

ASHTANG GHRITA: A NOBLE AYURVEDA DRUG FOR CENTRAL NERVOUS SYSTEM

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ABSTRACT:

Brain and mind disorders include a wide range of common neurological and psychiatric illnesses. They afflict a very significant portion of the population, right across the life span. Ayurveda has a deep insight about the treatment of the problems of the nervous system. The study was done with the aim to review the CNS protective and neurotropic activity of an Ayurveda drug *Ashtang Ghrita*. Contents of *Ashtang Ghrita* have been found to be effective against number of CNS disorders including Alzheimer's disease, Parkinsonism, Epilepsy, ADHD, Cerebral palsy etc. by their antioxidant, neurotropic, nerve regenerating, regularization of neurotransmitter etc. properties and also the drug is in the Ghee form hence by virtue of its lipid soluble property it can cross Blood brain barrier (BBB) thus proving as an effective drug for CNS. Toxicological analysis also proves the drug to be absolutely safe for use. The contents of the drug also possess properties of an effective nervine tonic by means of their endeavor in improving memory and intellect. Thus *Ashtang Ghrita* can prove to be a good neurotropic drug both as a prophylactic and curative medication for various CNS disorders and as a nervine tonic among children.

Key Words: *Ashtang Ghrita*, CNS Protective, Neurotropic.

INTRODUCTION:

The human central nervous system (CNS) is the most complex organ. It determines our most unique human function, namely, consciousness. Its activity underlies all aspects of our behavior from basic requirements such as breathing to supporting our thoughts and feelings^[1]. Brain diseases can result directly from intrinsic dysfunction of the brain or from complex interactions between the brain and the physical environment^[2]. Brain and mind disorders include a wide range of common neurological and psychiatric illnesses. They afflict a very significant portion of the population, right across the life span, and are prevalent in both developed and developing countries. Likewise, these diseases pose the largest health, economic and social capital burden worldwide of any disease group^[3]. Brain and mind disorders actually affect as many as 1.5 billion people worldwide, and the number is expected to increase. No less than 25% of the total burden of disease in the established market economies is at present attributable to brain and mind disorders^[4]. Indeed, the proportionate share of the total global burden of disease due to neurologic disorders is projected to rise to 14.7% by 2020^[5], highlighting an urgent need for more drugs to treat CNS disorders.

Drugs acting in the central nervous system (CNS) were among the first to be discovered by primitive human and are still the most widely used group of pharmacological agents. The CNS acting drugs are

invaluable therapeutically as they can produce specific physiological and psychological effects. From the vast array of material medica of the indigenous system, many plants have been reported to have activity against CNS disorders and act as very useful remedies for the alleviation of human suffering^[6]. Ayurveda has a deep insight about the treatment of the problems of the nervous system. The classical Ayurveda text have explained many nervous disorders with due emphasis on their management both prophylactically and curative and for improvement of intellect and memory. One such drug explained in a well-known Ayurveda text *Ashtang Hridya* called as *Ashtang Ghrita* have been reviewed in the present study for its action on CNS as an medication for various CNS disorders and as an nervine tonic.

AIM AND OBJECTIVES:

This review aims at scanning the scattered literature on the CNS protective and neurotropic action of the

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Access this article online: www.jahm.in

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Received on: 26/04/15, Revised on: 02/05/15, Accepted on: 19/05/15

contents of Ayurveda drug *Ashtang Ghrita* and to provide their scientific evidences, so that the information can be used for planning further clinical studies and it can be inculcated as major prescribed medication for CNS problems among children and adults both as curative and preventive medication.

METHOD:

Classical texts of Ayurveda as well as PUBMED, MEDLINE database were used for the search of relevant literature and research papers. Papers published between Jan 1960 to Jan 2015 were only considered. The key words used for the search was 'Ayurveda', 'Nervous System', 'Neuroprotective', 'neuro-regeneration' and 'Memory enhancer' etc. In-vitro analysis, experimental trials as well as clinical studies were included in the review to search out the reported therapeutic potential of Ayurveda drugs. Only research articles published in English language were considered.

Ashtang Ghrita:

It is mentioned in one of the classic Ayurveda text, *Ashtang Hridaya*, as a nervine tonic especially for children. It is mentioned for making the child *dhanyam* (Blessed, healthy), *Aayushyam* (long salubrious life), *vaak* (improves speech), *Medha* (Improves intelligence),

Smriti (Improves memory) and *Buddhikrita* (improves cognition, perception and/or comprehension)^[7].

Table 1: Showing constituents of Ashtang Ghrita

S.No.	Name	Botanical Name	Parts Used	Ratio
1.	<i>Vacha</i>	<i>Achorus calamus</i>	Root	1
2.	<i>Bakuchi</i>	<i>Psorelia corelifolia</i>	Seed	1
3.	<i>Vidhara</i>	<i>Argyreia Speciosa</i>	Seed	1
4.	<i>Shankhpushpi</i>	<i>Convolvulus pluricaulis</i>	Complete plant	1
5.	<i>Shatavari</i>	<i>Asparagus racemosus</i>	Root	1
6.	<i>Mandukaparni</i>	<i>Centella asiatica</i>	Complete plant	1
7.	<i>Brahmi</i>	<i>Bacopa monnieri</i>	Complete plant	1
8.	<i>Guduchi</i>	<i>Tinospora cordifolia</i>	Stem	1

All contents in equal quantity with Cow ghee four times that of a content and Cow Milk four times that of Cow ghee.

Table 2: Ayurvedic Pharmacological properties of the contents of Ashtang Ghrita.

S.No.	Ayurvedic Text	Rasa	Guna	Virya	Vipaka	Doshaghnana
1.	<i>Vacha</i>	<i>Katu, Tikta</i>	<i>Ruksha, laghu</i>	<i>Ushna</i>	<i>Katu</i>	<i>Kaphavata har</i>
2.	<i>Bakuchi</i>	<i>Kashay, tikta</i>	<i>Laghu</i>	<i>Sheet</i>	<i>Katu</i>	<i>Pittakaphahar</i>
3.	<i>Vidhara</i>	<i>kashay, Tikta</i>	<i>Sara</i>	<i>Ushna</i>	<i>Katu</i>	<i>Kaphavatahar</i>
4.	<i>Shankhpushpi</i>	<i>Katu, Tikta</i>	<i>Sara</i>	<i>Ushna</i>	<i>Katu</i>	<i>Pitta har</i>
5.	<i>Shatavari</i>	<i>Madhur, Tikta</i>	<i>Sheet, Guru</i>	<i>Sheet</i>	<i>Madhur</i>	<i>VataPitta Har</i>
6.	<i>Mandukaparni</i>	<i>Tikta, kashay, Madhur</i>	<i>Laghu</i>	<i>Sheet</i>	<i>madhur</i>	<i>Vatapitta har</i>
7.	<i>Brahmi</i>	<i>Kashaya Tikta</i>	<i>Sara, Laghu</i>	<i>sheeta</i>	<i>Madhur</i>	<i>Sarvadosha</i>
8.	<i>Guduchi</i>	<i>Katu tikta</i>	<i>Laghu</i>	<i>Ushna</i>	<i>Madhur</i>	<i>Tridosh har</i>

Vacha (*Achorus calamus*): Alcoholic extract of the plant have anticonvulsant action^[8]. High concentration of β -asarone enhances the GABA_A receptor, and thus have a good role as anti convulsant^[9]. Treatment with ethanol: water (1:1) extract of rhizome of drug increases the level of GSH (glutathione) content and GST (glutathione-S-transferase) activity in corpus striatum while dopamine receptor decreases compound with *Acorus* treated rats^[10]. It has demonstrated neuro-protective effects in the middle cerebral artery occlusion-induced ischaemia in rats^[11]. It have been found that vacha does improve cognition, in many trials over animals^[12]. Clinical trials have also shown it to

enhance memory^[13] in recent studies. Anti-amnesiac effects have been established of high dose β -asarone (constituent of *Acorus*)^[14]. Recent studies have shown Phenolic compounds present in the plants are capable in scavenging free radical and it shows antioxidant activity^[15]. As per studies Generation of reactive oxygen species, calcium channel over-activation and inflammation are major culprit in the axonal degeneration, *Acorus* has anti-oxidative, anti-inflammatory and neuroprotective actions, voltage activated calcium channel and also it is an important factor in attenuating peripheral neuropathic pain^[16].

Bakuchi (*Psoralea corylifolia*): Seeds of *Psoralea corylifolia* L. (Leguminosae), was found to strongly inhibit dopamine (DA) uptake by dopamine transporter (DAT) heterogeneously expressed cells (D8 cells) and noradrenaline (NE) uptake by noradrenaline transporter (NET) heterogeneously expressed cells, Hence can be effectively used in depression, Attention Deficit Hyperactivity Disorder (ADHD) and many other CNS disorders [17]. Adult neural stem cells (NSCs) persist throughout life to replace mature cells that are lost during turnover, disease, or injury. The investigation of NSC creates novel treatments for central nervous system (CNS) injuries and neurodegenerative disorders. Recent study have shown that Psoralen could effectively regulate the specific gene expression profile of NSC [18]. Studies have shown that *P. corylifolia* seed extracts stimulate mitochondrial respiration with uncoupling and induce an increased bioenergetics reserve capacity also significantly attenuated 3-NP-induced cell death, reduced ATP levels, and lowered the mitochondrial membrane potential hence it has potential to be used as therapeutic agents for treating neurodegenerative disease [19]. Nitrous Oxide (NO) act as neurotoxic mediator and results in neurological disease and microglia is the main source of NO production in CNS injury and inflammation, therefore the inhibitors of iNOS expression may have beneficial effects in the treatment neuro-inflammatory disease [20].

Vidhara (*Argyrea speciosa*): The extract of the root significantly delayed the latency to the onset of first clonus as well as onset of death in unprotected mice and exhibited protection of pentylenetetrazole treated mice. Whereas in case of maximal electroshock seizures, hydroalcoholic extract of the roots of the plant significantly reduced the duration of hind limb extension in mice [21]. Studies have shown it to be a good CNS depressant and hence useful as an anticonvulsant [22]. *A. speciosa* shows anticholinesterase activity and Nootropic activity as evaluated using elevated plus maze test and passive shock avoidance paradigm. It successfully reversed amnesia induced by diazepam, scopolamine and natural aging [23], newer studies have also confirmed its nootropic effect and anticonvulsant action [24]. Effect of hydroalcoholic extract of *A. speciosa* root on learning and memory were studied in mice using radial arm maze and Morris water maze test [25]. *A. speciosa* root showed in vivo antioxidant activity against oxidative stress in rats [26].

Shankhpushapi (*Convolvulus pluricaulis*):

Its Methanolic extract induce antioxidant machinery of the cell hence hold therapeutic value in the treatment and/or prevention of neurodegenerative disorders of oxidative stress [27]. *Convolvulus* treatment alleviated neurotoxic effect of scopolamine reflects its potential as potent neuroprotective agent [28]. It was also found that

convolvine potentiates the effects of arecoline, a muscarinic memory enhancer that ameliorates cognitive deficits in Alzheimer's disease [29-30]. *Convolvulus* methanolic extract can modulate serotonin or dopaminergic levels, which is the major pathway of OCD and ADHD also [31]. *Convolvulus* is effective in scopolamine-induced cognitive impairments [32]. Ethanol extract of CP possesses significant antioxidant activity when tested in vitro [33]. *C. pluricaulis* extracts have been shown to display high antioxidant activity in chemical assays along with anti convulsant action [34], in one study it shows reduction in the mean recovery time from convulsion [35]. *Convolvulus* significantly improved learning and memory in rats [36]. Another study also shows it to be a good memory enhancer [37], studies report that *convolvulus* having nootropic effect [38].

Shatavari (*Asparagus racemosus*): Methanolic root extract of *Asparagus* enhances memory and protects against amnesia in rodent models [39]. *Asparagus* showed high free radical scavenging as well as neurotropic modulatory property and as per a study it have a therapeutic potency in diseases associated with neuron cell loss [40]; the extracts were shown to exert an inhibitory effect on pro-inflammatory cytokines, namely interleukin1 β and tumour necrosis factor α , and on the production of nitric oxide in mouse macrophage cells [41]. It also demonstrated significant decrease in latency time during retention trials Hippocampal regions associated with the learning and memory functions showed dose dependent increase in AChE activity in CA 1 with *A. racemosus* which is attributed to its antioxidant, neuroprotective and cholinergic properties [42]. Administration of methanolic root extract of *Asparagus* prevented scopolamine and sodium nitrite induced experimental amnesia and may be a great potential in memory deficits [43]. *Asparagus* dose-dependently decreased the plasma NE levels, indicating its effects on the hypothalamic-pituitary-adrenal cortex axis and the sympathetic-noradrenergic system, respectively. It increased the levels of all monoamines in the Hypothalamus [44].

Mandookaparni (*Centella asiatica*): Study shows that *Centella* fresh leaf extract has neuronal dendritic growth stimulating property; hence it can be used for enhancing neuronal dendrites in stress and other neurodegenerative and memory disorders [45]. Study showed a significant increase in the dendritic length (intersections) and dendritic branching points along the length of both apical and basal dendrites in hippocampal CA3 neuronal dendritic arborization, asiatic acid significantly attenuated decreases in the levels of glutathione, glutathione peroxidase and other enzymes and significant neuroprotective effects on cultured cortical cells by their potentiation of cellular oxidative defense mechanism [46]. Extract inhibited the

neuronal damage induced by cerebral ischemia, and further indicated the potential use of the extract in preventing neuronal damage in stroke^[47], asiaticoside present in the water extract of *C. asiatica* inhibits cPLA2 and sPLA2 activities responsible for neurodegenerative condition^[48]. It has not accelerated the learning process, but rather significantly facilitated the retention of learnt task as a good retention of memory for longer period which provides the further support for the earlier reports on cognitive enhancing ability of CeA^[49]. Studies shows that it decreases the pentylenetetrazole seizures and showed improvement in the learning deficit as evidenced by decreased seizure score and increased latencies in passive^[50], recent studies have shown, it is highly effective in mild cognitive impairment^[51]. *Centella asiatica* is found to be a good drug for revitalizing the nerves and brain cells^[52]. The result of double blind trial of *Mandukaparni* on mentally retarded children showed a very significant increase in both general ability and behavioral pattern^[53].

Brahmi (*Bacopa monnieri*): Constituents present in its extract have neuronal dendritic growth stimulating properties^[54]. *Bacopa* has dual function as mitochondrial complex I and antioxidant activity due to which it have protective effect in neurotoxicity^[55]. Clinical reports showed that this drug is an anti-anxiety agent having adaptogenic effect. It is a brain tonic; sedation is associated with therapeutic doses of the drug^[56]. *Bacopa* extract treatment in adult rats showed improvements in learning and memory, including spatial learning and passive avoidance learning^[57]. Some studies indicate that there is enhancement in some factors of intelligence as memory (direct), arithmetic skill & some verbal factors^[58]. Its extract during growth spurt period of neonatal rats enhances learning and memory^[59]. It significantly improved memory acquisition and retention among people^[60]. It significantly improved speed of visual information processing measured by IT task learning rate and memory consolidation compared to placebo, with maximal effect evident after 12 wks.^[61]; It improved the acquisition, retention and retrieval of learned tasks^[62]; *Bacopa* reduces alpha synuclein aggregation, prevents dopaminergic neurodegeneration and restores the lipid content in nematodes, thereby proving its potential as a possible anti-Parkinsonian agent and a neuroprotective agent^[63].

Guduchi (*Tinospora cordifolia*): *Tinospora* ethanolic extract exhibited significant neuroprotection by increasing the dopamine and complex I activity, Iron asymmetry ratio was also significantly attenuated and it also reduced oxidative stress and restored locomotor activity^[64]. Study have shown its beneficial effects in conditions of cerebral ischemia^[65]. Animals treated with *Tinospora* for a period of 30 days brought back the

oxidative degradation. Due to flavonoids and tannins present in *Tinospora* that are likely responsible for free radical scavenging activity^[66], antioxidant effect was evaluated clinically in another study^[67]. Prophylactic benefits of *Tinospora* have been shown in middlecerebral artery occlusion model of stroke in rats. The benefits have been ascribed to its potential for preventing oxidative stress injury and regulation of cytokine levels and growth factors in the blood of angiogenesis-induced animals^[68]. A study provides the first evidence for the presence of anti-proliferative, differentiation-inducing and anti-migratory/anti-metastatic potential of *Tinospora* in glioma cells and it significantly reduced cell proliferation in dose-dependent manner and induced differentiation in C6 glioma cells, resulting in astrocyte-like morphology in glioblastoma multiforme^[69]. *Tinospora* have enhanced the cognition in normal rats as seen in behavioral test-Hebb William maze and the passive avoidance task by increasing the synthesis of acetylcholine an important neurotransmitter in learning and memory process^[70]; Its pure aqueous root extract showed enhanced verbal learning in a 21-day randomized, double-blind placebo-controlled study^[71]. Significant response to *Tinospora* was reported in children with moderate degree of behavioral disorders and mental deficit, with improvement in intelligence quotient levels^[72]. It have shown normalization of stress-induced biochemical changes in norepinephrine (NE), dopamine (DA), and 5-hydroxytryptamine (5-HT) in experimental rat models and improved levels of 5-hydroxyindoleacetic acid (5-HIAA) in mice with ethanolic roots extracts^[73].

Toxicological Assessment of the drug: All the contents of the formulation are safe even in high dose. The LD50 value of *Calamus* was found to be more than 5,000 mg/kg body weight^[74]. In an animal study for safety of *Psoralea* LD50 oral in mice was found to be 625mg/kg, LD50 oral in rat 1330 mg/kg^[75]. LD₅₀ of seed extract is 500mg/kg^[76]. The LD50 of the whole extract of *Convolvulus* by oral administration was found to be 1 250 (1 000-1 400) mg/kg^[77]. The LD50 of *Asparagus* is >1g/kg, no toxic effects or mortality were observed with doses ranging from 50mg/kg to 1g/kg for four weeks^[78]. LD50 value of *Centella asiatica* in mice is more than 10 g/kg suggesting a relatively high margin of safety in relation to its effective dose in enhancing memory at 10 and 30 mg/kg^[79]. LD50 of *Bacopa* total alkaloid fraction is 8.5mg/100gm in mice^[80]. No any Toxicity noted in *Tinospora* as any amount of dose^[81].

The drug is made with Ghee as carrier for better absorption and bioavailability of drug in CNS. Drug absorption also depends on a number of physicochemical factors, the two most important of which are lipophilicity and solubility^[82-83]. The membrane of the gastrointestinal epithelial cells is

composed of tightly packed phospholipids interspersed with proteins. Thus, the transcellular passage of drugs depends on their permeability characteristics to penetrate the lipid bilayer of the epithelial cell membrane, which is in turn dependent on the lipophilicity of the drugs^[84]. Owing to the presence of epithelial-like, high resistance tight junctions within the brain capillary endothelium, the intercellular pores that exist in the endothelial barriers in peripheral organs are absent in the endothelial barrier in the brain. In addition, there is minimal fluid-phase pinocytosis in brain capillary endothelium^[85]. Thus molecules in the circulation gain access to brain ISF (interstitial fluid) via only one of the two mechanisms: (1) lipid-mediated free diffusion through the BBB or (2) carrier- or receptor-mediated transport (RMT) through the BBB. Ghee being a lipid in nature is rapidly cross the BBB and make the drug available in the CNS.

CONCLUSION:

Ashtang Ghrita is quite safe for administration among children and can provide better bioavailability of constituent drug in CNS as a nervine tonic and for various disease of CNS both as prophylactic and curative medication.

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Cite this article as: Sumeet Goel, Nisha Kumari Ojha. Ashtang Ghrita: A Noble Ayurveda Drug for Central Nervous System, *J of Ayurveda and Hol Med (JAHM)*.2015;3(2):18-24.

Source of support: Nil, Conflict of interest: None Declared.