya* is described in much broader sense. *Medha* comprises of three factors – *Dhee* (Intellect), *Dhriti* (Retention), *Smriti* (Memory) and all these factors are inter-related. Stability of *Dhee*, *Dhriti* and *Smriti* is said to be *Medhya karma*^[5]. All these have involvement of *satva*, *rajas* & *tamas*. *Satva* being *manoguna* and *rajasika* and *tamasika* being the *manodoshas*. This *Rajasika* is having *chanchalatva*, which leads to the agitation of mind and *tamasika guna* is having *mandatwa*, which leads to the failure in proper perception. So the main aim here is to achieve the restoration of *satva* in a person.

Medhya can also be subdivided into the following faculties:

1. *Grahanashakti* (Power of Grasping)
2. *Dharanashakti* (Power of Retention)
3. *Vivekashakti* (Power of Discrimination)
4. *Smriti* (Power of recollection)

Medha changes from one person to the other person but still it depends on the *Satvaguna*, so anything which is other than *satvaguna* interferes with Learning and Memory process. To understand the *karmukata* of *medhyadravyas*, modern perspective of Learning & Memory process is needed. Learning and memory process are mediated through nervous system^[6]. Cerebral tissue is the chief site for learning and memory. Learning and memory process depends on conditioning and reflexes. There are different functions of conditioned reflexes.

Causes for Memory Impairment:

Some possible causes^[7] for learning & memory disabilities are Head trauma, brain infection, cerebral tumour, child abuse, drug abuse, poor nutrition, normal pressure hydrocephalus, Vitamin B12 or thiamine deficiency, infrequent participation in mentally or socially stimulating activities, high blood pressure and depression. Measures taken to manage the condition includes assessing the nutritional status of the person, ruling out the active diseases/metabolic impairment, making the subjects to involve in activities and improving quality of life. Sushruta has mentioned about *Buddhimedhakara gana*^[8]. “*Satath adhyayanam vadaha paratantra avalokanam tad vidhya acharyaseva cha buddhi medhakaro ganaha*”, which states that a person should repeatedly practice what, he has learnt. So learning & memory

process will always be the primary phase. Despite repeated attempts, if one cannot retain, drug plays a secondary role here. Pharmatherapy is just an adjuvant in learning & memory process whereas this *Medhakara gana* plays an important role.

Medhya rasayanam :

Medhya rasayanam is group of medicinal plants with multi-fold benefits, specifically given to promote or improve memory/intellect by its *Prabhava* [9] as per Ayurveda. *Medha* is intellect/retention & *rasayanam* is health promoter (helpful on general practice will support sustenance, life span, memory, invulnerability). Therapeutic procedure on regular practice will boost nourishment, longevity, memory and immunity. These drugs can be used in a single or combination form. Factors like attaining longevity, curing diseases, promoting strength, complexion and memory are seen fully or partially in old-age people, so to achieve all these objects this *Medhya rasayanam* will have to be used in young adults.

Charaka has mentioned 4 medhyarasayanam. They are –

1. *Mandukaparni (Centella asiatica)*
2. *Yashtimadhu (Glycyrrhiza glabra)*
3. *Guduchi (Tinospora cordifolia)*
4. *Shankhapushpi (Convolvulus pluricaulis).*

Apart from the medhyadravyas mentioned by charaka, there are few drugs which are seen in common use like *Vacha (Acorus*

Calamus), Brahmi (Bacopa Monerri), Jatamansi (Nardostachys Jatamansi), Kushmanda (Benincasa Hispida) and Jyotishmati (Celastrus Paniculata). Data available so far support pro-cognitive activity of herbs and at the same time it demands substantial evidences & revalidations in humans.

Nootropics^[10], as a smart drug or memory enhancing drugs are compounds that increase mental functions including memory, motivation, concentration and attention. There are two different nootropics: Synthetic, a lab created compound such as piracetam and notable natural and herbal nootropics like Ginkgo biloba and Panaxquinquefolius (American Ginseng). Natural nootropics are proven in boosting the brain function while at the same time making the brain healthier. Nootropics act as a vasodilator against the small arteries and veins in the brain^[11]. Introduction of natural nootropics in the system will increase the blood circulation to the brain at the same time provide the important nutrient and increase energy and oxygen flow to the brain. The administration of nootropics will protect the brain from toxins and minimising the effects of brain aging^[12]. Some natural nootropics are Huperzine A, Bacopa Ginkgo biloba and L- Theanine.

Unconventional drugs indicated as medhya/smritikara as per text but are not common in use are listed in the table below.

SL. NO	DRUGS	BOTANICAL NAME	FAMILY NAME
1.	<i>Vacha</i>	<i>Acorus calamus</i>	<i>Acoraceae</i>
2.	<i>Kushmanda</i>	<i>Benincasa hispida</i>	<i>Cucurbitaceae</i>
3.	<i>Jyotishmati</i>	<i>Celastrus paniculata</i>	<i>Celastraceae</i>
4.	<i>Gambhari</i>	<i>Gmelina arborea</i>	<i>Verbinaceae</i>
5.	<i>Nirgundi</i>	<i>Vitex negundo</i>	<i>Verbinaceae</i>
6.	<i>Jatamansi</i>	<i>Nardostachys jatamansi</i>	<i>Valerianaceae</i>

7.	<i>Dadima</i>	<i>Punica granatum</i>	<i>Punicaceae</i>
<p>There are some drugs which has been scientifically proven to have medhya karma. They are as follows:</p> <ol style="list-style-type: none"> 1. <i>Mandukaparni (Centenalla asiatica)</i> 2. <i>Yashtimadhu (Glycrrhiza glabra)</i> 3. <i>Guduchi (Tinospora cordifolia)</i> 4. <i>Shankhapushpi (Convolvulus pluricaulis)</i> 5. <i>Brahmi (Bacopa monnieri)</i> 6. <i>Jyotishmati (Celastrus paniculata)</i> 7. <i>Kushmanda (Benincasa hispida)</i> 8. <i>Vacha (Acorus calamus)</i> 9. <i>Jatamansi (Nardostachys jatamansi)</i> 10. <i>Ashwagandha (Withania somnifera)</i> 11. <i>Vidanga (Embelia ribes)</i> 	<p>1. <u>Mandukaparni (Centenalla asiatica):</u> <i>Mandukaparni (Centella asiatica</i> Linn.) is a prostrate, stoloniferous perinneal herb establishing at nodes^[13]. New entire plant juice is utilized for helpful purposes as medhya (subjective enhancer)^[14]. Significant constituents are saponin (medacoside, asiaticoside, medacassoside, asiatic corrosive, another triterpenicacid^[15]. They follow up on conduct other than being neuro-protectives^[16] and mind development promoter^[17]. Dendritic arborization should be the neuronal reason for enhanced learning and memory^[18]. <i>Centella asiatica</i> represses the memory impedance incited by scopolamine through the inhibition of Acetyl choline esterase^[19].</p>	<p>glabra has been examined as for spatial learning^[24] free radical scavenging^[25] cerebral ischemia^[26] and anti-oxidant limit towards LDL oxidation^[27].</p>	<p>3. <u>Guduchi (Tinospora cordifolia):</u> <i>Guduchi (Tinospora cordifolia</i> (Wild) Miers) is a huge glabrous, deciduous, climbing bush of Menispermaceae family found all through tropical India^[28]. Juice of entire plant is utilized remedially as Medhya. It is likewise utilized as decoction, powder and Satwa (starch concentrate of stem). <i>Tinospora cordifolia</i> has been professed to have learning and memory enhancing^[29], anti-oxidant^[30,31]. System of intellectual promotion is by insusceptible incitement and expanding the amalgamation of acetylcholine and this supplementation of choline improves the cognition^[32].</p>
<p>2. <u>Yashtimadhu (Glycrrhiza glabra) :</u> <i>Yastimadhu (Glycirrhiza glabra</i> Linn.) is a solid herb or under bush having a place with Fabaceae family^[20]. Fine powder of dried root is utilized for restorative reason as medhya. Potent phyto-chemicals are glycyrrhizine, flavonones^[21], isoflavones, glycyrrhethenic acid^[22] and six phenolic compounds^[23]. The roots and rhizomes of G.</p>	<p>1. <u>Shankhapushpi(Convolvulus pluricaulis):</u> <i>Shankhapushpi (Convolvulus pluricaulis)</i> is an enduring, prostate or sub-erect spreading bristly herb^[33], found all through India. Shankhapushpi enhances memory function due to its Antioxidant and Acetylcholinesterase Inhibitory Properties^[34]. Often viewed as Medhya (acumen promoter. Shankhapushpi compound containing Shankhapushpi, Sarpagandha, and Gokshura in measure up to quantities concentrated to be successful in Chittodvega (tension disorders)^[35]. Botanists trust that Shankhpushpi calms the nerves by modulating the synthesis of hormones like adrenaline and cortisol^[36].</p>	<p>2. <u>Brahmi : (Bacopa monneri)</u> <i>Aindri (Bacopa monneri)</i> ordinarily called as Brahmi has a place with Scrophulariaceae family^[37]. It is a little, crawling muddy herb</p>	<p>1. <u>Shankhapushpi(Convolvulus pluricaulis):</u> <i>Shankhapushpi (Convolvulus pluricaulis)</i> is an enduring, prostate or sub-erect spreading bristly herb^[33], found all through India. Shankhapushpi enhances memory function due to its Antioxidant and Acetylcholinesterase Inhibitory Properties^[34]. Often viewed as Medhya (acumen promoter. Shankhapushpi compound containing Shankhapushpi, Sarpagandha, and Gokshura in measure up to quantities concentrated to be successful in Chittodvega (tension disorders)^[35]. Botanists trust that Shankhpushpi calms the nerves by modulating the synthesis of hormones like adrenaline and cortisol^[36].</p>

become all through India^[38]. Most advantageous helpful shape is macerated entire plant juice. Properties are said to be like that of Mandukaparni^[39]. *Bacopa monneri* is a notable nootropic plant known for its memory enhancer^[40]. Neuroprotective action might be credited to having its reactive oxygen species neutralizing property^[41]. *Bacopa monniera* is a saponin rich plant^[42]. Bacosides are the fundamental active nootropic compound present in the alcoholic extract of the plant^[43]. It is predominantly used in the treatment of memory related disorders^[44].

3. **Jyotishmati : (Celastrus panniculata)**

It is an extensive, woody, climbing bush with praise or obovate leaves and found all over India. Seeds are yellowish, ellipsoid or ovoid encased in a red aril^[45], Seed oil (Jyotishmati Taila) is known for Medhya action^[46]. Seed oil of *Celastrus panniculata* (Malkangni) switched scopolamine-actuated deficiencies memory impaired young rats^[47].

4. **Kushmanda :(Benincasa hispida)**

Kushmanda (Benincasa hispida) having a place with Cucurbitaceae, a broad trailing or climbing herb grown all through the fields of India as a vegetable^[48]. The organic product, extensively tube shaped, is secured with a waxy bloom^[49]. Phytochemical investigation of *Benincasa hispida* indicates presence of alkaloids, flavonoids, saponins and steroids^[50]. Kushmandadi Ghrita demonstrated noteworthy outcomes in the administration Chittodvega (tension disorders)^[51].

5. **Vacha :(Acorus calamus)**

Vacha (Acorus calamus) of Araceae family is a semiaquatic, perpetual, fragrant herb with its rhizome being even, to some degree

vertically compressed and found all over India^[52]. Rhizome is valuable part having Medhya quality. It has been utilized in Indian and Chinese system of medication for many years to fix sicknesses particularly the focal sensory system (CNS) abnormalities^[53,54].

6. **Jatamamsi (Nardostachys jatamamsi)**

It is an erect perpetual fragrant herb with long, strong, woody, grayish, rhizomatous, tail-like rootstock secured with rosy dark colored hairs or tufted sinewy stays of the petioles of shriveled radical leaves^[55], and has a place with Valerianaceae family. Rhizome is utilized for restorative purposes as it is Bhutaghna or Manasa Doshahara (mitigates of mental issues) and Medhya^[56]. Rhizomes contain a terpenoid ester, nardostachysin I^[57]. It is demonstrated to enhance learning and memory in mice^[58] and furthermore to upgrade biogenic amine activity^[59].

7. **Ashwagandha (Withania somnifera) :**

Mood stabilizer in clinical states of uneasiness and melancholy, reverses social deficiencies and pathology found in Alzheimer's ailment models.

8. **Vidanga (Embelia ribes) :**

Defence against MCAO-initiated central cerebral ischemia in rats and shows neuroprotective action, valuable assistant in the treatment of stroke.

Apart from above mentioned herbs, plants like *Nirgundi (Vitex negundo* Linn) and *Gambhari (Gmelina arborea)* have been tested for their role on learning and memory process experimentally and clinically^[60,61,62,63]. **Leaves of Nirgundi and fruits of Gambhari** have exhibited promising outcomes with respect to memory

related tasks. Mode of pharmacological activity is still unclear, but on the basis of primary phyto-chemical analysis, it can be emphasized that the anti-oxidant compounds present in these plants may be responsible for memory promotion.

DISCUSSION:

Medhya is the *prabhavajanya karma* and hence exact mode of action based on *Rasapanchaka* is difficult to explain. Even in modern science, many modes of actions have been explained about cognitive enhancers, which may be adapted to the herbal drugs. Plant based drugs having lots many phyto-constituents exert multi dimensional activities on body including nervous system. Though *Medhya Rasayana dravyas* have been explained in early classical literature, plants added later during medieval period are not been given proper attention in medical practice. Difficulty in availability and also regional variations necessitates the usage of un-conventionally used plants to be brought in to practice based on scientific evidences.

Ultimately maintaining harmony between different parts of central nervous system will be basic requirement in learning and memory process. Such functions can be understood based on *Shareerika Dosha* and *Manasika bhavas* such as *Tridosha* and *Satvadi bhavas* respectively. *Vata dosha* being the important factor in co-ordinating other factor of the body plays a pivotal role in learning and memory. Stability and control over *vata dosha* is utmost important to maintain the activities of other doshas like *Pitta* and *Kapha*. *Sadhaka Pitta* and *Tarpaka kapha* are the one which play rather important role in the functions of *Mastishka*.

Satva guna of *manas* maintains harmony of *mano karma* like *Dhee*, *Dhruthi* and *Smriti*. *Mano doshas* like *Rajas* and *Tamas* disrupt the functions of *Manas*. Hence maintaining *satvika guna* becomes essential. Medicinal plants used for *medhya* activity may be having their role to play over *Shareerika* and *Manasika Doshas*. Most of the drugs have either *vata pittahara* or *vata kaphahara* actions, which needs to be chosen wisely during treatment.

Nootropics are the word used for memory enhancers derived from natural origin. Such products even have food value and hence may be used regularly in day to day life. Recent studies conducted on *Nirgundi* and *Gambhari* have suggested the nootropic value of such plants. *Nirgundi* though doesn't have much food value, literature based studies reveal that the usage of its fruits in the cooked form for consumption. Further studies based on neuro-transmitters may throw more light on the possible mode of action of such plants. Recent studies have suggested the role of GABA receptors^[64] in maintaining the balance among stimulation and inhibition of neuronal activities. Future studies on unconventional memory enhancers needs to be focused on Nutraceutical perspective as well as on neuronal regenerative capabilities.

CONCLUSION:

It is very unfortunate that in spite of advancements in modern medicine today its success is very limited in context with neurological and psychiatric disorders due to multi-factorial nature of these diseases. Therefore, the concept of modern medicine based therapy for treatment of such patients may be more effective when based on

psychoactive drugs. Hence, the need to explore medicinal plants globally for improving cognitive function owing to their less adverse effects is must today so as to overcome the cognitive deficit diseases. The above said herbs act on the basis of antioxidant, adaptogenic or essential trace elements present in them. Their activity on modulation of biological axis and neurotransmitters requires further investigation.

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Source of support: Nil,

Conflict of interest: None Declared

Cite this article as

Satish Pai: Applicability of Exploring Unconventional Cognitive Enhancers Through Evidence Based Scientific Studies – A Review; *ayurpub*; IV(6): 1412-1422