

Pharmacological and therapeutic review of ashtamangal ghritha – An amazing ayurvedic formulation for CNS

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ABSTRACT

Cognitive dysfunction and neurological disorders are major concerns in pediatrics. Ayurveda has a deep acumen for the prophylactic and curative management of neurological disorders in the developing brain. This study is done to review the neuroprotective and nootropic activity of an Ayurvedic drug *Ashtamangal Ghritha* (AMG). Various experimental and clinical studies on AMG and its contents demonstrate their efficacy against several Central Nervous System (CNS) ailments such as cerebral palsy, seizure disorders, autism, and attention deficit hyperactivity disorder by their neuroprotective, nerve regenerative, nootropic, anticonvulsant, antioxidant, and adaptogenic properties. The drug AMG is in the *Ghritha* form, thereby advantage of its lipid solubility, is it can pass through the Blood-brain barrier thus corroborating it as an excellent drug for CNS. Toxicological studies also substantiate the safety of the drug for therapeutic usage. The constituents of AMG also own CNS protective and nootropic properties, thereby helping in improving intellect and memory in children. Hence, AMG can prove to be a promising neuroprotective and intellect-promoting drug for cognitive dysfunction and various neurological disorders in children. The present review aims to analytically evaluate and systematically summarize experimental and clinical trial outcomes and the safety profile of AMG.

Key words: Anticonvulsant, *Ashtamangal Ghritha*, Ayurveda, CNS, nootropic

INTRODUCTION

The Central Nervous System (CNS) is the most important and complex system in the human body. It defines the unique human function, that is, consciousness. It regulates all the vital activities and behavioral functions of the body.^[1] From a worldwide perspective, neurological disorders collectively account for 28% of all disabled persons.^[2] The Census report of 2001 shows that 45% Indian population is below 20 years of age.^[3] Recent community-based research in India has documented the prevalence of neurodevelopmental ailments to be about 12% in children aged 2–9 years.^[4] INCLIN study estimated a 7.5–18% prevalence of neurological disorders such as cerebral palsy (CP), epilepsy, febrile seizures, ADHD, autistic spectrum disorders, and mental retardation in the 2–9 years age group.^[5] The estimated average prevalence of epilepsy is calculated to be 533/100,000 and of febrile convulsions ranges from 328 to 571 per 100,000.^[6,7] Studies of communities from the east, north, and south of India have documented that prevalence of CP ranges from 21 to 173/1

lakh and of tics is about 2/1 lakh of the pediatric population.^[8-10] Encumbrance of neurological illness in the pediatric age group leads to the biggest economic load globally of a disease group.^[11] The yearly financial burden of antiepileptic treatment as single-drug therapy is expected to be 4–30% of GNP.^[12] At present, the burden attributed to neurological disorders is more than 25% of the overall burden of disorders in global market economies.^[13] Thus, there is always a need for more potent medications to manage CNS disorders.

Ayurvedic classics have defined several neurological maladies, along with their prophylactic and curative management. Materia medica of the Ayurveda also contains various drugs owning persuasive efficacy against neurological disorders and can be used very effectively for the mitigation of human suffering.^[14]

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One such miraculous drug mentioned in a classical Ayurveda text, *Yoga Ratnakar* known as *Ashtamangal Ghrita* (AMG) is reviewed in this study for its efficacy on CNS as a medication for neurological disorders and cognitive dysfunction in children.

AIM AND OBJECTIVES

The study aims to review the scattered literature on the neuroprotective and nootropic action of an Ayurvedic drug, *Ashtamangal Ghrita*, and its contents along with their evidence-based scientific studies so that the knowledge can be utilized for therapeutic purposes and for designing further multicentric clinical trials for CNS-related disorders among children both as prophylactic and curative medicine.

METHOD

This study was done by compiling the relevant knowledge from conventional Ayurvedic texts, MEDLINE database, PUBMED, Google scholar, etc., which were also searched for relevant research papers. Scientific papers published from 1969 to 2020 were included in the study. The keywords used for the search were “Ayurveda,” “Nervous System,” Neuroprotective, neuroregeneration, and “Memory booster,” *Ashtamangal ghrita*, etc. Experimental trials, *in vitro* studies, and clinical trials were incorporated into the study and discussed to conclude. Research studies published in the English language were only included in the study [Tables 1-4].

Table 1: Ingredients of Ashtmangal Ghrita

S. No.	Ingredient	Botanical name	Parts used	Ratio
1.	Vacha	<i>Acorus calamus</i> Linn.	Root	1
2.	Kushtha	<i>Saussurea lappa</i> Linn.	Root	1
3.	Brahmi	<i>Bacopa monnieri</i> Linn.	Complete Plant	1
4.	Sariva	<i>Hemidesmus indicus</i> R.Br.	Root	1
5.	Pippali	<i>Piper longum</i> Linn.	Root	1
6.	Siddharthak	<i>Brassica campestris</i> Linn.	Seed	1
7.	Goghrita (cow's ghee)	-	-	4
8.	Saindhava	-	-	1
	Water	-	-	16

Table 2: Ayurvedic pharmacological properties of the constituents of AMG.^[21]

S. No.	Ayurvedic Text	Rasa	Guna	Virya	Vipaka	Properties
1.	Vacha	Katu, Tikta,	Ruksha, laghu, tiksna	Ushna	Katu	Vata Kaphahara, Pittavardhak, Mala Mutravisodhanl, Kanthya, Krimihara, Vamak, Dipan Prabhava- Medhya
2.	Kushtha	Katu, tikta	Laghu	Ushna	Katu	Kapha-Vatasamak, Rasayan, Raktasodhaka, Varnya
3.	Brahmi	Kashaya Tikta, Madhura	Sara, Laghu	Sheeta	Madhura	Vata-Kaphahara, Rasayana, Ayushya, Medhya, Swarya, Visahara Prabhava- Medhya
4.	Sariva	Madhura, Tikta	Guru, Snigdha	Sheeta	Madhura	Tridosahara, Raktashodhaka, Vishaghna, , Dipana, Jvarahara,
5.	Pippali	Katu	Laghu, Snigdha, Tikshna	Anushna sheeta	Madhura	Kapha-Vatahara, Deepana, Hridya, Rucya, Rasayana, Rochaka
6.	Siddarthaka (Sarshap)	Katu, Tikta,	Snigdha, ushna	Ushna	Katu	Kapha-Vatahara, Pittavardhak, Vatahara, Depana, Vidahi, Hridya
7.	Goghrita (cow's ghee)	Madhura	Snigdha	Sheeta	Madhura	Vata-Pittashamak Prabhava-Medhya
8.	saindhavaa	Lavan,	Snigdha, Tikshna, Sukshma	Sheeta	Madhura	Tridosha shamak, parshva shula, jirnakasa, shwasa

Table 3: Pharmacological properties of *Ashtamangal Ghrita* on experimental and clinical research

S. No	Pharmacological property on the basis of experimental/Clinical research	References
1.	Increases the brain AChE activity in the developing brain.	[29]
2.	Effective in the management of mental retardation when compared with behavior modification therapy. Improves IQ level	[26]
3.	Nootropic effect – improves mental status parameter and IQ	[27]
4.	Effective analgesic action with no any motor in-coordination. CNS depressant – CNS agent for the treatment of over-excitation.	[30]
5.	Anticonvulsant effect in higher doses.	[30]
6.	Reduction in spasticity and improved muscle power in CP children. Significant improvement in head holding, sitting, teacher drooling scale standing, fine motor, personal/social, mental status, language, performance, and memory.	[25]
7.	Immunostimulant activity in rats.	[32]

ASHTAMANGAL GHRITA (AMG)

Classical Reference

Ashtamangal ghrita is a polyherbal *Ghruta*-based (extracted in *Ghee* or butter fat of cow's milk) Ayurvedic formulation. AMG is mentioned in *bala roga chikitsa prakarana in Yoga Ratnakara*.^[15] and *Chakra datta in bala roga chikitsa*.^[16] Acharya Vagbhata is also described as *Brahmi ghrita in Ashtanga Sangraha*^[17] and *Shishukalyanaka ghrita in Ashtanga Hridaya*^[18] with same constituents and therapeutic usage. In *Kashyap Samhitalehaadhyay*,^[19] Acharya Kashyap has also mentioned *Abhaya ghrita* containing the same ingredients as AMG and stated it as one of the *lehana aushadha*. *Lehana aushadha* are the especially formulated recipes in *Ayurvedic* classical texts for children, intended to improve agni (appetite and metabolism), *medha* (cognitive functions) and *bala* (growth and immunity). *Lehana Karma* is indicated for a child whose mother is not healthy or not having the good quality or quantity of milk or child is suffering from inadequate growth and development without having any disease.^[20] AMG contains eight crude drugs-*Vacha* (*Acorus calamus* Linn.), *Kushtha* (*Saussurea lappa* Linn.), *Brahmi* (*Bacopa monnieri* Linn.), *Sariva* (*Hemidesus indicus* R. Br.), *Pippali* (*Piper longum* Linn.), and *Siddarthaka* (*Brassica campestris* Linn.). Besides these, *saindhava* (sodium chloride) and *Goghruta* (cow's ghee) are also used. It is commendably stated for refining *Medha* (perception), *kshpra medha* (grasping power), *dridhaSmriti* (strong retention power), and *Buddhi* (intellect and comprehension). It is also told as *Rakshoghna* (protects from the infection).^[15]

Shelf-life

The shelf-life of a drug is the duration of time in which, under labeled storage conditions, it retains all its important characteristics within specific prescribed limits.^[22] Its estimation guarantees the efficacy and quality of medicine and establishes its expiry time. As per ancient Ayurvedic texts, recommended shelf-life of *Ghruta* preparations is

from 6 months to 2.^[23] In a study by Sharma *et al.*, 2016, physicochemical parameters for freshly prepared AMG samples were calculated as specific gravity, refractive index, iodine value, acid value, saponification value, and peroxide value. These are found within the adequate limit and per Ayurvedic classics. The shelf-life of samples was found >2 years for countries under climate zone I and II and <2 years for zone III and IV.^[24]

Mode of Administration

AMG can be administered as oral and as *nasya* (nasal route).^[25-27]

Physicochemical Parameters^[28]

Physical analysis of AMG shows that it has a greenish-yellow color with an acrid taste, specific odor, smooth texture, and semisolid greasy appearance. The quantitative chemical test demonstrates that the refractive index and specific gravity of AMG are equal to 1.459 and 0.9013, respectively. Furthermore, the acid value, saponification value, and iodine value are calculated as 0.56, 210.19, and 31.37, respectively, whereas the peroxide value was found zero.

Pharmacological Properties AMG Based on Experimental and Clinical Research

An experimental study shows that AMG elevates the brain AChE release in the developing brain. This effect was more pronounced in undernourished animals.^[29] AMG is found to be beneficial in the treatment of mental retardation in comparison to behavior modification rehabilitation. It has also shown significant improvement in the IQ level in the children. The evaluation was done with Malin's IQ scale. AMG is also found efficient in several spheres of MDPS as compared to behavioral management.^[26] AMG in the *nasya* therapy is found effective in improving mental status parameters and IQ in children and thereby proving its nootropic effect.^[27]

Table 4: Pharmacological properties of herbal ingredients of AMG based on experimental and clinical research

Herbal Ingredients of AMG	Pharmacological Properties Based on Experimental/Clinical Research	References
<i>Vacha</i> (<i>Achorus calamus</i> Linn)	Improves cognition	[33]
	Enhance memory	[34]
	Anti-amnesiac effects	[35]
	Neuroprotective activity	[36,38]
	Attenuates peripheral neuropathic pain.	[39]
	Acetylcholinesterase inhibitory action	[40,43]
	Enhances spatial recognition and acquisition recalling.	[41,43]
	Antiepileptic activity.	[44]
	Antidepressant, Anxiolytic, and Tranquilizing activity	[50,55]
<i>Kushtha</i> (<i>Saussurea lappa</i> Linn)	Antioxidant activity	[57,58]
	Anticonvulsant activity	[59]
	Antiepileptic activity	[60]
	Anti-anxiety and CNS depressant activity – Found to reduce labor pain, allay anxiety and apprehension. Produces mild sedation	[61]
	Anti-inflammatory	[62]
<i>Brahmi</i> (<i>Bacopa monnieri</i>)	Immunomodulator	[65]
	Neuroprotective activity – Increases kinase and neuronal activity and restores neuronal synapsis thereby helps in impulse transmission	[68,69]
	Stimulates growth of dendrites.	[70]
	Neuroprotective effect facilitated by mitochondrial complex I formation antioxidant property.	[71,72]
	Anti-Parkinsonian agent and a neuroprotective agent	[73]
	Anti-anxiety activity – anti-anxiety, adaptogenic, and sedative effect. Brain tonic	[74]
	Improves cognition – Significant effect on memory, passive avoidance and spatial learning.	[75,77,79,81]
	Enhancement in intelligence, memory, arithmetic skill, and some verbal factors.	[76]
	Improvements in memory acquisition and retention	[78]
	Significant improvement in the capacity to perceive, retain and recall tasks and events.	[80]
	Improvements in brain growth and development. Significant effect on intellect and memory	[100]
<i>Sariva</i> (<i>Hemidesmus indicus</i> R.Br.)	Marked improvements in perceiving and retaining new information.	[81]
	Antiepileptic Activity	[82]
	Anticonvulsant activity	
	Significant reduction in the duration of post-ictal depression and tonic extensor phase in maximal electroshock method.	[83,84]
	Anti-psychotic activity.	[85]
	Neuroprotective Activity – antagonized property against the release of excess glutamate, increases the level of dopamine, decreases of acetylcholine esterase, and releases of Acetylcholine at the nerve terminals, which restores normal memory function.	[86]
	Antioxidant activity	[87]
<i>Pippali</i> (<i>Piper longum</i> Linn)	Anticonvulsant activity – delays onset of generalized tonic clonic and myoclonic seizures (piperine dosage – 40 and 80 mg/kg)	[88]
	Anti-depressant activity – helps with insomnia	[90,91]
	Bioavailability Enhancer	[92,95]
<i>Sarshap</i> (<i>Brassica campestris</i> Linn)	Neuroprotective activity	[98]
	Antiepileptic Anti-bacterial activity	[90,99]

A study by Biyani *et al.*, on AMG demonstrates the reduction the motor activity and attentiveness in mice. It is found to enhance overall calmness and sleeping time in a dose-dependent manner. AMG was also found to antagonize the action of amphetamine which is suggestive of its therapeutic use as a CNS depressant.

It also demonstrated potent analgesic activity with no motor in-coordination. The overall study advocates that AMG can be therapeutically used for the successful management of the over-excitation of CNS. The anticonvulsant outcome is also attributed to AMG in higher doses.^[30]

A clinical study of oral administration and Nasya^[31] of AMG reveals that there is a reduction in muscle spasm and improvement in muscle power after 3 months of therapy with AMG in children suffering from spastic CP thereby improving their quality of life in both groups. AMG was found safe and effective through both routes. However, the oral group was found slightly better outcomes in neck holding, sitting, muscle spasticity, and teacher drooling scale. On the other hand, the nasya group shows superior results in other parameters including standing, fine motor, personal/social, mental status, language, performance, and memory. No adverse effects of AMG were noticed during or after the clinical study.^[25]

An experimental study in rats demonstrates the immunostimulant activity of AMG. Oral administration of AMG results in a significant elevation in hemagglutinating antibody titer, neutrophil adhesion, and delayed-type hypersensitivity reaction. AMG also improved humoral antibody response and cellular immunity by dropping the foot-pad thickness in sheep RBC in immunized rats. The values of HAT and DTH responses by giving a dosage of 300 mg/kg/day were 455.08 ± 0.75 and 31.0 ± 10.72 , respectively. The difference in the groups was found statistically significant.^[32]

INGREDIENTS OF ASHAMGTAMANGAL GHrita

Vacha (*Acorus calamus* Linn)

Improves cognition

Vacha is found to improve cognition, in various experimental studies.^[33] Many clinical studies have established that *Acorus calamus* enhance memory.^[34] Anti-amnesiac effects have also been found in a recent study with a high dosage of β -asarone, a phenylpropanoid present in *Acorus*.^[35]

Neuroprotective activity

In an experimental study, acrylamide was introduced to rats causing hind limb paralysis and reduced behavioral parameters on day 10 in 58% of the rats. It was found in the study that when the animals were treated with rhizomes extract of *A. calamus*. Neurobehavioral changes did not appear.^[36] It has also demonstrated neuroprotective activity in rats in the condition of ischemia due to middle cerebral artery occlusion.^[37,38] As per research studies, major offenders in axonal degeneration are inflammation, calcium channel over-activity, and reactive oxygen species, which can be overcome by the anti-inflammatory, neuroprotective, and antioxidant potential of *A. calamus*. Furthermore, due to its voltage-activated calcium channel, it helps in alleviating peripheral neuropathic pain.^[39] *In vitro* studies on *A. calamus* and its constituents demonstrate their potent acetylcholinesterase inhibitory activity.^[40,41] Furthermore, methanolic extract of *Acorus* at 200 mcg/mL shows significant AchE reduction.^[42]

The ethanolic extract of *Acorus* was also studied for nootropic and memory-boosting activity in 25, 50, and 100 mg/kg doses through intraperitoneal and oral routes in male rats, through shuttle box tests and Y-maze models. The outcome of the study was an increase in data of acquisition-recalling and spatial recognition.^[43]

Anticonvulsant activity

Various research shows that alcoholic extract of the *A. calamus* exhibits anticonvulsive and analgesic action that can be facilitated by GABA activity.^[44] β -asarone, a bioactive phytochemical in *A. calamus* in higher concentration, activates the GABA receptor and thus produces potent anticonvulsive activity.^[45,46] In an experimental study, extent of glutathione and glutathione-S-transferase action in the corpus striatum was found to increase whereas dopamine receptors get reduced in *A. calamus*-treated rats.^[34] In an experimental study on rats, the rhizome of *A. calamus* showed remarkable anticonvulsive effects. The span of the tonic extensor period gets minimized significantly.^[47] The oil extracted from the rhizome of *A. calamus* rhizome was found effective against minimal clonic seizure (MCS), maximal electroshock seizure, and pentylenetetrazol (PTZ) models. In the MCS test, the oil was found effective at 6 Hz and neurotoxic at 300 mg/kg. The protective index value of *Acorus* oil was found to be 4.65.^[48] Ethanolic rhizome extract of *A. calamus* (0.5 mL/kg, i.p.) was found to potentiate sleep periods induced by pentobarbitone-created, which showed a decrease in conditioned avoidance reaction in rats and significant prevention of PTZ-induced convulsions.^[49]

Anxiolytic and antidepressant activity

In a study done by Monica Shetty in mice, *A. calamus* at a dosage of 200 mg/kg and 400 mg/kg showed remarkable improvement in anxiety problems.^[50] Methanolic extract of rhizome *A. calamus* also exhibits anxiolytic and antidepressant activity by interacting with adrenergic, dopaminergic, serotonergic, and GABAergic systems.^[51] Methanolic extract of the leaf of *A. calamus* showed marked anxiolytic activity through a decrease in immobility time in the Tail Suspension Test and Forced Swim Test.^[52,53] In another study, hydroalcoholic extract of *A. calamus* was found to normalize the over-activity of the hypothalamic-pituitary-adrenal axis by interacting with dopaminergic and adrenergic pathways.^[54] *A. calamus* also showed sedative and tranquilizing effects.^[55] Tensarin, a conventional medicine widely used in Nepal contains *A. calamus* as the main constituent and was evaluated in an experimental study for its efficacy on anxiety. The result showed a potent dose-dependent anxiolytic effect in mice using passive avoidance, activity monitoring, and open-field assessment.^[56]

Antioxidant activity

A. calamus is a powerful antioxidant. An experimental study on rats showed the protective action of alcoholic extract of *A. calamus* on free radicals and lipid peroxidation in distinct brain areas exposed to noise stress.^[57] Furthermore,

the phenolic compounds in the *A. calamus* are helpful in neutralizing free radicals.^[58]

Kushtha (*S. lappa* Linn)

Anticonvulsant activity

In a study done in mice, alcoholic, ether, and aqueous root-extract of *S. lappa* exhibited anticonvulsant activity toward convulsion produced by PTZ and picrotoxin.^[59] In another study, also the alcoholic extract of the root of *S. lappa* showed potent antiepileptic activity in mice against convulsions induced by maximal electroshock. The effect was found dose-dependent.^[60]

Anti-anxiety

In a research study costunolide and dehydrocostus lactone, natural sesquiterpene lactones from *Saussurea* were found to decrease body temperature, increase sleep time, and show CNS depressant activity.^[61] It is also proven to decrease anxiety, along with related symptoms. No untoward effect was noticed on the mother and fetus during the study.^[61]

Anti-inflammatory

Saussurea is a potent anti-inflammatory herbal drug. In an experimental study, 0.1 mg/methanol extract of *Saussurea* shows >50% of reduction of cytokine-induced neutrophil chemotactic factor.^[62] In another study, ethanolic extract of *Saussurea* was found to cause a reduction of >50% of inhibition on tumor necrosis factor- α .^[63] Costunolide and dehydrocostus lactone, natural sesquiterpene lactones from *Saussurea*, were tested in rats. The results show anti-inflammatory due to anti-proliferative effects and lysosomal membranes stabilization.^[64]

Immunomodulator

Costunolide and dehydrocostus lactone, isolated from an extract of *Saussurea*, were found to be the inhibitors of the killing activity of cytotoxic T lymphocytes. Costunolide inhibited the killing activity of CTL by preventing the increase in tyrosine phosphorylation in response to the cross-linking of T-cell receptors.^[65] Mokko lactone and dihydrocostus lactone isolated from roots of *Saussurea costus* showed protective action against stress-induced ulcer formation in mice.^[66] It was also found that the guaianolides, a type of sesquiterpene lactone, consisting of α -methylene- γ -lactone show the remarkable inhibitory response to the killing function of cytotoxic T lymphocytes and ICAM-1.^[67]

Brahmi (*B. monnieri* Linn)

Neuroprotective activity

The neuroprotective activity of *B. monnieri* is established by various research studies. The triterpenoid saponins and bacosides were isolated from *B. monnieri* and their neuropharmacological efficacy was assessed. They are found responsible for

enhancing nerve impulse transmission by the mechanism of dephosphorylation of the membrane. This leads to a rise in protein and RNA in certain brain areas. The nootropic effect of *B. monnieri* is attributed to the increased activity of protein kinase in the hippocampus.^[68] *B. monnieri* extract was noted to remarkably improve cholinergic neuronal density in the hippocampus when orally given in the dosage of 40 mg/kg.^[69] Components of the extract of *B. monnieri* were found to stimulate the dendritic growth of neurons.^[70] *B. monnieri* exhibits neuroprotective behavior due to its ability to produce mitochondrial complex I and antioxidative effects.^[71] In an experimental study by Anbarasi *et al.*, bacoside is found to be a potent neuroprotective agent effective against oxidative stress by measuring concentrations of antioxidants as well as trace elements in rats, that were exposed to cigarette smoking.^[72] *B. monnieri* has also shown efficacy in Parkinson's disease due to its neuroprotective activity. It prevents dopaminergic degeneration of neuronal cells and decreases alpha-synuclein aggregation.^[73]

Anti-anxiety activity

Various clinical and experimental studies on *B. monnieri* showed that it is an effective adaptogenic and anti-anxiety drug. Its therapeutic effects are also serenity and sedation, which are dose-dependent.^[74]

Improves cognition

Bacopa extract treatment in adult rats showed improvements in memory, passive avoidance learning, and spatial learning.^[75] Various research studies on *Bacopa monnieri* showed improvement in intellect, speech, memory, and arithmetic skill.^[76] Bacopa extract when inoculated during the growth spurt of neonatal rats found to increase learning rate and memory.^[77] Bacopa extract also appreciably enhanced grasping and memory retention among people.^[78] It has also shown significantly improved visual information speed dispensation when calculated by IT task learning rate and memory consolidation, with significant results in 12 weeks.^[79] *B. monnieri* has shown remarkable improvement in perception, memory, and recall of learned tasks and events.^[80] In a recent randomized controlled double-blind clinical trial on human adults, efficacy of *B. monnieri* was assessed on memory scale and anxiety level. The outcome of the study presented remarkable improvement in the retention and reclamation of new information.^[81]

Antiepileptic activity

In an experimental study, hirsaponin, an active component, isolated from an extract of *B. monnieri* exhibited protection against seizures in mice and can be used as an added medicine in the management of convulsive disorders.^[82]

Sariva (*Hemidesmus indicus* R. Br.)

Anticonvulsant activity

H. indicus shows antiepileptic effects.^[83] In an experimental study, the ethanolic extract of *H. indicus* significantly

decreases the period of postictal depression and also the tonic extensor phase in adult albino rats in the maximal electroshock method. The study shows that *H. indicus* has potent antiepileptic property.^[84]

Anti-psychotic activity

In an experimental study, *H. indicus* was orally given to rats and anti-psychotic activity was noted. The assessment was done by haloperidol-induced catalepsy models and apomorphine-induced stereotyped behavior. The outcome showed marked improvement in the stereotyped behavior in experimental models and it also intensified the catalepsy.^[85]

Neuroprotective activity

In an experimental study, it was proved that the methanolic extract of *H. indicus* root-bark showed antagonized property against the release of excess glutamate and, thus, reduced the level of glutamate. It was also found to increase the level of dopamine which is already lowered in neurodegenerative conditions. It also helps in the decrease of acetylcholine esterase and the release of acetylcholine at the nerve terminals, which restores normal memory function.^[86]

Antioxidant activity

Ravishankara *et al.* proved that the presence of tannins and phenolic compounds along with flavonoids such as hemidesmin 1 and 2, and 2-hydroxy-4-methoxy benzoic acid of methanolic extract of *H. indicus* root bark shows antioxidant activity by scavenging DPPH and harmful superoxide radical.^[87]

Pippali (*P. longum* Linn)

Anticonvulsant activity

The anticonvulsant activity was examined in mice. There was found a significant result in delaying of onset myoclonic and generalized tonic-clonic seizures with the administration of piperidine alkaloid. The outcome was found to be dose-dependent.^[88]

Anti-depressant activity

In a research study, piperine showed protective action against MAO-A and B-induced antidepressant effects.^[89] *P. longum* is advocated for use in insomnia.^[90] Anti-depressant activity was also evaluated in corticosteroid-induced mice by developing depression-like behavior in them. Injection of corticosterone was given for 3 weeks to mice. The anti-depressant activity of piperine was assessed by the marked decrease in sucrose consumption in mice. Furthermore, in the forced swim test, significant rise in immobility time was observed. Besides these, neurotrophic factor protein and mRNA in the hippocampus were found reduced. All biochemical and behavioral parameters also showed a marked reduction.^[91]

Antioxidant and immunomodulatory activity

Piperine, a known piperidine alkaloid, exhibits marked antifungal, anti-inflammatory, antioxidant, and anticancer activities, as evidenced by numerous researches.^[92] Experimental data, on piperine, have shown its anticancer and immunomodulatory potential.^[93,94]

As bioavailability enhancer

P. longum Linn. enhances the bioavailability of drugs due to the virtue of piperine, an active alkaloid present in it.^[92,95] In an experimental study, piperine was found to increase the bioavailability of several formulations including propranolol, rifampicin, and theophylline.^[96,97]

Sarshap (*Brassica campestris* Linn.)

Neuroprotective activity

B. campestris shows significant neuroprotective activity. Its neuroprotective behavior is attributed to its ability to stimulate nerve impulses to proceed healing effect.^[98]

Antiepileptic activity

B. campestris has potent antiepileptic properties.^[90] In research studies, the ethanolic extract of the whole plant, ethyl acetate extract of leaves, methanolic extract of stem, and petroleum ether extracts of roots of *B. campestris* was found highly effective and also exhibited good anti-bacterial activity against all bacterial strains.^[99]

Saindhava (Rock salt)

As per Acharya Sushrut, saindhava (rock salt) is having *hridya* (good for heart) *rochana* (improves taste), *laghu* (easy to digest), *deepana* (appetizer), *tridosahara* (vitiates three doshas), *sheeta* (cool effect), and best among all salts.^[101] Salt is vital for enhancing communication between the cells and the functioning of the body. It is also important for water absorption and nourishment of minerals. Salt helps in invigorating the mind by balancing electromagnetic radiation. Thus, it is used to enhance the internal environment of the body.^[102]

It stimulates blood circulation and balances minerals in the body and thus helps in getting rid of toxic substances in the body.^[103] It also helps in maintaining low and high blood pressure and thus stabilizes blood pressure. It also helps in controlling obesity by equalizing minerals which eliminate dead fat cells.^[104]

Ghrita (Ghee)

AMG is *aghrta* formulation. Ayurveda considers *ghrita* as the best source of *sneha* (fat). It is a daily consumable *rasayana* (rejuvenating diet or drug) with several valuable properties. It prolongs a healthy life and protects the body

from various diseases by fortifying the immune system. *Ghrita* pacifies *vata* and *pitta doshas* and nourishes *rasa dhatu* and *ojas* in the body. *Gunas* (properties) of *ghrita* are *sheeta* (cooling effect), *mridu* (soft), *swarya* (improves speech), *varnya* (improves complexion), *medhya* (enhances intellect), *swadu* (sweet), *deepana* (appetizer), *balya* (improves strength), and *chakshushya* (improves vision).^[105,106] *Ghrita* is used to treat various diseases in Ayurveda. It can be consumed as it is or in combination with other herbs. There are more than 50 types of medicated *ghritas* are mentioned in the Ayurvedic classics.^[107] Cow ghee is considered the best among all *ghritas*. It is easily digestible and contains essential nutrients and anti-oxidants for the proper growth and development of children.

Ghrita is said to be *Yogavahi* in Ayurveda, that is, it easily attains the therapeutic properties of the herbs combined with it and carries to the tissue level. Thus, it acts as an active ingredient as well as a vehicle for medicine. *Ghrita* is lipophilic in nature. As the cell membrane also consists of lipids, the lipophilic property of *ghrita* facilitates access of herbal ingredients to the target organ and finally to the cellular level. Thus, *ghrita* acts as a medium and bioavailability enhancer for numerous drug formulations.^[108] When AMG is used for *Abhyanga* (ayurvedic massage), *Nasya* (nasal administration) or *Basti* therapy (therapeutic enema) *ghrita* directly penetrates the deeper tissues and facilitates the availability of drugs all over the body.^[109] By this property, *ghrita* preparations to a certain extent can pass through the weaker blood–brain barrier in the early infancy and proved to have nootropic and CNS protective effects.^[110]

TOXICOLOGICAL ASSESSMENT OF AMG

The safety profile of any herbal medicine is an important factor that should be considered to determine its therapeutic utility.^[111] Individual studies of the constituent drugs of AMG shows that the contents of the formulation are safe even in high dose.

The LD₅₀ value of *A. calamus* was found to be more than 5000 mg/kg body weight.^[112] In another study, LD₅₀ of *Bacopa*'s total alkaloid fraction is 8.5 mg/100 g in mice. Furthermore, the decoction of *B. monnieri* did not exhibit any toxicity up to 10 ml/kg.^[113] A toxicological study on *P. longum* suggested that a single oral dose of *P. longum* of 3g/kg body weight and 100 mg/kg body weight for 90 days showed no untoward effects in experimental animals.^[114]

H. indicus when administered by gastric intubation at 1000 and 2000 mg/kg body weight dose in rats showed a stimulative effect and, at 3000 mg/kg body weight, showed a depressive effect such as sedation and analgesia up to 4000 mg/kg body weight. None of the animals died during the study.^[115]

A toxicological study on *S. lappa* resolute LD₅₀ of *S. lappa* in Swiss albino mice verified that no sign of toxicity or death

was observed in experimental animals treated with the extract *S. lappa* up to doses of 2000 mg/kg body weight.^[116]

DISCUSSION

AMG is a *Ghrita* preparation. Ghee facilitates better absorption and bioavailability of drug in CNS. Drug absorption depends on a number of physicochemical factors, of which the two most important are lipophilicity and solubility.^[117,118] Lipid-soluble preparations can pass readily through the surface of the capillary endothelium.^[119]

The gastrointestinal epithelial cell membrane is composed of firmly packed phospholipid bilayer. The transcellular access of medicines depends on their permeability to penetrate this phospholipid bilayer membrane of the epithelial cell, which, in turn, depends on the lipophilic property of the drugs.^[120] Due to the presence of 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 brain. In addition, there is minimal fluid-phase pinocytosis in the brain capillary endothelium.^[121] Thus, molecules in the blood circulation can enter the brain ISF (interstitial fluid) by means of only one of the two mechanisms: (1) lipid-mediated free diffusion through the blood–brain barrier (BBB) or (2) carrier- or receptor-mediated transport through the BBB. Ghee being a lipid in nature can easily cross the BBB and make the drug available in the CNS. Furthermore, *ghrita* act as a base in a drug to extract lipid-soluble active fraction from the ingredients used.

As the study drug, AMG was in lipid form, it facilitated drug absorption through mucous membrane and capillaries. It was believed previously that neurons do not repair or rejuvenate after any damage, but the new concept of neuroplasticity proves that CNS has the ability to repair their neurons by axonal sprouting to take over the function of damaged neurons.^[122]

Along with go-*ghrita*, other ingredients present in AMG are *Vacha* (*A. calamus* Linn.), *Kushtha* (*S. lappa* Linn.), *Brahmi* (*B. monnieri* Linn.), *Sariva* (*Hemidesus indicus* R.Br.), *Pippali* (*P. longum* Linn.), and *Siddharthaka* (*B. compestris* Linn.) and Rock salt. All of these ingredients and *ghrita* are evidenced to have neuroprotective, nootropic, anxiolytic, anti-depressant, antioxidant, anticonvulsant activity, etc. On evaluation of ayurvedic pharmacodynamics properties of AMG's ingredients, the predominant ayurvedic pharmacodynamic properties of AMG are *madhura*, *katu*, *tikta rasa*, *guru*, *snigdha* and *laghu guna*, *katu vipaka*, *ushna veerya*, *tridosha shamaka*, *medhya prabhava*, and *agnideepaka*. *Madhura rasa* is *sarvadhaturvadhaka*, *brihmana*, *jeevaniya*, *preenan*, and *sthairyakaran*. *Madhura rasa* is formed by *prithvi* and *jala mahabhuta*. *Madhura rasa* helps in nourishment. Due to *sarvadhaturvadhaka guna*, it provides support and proper nourishment to neurons. Its *ksheenakshata sandhankara guna* (rejuvenating property) helps in regenerating damaged neurons. *Katu rasa* is *indriyouttejaka* (to stimulate sensory/motor

organs to perceive their subjects), *agnideepaka* (appetizer and normalizes secretion of hormones in synaptic vesicles), and *marganavivrunoti* (to create new pathway for proper functioning and replacement of damaged neurons). *Tikta rasa* also has *sthirikarana* property (provides strength to muscles and tissues). *Guru* and *Snigdha* are *vatahara* and provide nourishment to the body. *Ushna veerya* acts by *vatahara* property and also increases blood circulation in the brain.

CONCLUSION

AMG, a classical ayurvedic preparation, is quite safe and effective for administration among infants and children and can provide better bioavailability of constituent drug in CNS as a nervine tonic and for various CNS disorders both as prophylactic and curative medication.

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