Review Article

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RELEVANCE OF CHARAKOKTA MEDHYA RASAYANA FOR PREVENTION AND MANAGEMENT OF DEMENTIA: A REVIEW

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ABSTRACT

Ageing includes not only the physical deterioration but also the mental and emotional difficulties. Mental health is a critical aspect of overall well-being for older adults. As per WHO, over 55 million people worldwide suffer with dementia. Currently the seventh most common cause of mortality worldwide, dementia is also a major contributor to impairment and dependency among the elderly. While age remains the most significant known risk factor for dementia, up to 9% of cases are young onset dementia, which is characterized by the beginning of symptoms before the age of 65 years. Acharya Charaka in Rasayana Chikitsa Karaprachitiya Rasayana Pada mentioned Mandukaparni Swarasa, Guduchi Swarasa, Yashtimadhu Churna and Shankhapushpi Kalka for rejuvenation of mind, and has termed them as Medhya Rasayana. Renowned for their impact on the central nervous system, these herbs can regulate neurotransmitters and offer neuroprotective advantages. The drugs of Medhya Rasayana exhibit antioxidant, antidepressant, memory enhancing, nootropic properties. These drugs stimulate the production of new brain cells, improves blood flow throughout the brain, modifies neurotransmitter concentrations, reduces inflammation in the brain, and protects the brain from free radical damage. These properties may contribute to the prevention and management of dementia.

Keywords: Dementia, Rasayana, Medhya Rasayana, Charaka

INTRODUCTION

Dementia is a clinical syndrome characterised by a loss of previously acquired intellectual function in the absence of impairment of arousal. Nearly 5% of people aged over 65 years and 20% over 85 years of age are commonly affected by dementia[1]. A rapidly expanding public health concern, approximately 9.9 million people suffer from dementia each year, with the majority of these individuals (63%) living in low- and middle-income nations[2]. An essential component of older persons' general wellbeing is their mental health. The aging process causes several structural, molecular, cellular, and functional changes in the brain. Significant neuron loss and decreased production of neurotransmitters such as glutamate, acetylcholine, and dopamine contribute to the development of plaques and tangles. Additionally, the buildup of lipofuscin in nerve tissue leads to nerve degeneration[3]. Mental health issues including Anxiety, Depression, and cognitive problems like Dementia can all be influenced by these factors. It can have a catastrophic impact on physical, psychological, social and economic well-being of not only of those who are affected but also their caretakers, and their families[4].

The idea of Jara, or aging, in Ayurveda includes not only the physical deterioration but also the mental and emotional difficulties that come with growing older. Charaka Samhita[5] and Ashtanga Hridaya[6] has mentioned Jaravastha or Vriddhavastha (old age) after age of 60 years while Sushruta Samhita[7] and Ashtanga Sangraha[8] after 70 years. Various degenerative alterations, such as Balahani (loss of physical strength), Varnahani (Diminished color or complexion), Indriya Daurbalya (loss of strength of sensory faculty) etc., are present in this stage. The Vata Dosha become prominent in older age, leading to decline of various anatomical structure and cognitive abilities[4]. As per Ayurveda, the main cognitive function of the brain (Medha) begins to diminish by the 40th year of life, and beyond the 80th year, the loss of Buddhi (intelligence), or the ability to make decisions occurs. Acharya Charaka describes the benefits of Rasayana Chikitsa, which helps regenerate Dhatu (body tissues/structural components) and hereby checks the Jaravastha[9].

The Rasayana is the most advanced form of preventive application specific to age, disease, climate etc. Rasayana enhances metabolic functions, facilitating optimal biotransformation and the production of superior-quality tissues (dhatus). This process effectively mitigates the onset of senility and other age-related disorders. The term Rasayana specifically refers to 'drugs, diet, and regimens' that enhance longevity by slowing the aging process and preventing diseases[10]. Rasayana is said to have both preventive and therapeutic effect on Jara and Vyadhi[11]. In Chikitsa Sthana- Rasayana Adhyaya 3rd Pada (Karaprachitiya Rasayana)[12], Acharya Charaka has mentioned Medhya Rasayana consisting of Mandukaparni (*Centella asiatica*) Swarasa, Yashtimadhu (*Glycyrrhiza glabra*) Churna, Guduchi (*Tinospora cordifolia*) Swarasa and Shankhapushpi (*Convolvulus pluricauris*) Kalka. All these drugs of Medhya Rasayana exhibit antioxidant, antidepressant, memory enhancing, nootropic properties. These herbs are renowned for their actions on the central nervous system, which include balancing neurotransmitters and offering neuroprotective benefits. These attributes are instrumental in the prevention and management of dementia.

This review explores the efficacy of Charakokta Medhya Rasayana, which includes herbs such as Guduchi, Yashtimadhu, Mandukaparni and Shankhapushpi in improving cognitive functions, reducing anxiety, and enhancing memory.

Prevalence of Dementia

An individual's level of mental health is determined by a multitude of social, psychological, and biological elements at any one time[13]. The term "Dementia" refers to a syndrome of cognitive impairment that impairs memory, cognitive function, behaviour, and greatly impairs an individual's capacity to carry out everyday tasks. The most prevalent type of dementia, accounting for 60–70% of cases, is Alzheimer's disease. Globally, there are about 50 million people suffering from dementia; this figure is expected to rise to 82 million by 2030 and 152 million by 2050. It ranks eighth in terms of primary cause of death and is the second most common cause of disability for people 70 years of age and beyond[2]. In India, 7.4% people aged 60 years or older are estimated to be suffering from dementia (8.8 million individuals) and prevalence of age standardized dementia is found to be 8.0%[14]. While age remains the most significant known risk factor for dementia, up to 9% of cases are young onset dementia, which is characterized by the beginning of symptoms before the age of 65 years[4]. Several urban studies in India reveal varied rates of Alzheimer's disease, with rates ranging from 2.44 to 4.1% in West India, 1.83% in North India, 0.8-1.28% in East India, and 3.6% in South India[15]. Alzheimer's disease has been studied in North India; the incidence was found to be 4.7 per 1000 person-years, while the Monongahela Valley in the United States had 17.5 per 1000 person-years among those aged 65 years and older[16].

REVIEW OF DRUGS OF MEDHYA RASAYANA

Acharya Charaka has mentioned Medhya Rasayana in Rasayana Chikitsa in Chikitsa sthana. It comprises of Mandukaparni, Guduchi, Madhuyashti and Shankhapushpi as depicted in Table 1.

Table 1: The drugs of Charakokta Medhya Rasayana

Drug	Botanical Name	Dosage Form
Mandukaparni	*Centella asiatica*	Swarasa (Expressed juice)
Guduchi	*Tinospora cordifolia*	Swarasa (Expressed juice)
Madhuyashti	*Glycyrrhiza glabra*	Churna (Powder)
Shankhapushpi	*Convolvulus pluricauris*	Kalka (Paste)

Mandukaparni

Commonly known as Indian pennywort, Mandukaparni *(Centella asiatica)* belongs to family Apiaceae. It is a perineal herb and grows wildly in wet conditions.

Terpenoids like triterpenes, asiaticoside, centelloside, brahmoside, asiaticentonic acid, centellic acids, madecassic acid and flavonoids like kaempferol, castilliferol, quercetin, apigenin constitutes the phytochemistry of Mandukaparni. Pharmacological activity consists of anti-inflammatory, anti-oxidant, antidepressant, memory enhancing, neuroprotective, antiepileptic and immunomodulatory potentials[17].

Related Pharmacological Researches

Mandukaparni simultaneously decreases beta wave activity and boosts alpha wave activity of Central Nervous System. A higher level of alpha wave activity in the EEG has been linked to a state of body and mind relaxations and decreases mental fluctuations. As a result, an improvement in overall mental health and the concentration activity improvement was observed[18]. *Centella* components may expedite the healing of damaged neurons due to the plant's capacity to accelerate nerve regeneration following oral administration and the existence of multiple active fractions that promote neurite elongation *in vitro* [16]. Mandukaparni along with Guduchi was found to reduce the stress induced rise in corticosterone level in blood, hereby preventing the hypothalamus-adrenal-pituitary axis, rationalising the use for their tonic properties[19]. A study by S. Mukharjee *et al* demonstrated 46% Nitric Oxide (NO) scavenging activity of ethanolic extract of *Centella asiatica* at concentration of 1000 µg/ml *in vitro.* NO, a free radical found in tissues and organ systems, is thought to play an important function in neuromodulation and as a neurotransmitter in the central nervous system[20]. In rats treated with *Centella asiatica* leaf extract, hippocampal CA3 (cornu ammonis region, a key structure of the brain involved in learning and memory) neuronal dendritic examination revealed increased length and branching in both apical and basal dendrites[21]. *Centella asiatica* suppresses acetylcholinesterase (AChE), which induces scopolamine, preventing memory impairment. It also improves neurotransmitter levels, including 5HT, acetylcholine (ACh), epinephrine, nor-epinephrine, GABA, and glutamate. Research indicates that it enhances mental performance and reduces fatigue in stress-related situations[22]. *Centella* has been shown to promote nerve regeneration and neurite elongation *in vitro*, implying that its components could aid in the repair of injured neurons[23]. Mandukaparni also improves brain cell oxygenation and glucose utilization. Improved blood circulation leads to improved psycho-stimulation, improving cognitive functions such as memory, intelligence, and learning[17].

Guduchi

Commonly known as Giloy, Amrita or Gurcha, Guduchi is a large, glabrous, deciduous climbing shrub. It is found throughout tropical India[24].

Alkaloids like berberine, magnoflorine, choline palmatin, tembetarine, tinosporine, isocolumbin, Glycosides like tinocordiside, tinocordifolioside, cordioside, 18-norclerodane glucoside, palmatosides, cordifoliosides, Aliphatic compounds like heptacosanol, octacosanol, nonacosan-15-one dichloromethane constitute the phytochemistry of Guduchi. Pharmacological properties include immunomodulatory, neurological, anti-inflammatory, anti-microbial nature[25].

Related Pharmacological Researches

The methanolic extract of *Tinospora cordifolia* inhibited actylcholinesterase and improved cognitive function[26]. Berberine, an alkaloid found in Guduchi, has been shown to alleviate neurodegenerative disorders, including Alzheimer's disease (AD). AD is characterized by amyloid beta (Aβ) accumulation, tau hyperphosphorylation, and neuronal loss. Berberine and its derivatives were discovered *in vitro* to reduce Aβ aggregation and acetylcholinesterase (AchE) activity. It could mitigate Aβ-induced cell toxicity by improving cell viability and preventing apoptosis. It also inhibited tau hyperphosphorylation in HEK293 cells most likely by boosting the activity of protein phosphatase 2A and preventing the activation of GSK-3β (glycogen synthase kinase-3β)[27]. Another study by Subarna Pokhrel *et al*. demonstrated that synergistic effects for AChE inhibition were shown when combinations of the alkaloids palmatine and berberine were used indicating the synergism of the isoquinoline alkaloids likely responsible for the AChE inhibition induced by the *Tinospora cordifolia* methanolic extract[28]. A study by Ashutosh Agarwal *et al*. depicted that *Tinospora* extract improves cognition in normal rats and effectively reverses cyclosporin-induced memory deficit and also reverses cyclosporin induced hippocampal neuronal degeneration[29]. Another study delineates that *Tinospora cordifolia, Rubia cordifolia* and *Fagonia cretica* exert cell/neuroprotective effects by reducing oxidant levels by direct scavenging, reducing iNOS (Inducible nitric oxide synthase) expression, enhancing the antioxidant gene Cu-Zn superoxide dismutase (Cu-Zn SOD), and preventing the depletion and raising glutathione (GSH) levels by stimulating GCLC gene expression[30]. A study by Rachna Mishra *et al.* evidenced that in sleep deprived animals, 50% ethanolic extract of *Tinospora cordifolia* (TCE) reduced anxiety-like behavior and enhanced exploratory behavior. Also, TCE regulated the expression of proteins related to the maintenance of Long-Term Potentiation and synaptic plasticity and slowed down the inflammatory response of neurons and glial cells thus exhibiting Nootropic potential[31]. *Tinospora cordifolia* ethanolic extract raised dopamine in a rat model of Parkinson's disease produced by 6-hydroxydopamine (6-OHDA). Reduced oxidative stress and improved locomotor activity provided additional evidence of neuroprotection[32].

Madhuyashti

Liquorice, commonly known as Mulethi or Yashtimadhu, belonging to family Fabaceae is a hardy herb or undershrub attaining height up to 2 m. It is distributed in sub-tropical and warm temperate region of world[33].

The roots include bioactive substances like glycyrrhizin (about 16%), sugars (up to 18%), flavonoids, saponins, starches, gums, and essential oils. Licorice roots contain 25-30% starch, 3-10% D-glucose, sucrose, 3-5% glycyrrhizin, and trace amounts of flavonoids, saponins, sterols, and amino acids. It also contains phenolic compounds (e.g., coumarin compounds, glycerol, glycerine, glycy coumarin, herniarin, umbelliferone, licopyrano coumarin, licoarylcoumarin, and licocoumarone), amines (1-2% asparagines, betaine, and choline), amino acids, and sterols (stigmasterol and β-sitosterol)[34].

Related Pharmacological Researches

Mulethi is a powerful nervine that helps to revitalize the brain. Mulethi has a calming and relaxing effect by stimulating cerebral functioning during stressful situations. Mulethi regulates blood sugar levels and improves circulation to the central nerve system[35]. The antioxidant quality of aqueous root extract of *Glycyrrhiza glabra* may be responsible for the neuroprotective action, since it reduces oxidative stress on vulnerable brain cells, hence improving neuronal function and minimizing brain damage. In a study, when three-month-old rats were administered aqueous root extract of *Glycyrrhiza glabra* at different doses (75, 150, and 300 mg/kg, p.o.) for four weeks, their memory improved as seen by a decrease in Transfer Latency when compared to control rats. Additionally, the mice were shielded against learning and memory impairment caused by interoceptive stimuli (Diazepam) by a 4-week pretreatment with aqueous root extract of *Glycyrrhiza glabra*[36]. An additional investigation revealed that the aqueous root extract of *Glycyrrhiza glabra* at 150 and 225 mg/kg/p.o. significantly ($P<0.01$) increased dendritic intersections and arborization in hippocampal CA3 pyramidal neurons. The increased learning and memory in the hippocampus CA3 pyramidal neurons may be due in part to changes in synaptic connections caused by an increase in dendritic arborization and dendritic intersections[37]. The anti-inflammatory properties of licorice may possibly play a role in its memory-boosting effects. When given orally for seven days, 150 mg/kg of liquorice extract markedly improved the learning and memory of mice in both of the exteroceptive behavioural models used. The rats were shielded against learning and memory impairment caused by interoceptive stimuli (scopolamine and diazepam) by a seven-day pretreatment with liquorice extract (150 mg/kg)[38]. These findings suggested the prospect of licorice having neuroprotective qualities.

Shankhapushpi

Shankhapushpi belonging to family Convolvulaceae is a perineal, prostate or sub-erect, spreading hairy herb, commonly found in Gujarat, Rajasthan, Punjab, Bihar, some parts of Maharashtra and Madhya Pradesh[39].

Convolvine, convolamine, phyllabine, convolidine, confoline, convoline, subhirsine, convosine, and convolvidine are the main phytoconstituents, together with scopoline and β-sitosterol[40]. Pharmacological activities include antioxidant, anticonvulsant, antidepressant, anxiolytic, memory enhancer, neuroprotective and nootropic activities[41].

Related Pharmacological Researches

Shankhapushpi is a nootropic that improves brain function and memory by improving oxygen supply and blood flow to the brain. This increases nutrient supply and stimulates nerve growth [42]. Shankhapushpi may improve memory by two different mechanisms: either by acting as a muscarinic agonist and reducing the production of β-amyloid, or by altering the amount of acetylcholine in the brain by either increasing its synthesis or suppressing the acetylcholinesterase enzyme[43]. Shankhapushpi is advised for nervous system conditions like tension, anxiety, mental exhaustion, and sleeplessness. According to certain theories, Shankhapushpi calms the body by controlling the release of stress hormones, cortisol and adrenaline[44]. It has also been discovered that the alkaloid convolvine blocks the M2 and M4 cholinergic muscarinic receptors (inhibitory autoreceptors that inhibits Ach release). Additionally, convolvine helps to augment the effects of arecoline, another muscarinic memory enhancer, giving *Convolvulus prostatus* nootropic benefits[45]. According to a recent study, it prevents Aβ accumulation in the brain, which guards against memory loss in Alzheimer's Disease. Additionally, it increases the activity of antioxidant enzymes and regulates tau-induced oxidative stress via restoring the activity of acetylcholinesterase[46]. Polyphenol-like flavonoids found in *Convolvulus pluricaulis* may contribute to the lowering of τ hyperphosphorylation and attenuate multiple Alzheimer's Disease pathways, including ROS production, LPO, DNA fragmentation, caspase activation, and Aβ accumulation. Amyloid-β precursor protein (AβPP), Aβ production, and τ protein and mRNA levels are all decreased in rats treated with *Convolvulus pluricaulis*[47].

DISCUSSION

Dementia is a global disease with approx. 9.9 million people suffering worldwide. It is a syndrome characterized by the gradual destruction of nerve cells and brain damage, usually with a decline in cognitive ability[4]. Dementia is more common in adults but prevalence of young onset dementia is alarming, affecting nearly 9% population worldwide. Dementia is characterised by progressive loss of memory, followed by impaired mental abilities, including language, judgement, and planning, can lead to difficulties with daily activities[14]. There is presently no known treatment for the crippling illness known as dementia, only the symptoms can be managed through various medicaments like Cholinesterase inhibitors (donepezil), NMDA receptor antagonists (memantine), medicines for hypertension to prevent any additional damage to brain etc[4].

In Ayurveda, Medhya Rasayana is the term mentioned for the drugs promoting Medha (intellect) and Smriti (memory). Acharya Charaka has mentioned use of Mandukparni Swarasa, Yashtimadhu Churna, Guduchi Swarasa and Shankhpushpi Kalka as Medhya Rasayana. The Medhya Rasayana are medicaments specific to brain and nervous system, claimed to promote cognitive functions of brain, enhance neurotransmitter production and having nootropic properties. These drugs stimulate the production of new brain cells, improves blood flow throughout the brain, modifies neurotransmitter concentrations, reduces inflammation in the brain, and protects the brain from free radical damage[48]. Mandukaparni, Mulethi enhances the use of glucose and oxygen in brain cells, providing fuel for its adequate functioning. Also, sufficient blood glucose levels promote the synthesis of neurotransmitters, which are critical for neuronal communication[49]. Adequate oxygen supply is important to prevent the brain from oxidative stress and maintain neuronal health thereby preventing any damage to the neurons.

Mandukaparni exhibited NO scavenging activity and Guduchi inhibits iNOS expression, restricting production of nitric oxide (NO). NO free radical reacts with superoxide radical to form toxic peroxynitrite anion (ONOO-), which then reacts with tissue or bodily fluid to produce nitrotyrosines[19]. This nitrotyrosine is a marker for oxidative stress and is linked to neurodegenerative disorders[50]. Mulethi and Shankhapushpi also exhibit antioxidant properties, reducing oxidative stress on brain cells, hence, reducing brain damage and enhancing neural function. They also inhibit AChE activity, an enzyme responsible for breakdown of ACh, leading to lower levels of ACh in brain. ACh is essential for cognitive processes, as it promotes effective neuronal connection in the brain, which improves learning, memory formation, and attention. Inhibition of AChE activity reduces ACh breakdown ensuring optimal amount of ACh and thus improved cognitive ability of brain.

An essential neurophysiological mechanism involved in brain network formation and rearrangement following damage is synaptic plasticity, which is the capacity of neurons to change the strength of their connections[51]. Synaptic plasticity is the capacity of synapses to change over time in response to variations in their activity level, either becoming stronger or weaker. Synaptic plasticity is one of the key neurochemical aspects of learning and memory since memories are thought to be represented by intricately linked neuronal circuits in the brain[52]. By providing vital nutrients and bioactive substances that maintain brain health, Medhya Rasayana is essential in promoting synaptic plasticity. These anti-inflammatory, nootropic Ayurvedic herbs promote neurotransmission, minimize neural inflammation, reduce the oxidative stress to the brain, enhancing learning, memory, and cognitive flexibility.

CONCLUSION

The present review depicts about the Medhya Rasayana described in Rasayana Chikitsa of Charaka Samhita Chikitsa Sthana. The phytoconstituent of the drugs of Medhya Rasayana and their therapeutic potentials as concluded in various research studies have been compiled in the review. This article concluded that the drugs of Medhya Rasayana can be useful in prevention and management of Dementia by virtue of their antioxidant, antidepressant, memory enhancing, nootropic properties.

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