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Ghrita and different herbal inclusions on neurological disorders - A perspective review

Review Article

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Abstract

Introduction: Ayurveda *ghrita* dosage forms are well appreciated in the Classical treatises for different diseases and may be useful in neurological conditions such as these formulations are recommended since birth for memory enhancement and improving intellect as the major development of brain completes within the initial 5 years. So, these PUFA embedded preparations with DHA, AA, BA, etc are extensively screened out for the cognition, memory, neuro-protective, genesis of plasticity, etc in terms of herbal constituents added with the dosage form. Material and Methods: The Classical Ayurveda treatises and the databases like Pubmed, Scopus, Web of Science, etc were searched with the words like nootropic, PUFA, DHA, etc. The articles related with synaptic transmission and the phytochemical domination in the neurotransmission were separated for further understanding of mechanism. Results: AChE inhibitory action can preserve the acetyl choline activity while the synaptic transmission exhibited by α-Asarone of AC, BM, etc. Similarly, the Glutamate transmission with the NMDA receptor protected the neuronal degeneration from β-Amyloid like protein accumulation in CP constituents. The Serotonergic and Dopaminergic neurotransmission pathway were also regulated by the herbal and the lipid factors. These different pathways were somehow involved in the memory enhancement. Conclusion: The *ghrita* and the herbals mentioned were maintaining the neuronal synaptic transmission. Further clarification is necessary regarding the intrinsic pathway related to the mechanism of *ghrita* dosage form.

Keywords: *Ayurveda, Medhya, Ghrita,* Nervous System, Neuroprotective, Psychiatric, and Memory enhancer, Glutamate activity, Acetylcholinesterase activity.

Introduction

The incidence of neurological diseases are at such an alarming rise that every third person has been reported as a vulnerable candidate. The cardinal factors that are contributing for such a situation includes stress circumstances, sedentary life style adoptions, changing environmental conditions and anthropological activities apart from the microbial contributions. In 2019, a research involving 204 countries, there were 805.17 million neurological disorder cases with an age-standardised incidence rate of 10 259.50 per 100 000 population and death around 10 million worldwide.(1) In India only, the prevalence rate in 2019 range from 3·0 to 11·9 per 1000 of the population and incidence from 0·2 to 0·6 per 1000 of the population per year. (2) These neurological diseases include Alzheimer's disease, Parkinson's disease, idiopathic epilepsy bipolar disorder, autism spectrum disorders, neurological cancers and different type of dementia. These diseases are not only concerned with individual disabilities but also drains out the economical and stability of livelihood of the individual, society and nation. Despite the tremendous achievement in medical and technological realms, there still exists the need of either a preventive strategy or a treatment aspect to be generated for combating these group of diseases.

Traditional medicine from Indian sub-continent practices the use of clarified butter or *ghrita* as daily regimen to be followed. The use of *ghrita* can be seen in the early hours of birth *Kashyapa Samhita* emphasizes the use of *ghrita* along with the practice of *Swarna Bhasma* in young children for intellect and immunological significance. The traditional form of this includes the custom of rubbing gold against the stone along with *ghrita* and given to the baby. The conventional medicine also has accepted the lipid collection in *ghrita* can surpass the Blood Brain Barrier (BBB). The endothelial cells of brain tissue can passively diffuse many lipid compounds when the same is impermissible to polar compounds that are more than 80 $Å^2$ in surface area.(3) Similarly, the *ghrita* can be seen extensively used in neurological conditions i.e.

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Unmada and *Apasmara* in the relevant classical treatises. *Ghrita* therapeutically purposes in every type of *Shodhana* protocol either as a pre-procedure or as a treatment regimen. In *Shamana* form *ghrita* pacifies the *Vata-pitta dosha* combination. Many studies have been conducted on different herbal plants which are mentioned in these formulations for both neurological and psychiatric manifestations such as *Vacha (Acorus calamus* Linn.*),Shankhpushi* **(***Convolvulus pluricaulis* Choisy*), Guduchi (Tinospora cordifolia* (Willd.) Hook. f. & Thomson*), Yashthimadhu (Glycyrrhiza glabra* (Licorice)*), Bramhi* **(***Bacopa monnierie*), *Mandukaparni (Centella asiatica* (Linn.)*), Kushmanda (Benincasa hispida*(Thunb.) Cogn.*)) etc* and are incorporated in such *ghrita* formulations. Ayurveda explains this property of *ghrita* as *'Samskara Anuvartana'*, which specifies the imbibing nature of phytochemicals. This work extensively screens out the common ingredients in the mentioned *ghrita* formulas and revalidates among the available literature the contributory role in neurological manifestation.

Materials and Methods

Ghrita and the above mentioned herbal constituents were thoroughly checked for the protective action against the neuronal fraction in various in-vitro, in-vivo and clinical trials. The interrelated literatures were derived from Ayurvedic classical texts, research articles and journals. The search in digital databases were conducted using the following keywords: "Ayurveda", Nervous System, Neuroprotective, Psychiatric, and Memory enhancer, Glutamate activity, Acetylcholinesterase activity, etc. Among the search, 100 related articles were screened out and those related to the core synaptic activity were separated for further validation. The studies related to neurogenic transmission and the neurotransmitters interfered with the herbal constituents as a whole or the respective phytochemicals were validated for the neuroprotective activity.

Result

The interrupted neuronal transmission is one of the early disturbances that deteriorates the further cascade of functions. The impairment of memory or cognition and even the coordination of both the central or peripheral motor activity is disrupted due to deranged neuro transmitter metabolism and receptor bindings. The AChE inhibition promotes the Acetyl choline to bind to the related receptors. Similarly, the NMDA receptor activity binds with the glutamate fraction. The Serotonin and the Dopamine levels directly surmount in the quantification aspects to the related receptors. Table no:1 denotes the frequent herbal constituents denoted in the various *ghrita* formulations. Table 2 represents the various experimental models on neurological degradation and the pathways maintained by the herbal inclusions.

Table 1: Various *ghrita* preparations and the respective herbal constituents

S.No.	Name of the *ghrita*	Contents
1	*Brahmi ghrita*	*Brahmi, Vacha, Kushtha, Shankhapushpi* (4)
2	*Saraswata ghrita*	*Abhaya, Trikatu, Patha, Vacha, Shigru*(5)
3	*Ashtanga ghrita*	*Mandukaparni, Vacha, Shankhapushpi, Brahmi, Guduchi, Shweta Bakuchi, Shatavari, Brahmasoma*(6)
4	*Saptanga ghrita*	*Shankhapushpi, Guduchi, Vacha, Shatavari, Arkavallika, Malapu,*
5	*Ashtamangala ghrita*	*Vacha, Kushtha, Brahmi, Siddharthaka, Sariva, Pippali* (8)
6	*Shankhapushpadyam ghrita*	*Shankhapushpi, Vacha, Kushtha, Brahmi* (9)
7	*Vachadi ghrita*	*Vacha, Guduchi, Shathi, Haritaki, Shankhapushpi, Vidanga, Shunthi,*
8	*Mahapaishachik ghrita*	*Jatamansi, Haritaki, Shankhapushpi, Bharangi, Markati, Vacha, Trayamana, Jayanti, Veera, Chorak, Katurohini, Kutki, Brahmi, Varahi, Soya, Palankasha, Guggulu, Shatavari, Kayastha, Rasna, Prasarini, Vrishchikali,*
9	*Pathadya ghrita*	*Patha, Vacha, Shigru, Pathya, Trikatu,* (12)
10	*Phala ghrita*	*Manjishtha, Kushtha, Tagara, Triphala, Vacha, Haridra, Daruharidra, Madhuka, Meda, Dipyaka, Katurohini, Payasya, Hingu, Kakoli,*
11	*Abhaya ghrita*	*Brahmi, Siddharthaka, Kushta, Vacha, Sariva, Pippal, Saindhava lavanan* (14)

Table 2: Herbal constituents and the targeted activity in different experimental models

Herbs	Results	Functions/Outcome measure
Vacha *(Acorus calamus* Linn.)	1.Both α- and β-asarone exhibit multiple pharmacological properties including anti-apoptotic, and neuroprotective effects. Surpasses the blood-brain barrier. (15) 2. β-Asarone inhibited the ACh esterase activity. (16) 3. α-Asarone induced memory traits with d by its GABA antagonist and N-methyl-D-aspartate	Antioxidant, anti-inflammatory, anti-apoptotic, neuroprotective, inhibits AChE and suppresses TNF-α and IL-1β, GABA antagonist and NMDA receptor agonist learning and memory-enhancing activity

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Shankhpushpi *(Convolvulus pluricaulis* Choisy*)*	Reduced the oxidative stress in aluminium induced toxicity and scopolamine induced amnesia in brain of male albino Wistar rats. (18) 2. CP reduced the β-amyloid deposition in the brain to protect from memory dysfunction. (19) 3. It possess memory-enhancing, anxiolytic and CNS-depressant activity with CP showing the maximum activity.(20)	Reduce the production of Aβ, anxiolytic and CNS-depressant activity. Improves the cholinergic behaviour, reduction in oxidative stress, neuroprotective, and immunomodulatory
Brahmi (*Bacopa monnieri*)	Neuronal protection from beta-amyloid-induced cell death. This neuroprotection was possibly due to its ability to suppress cellular acetylcholinesterase activity. (21) 2.BM extract reduced the oxidative stress and prevent the loss of memory. (22) 3. BM reportedly downregulated the activity of MMP-3 and caspase 1 and 3 enzymes that modulate systemic inflammation in N9 microglial cell line. BM inhibits the release of inflammatory cytokines from microglial cells and inhibits enzymes associated with inflammation in the brain. (23)	Reduced the neuronal cell death and improved the memory cognititon, as well as the blocking in production of Aβ
Guduchi *(Tinospora cordifolia* (Willd.) Hook. f. & Thomson)	1.Butanol extract of TC pre-treatment given in Glutamate induced neurotoxicity resulted in downregulation in the expression of neuronal markers and anti-apoptotic marker Furthermore, Butanol extract of TC was observed to promote regeneration, migration and plasticity of cerebellar neurons. (24) 2. TC produced significant neuroprotection by increasing the dopamine level. Parkinson's disease in male Wistar rats. (25) 3. TC effectively mitigated ROS generation and prevented oxidative stress in mitochondrial dysfunction. (26)	Neuronal plasticity maintenance and protection against degeneration.
Shatavari *(Asparagus racemosus)*	1.*Shatavarin* improved Parkinson's disease symptoms by reducing accumulation of alpha-synuclein, lipid accumulation and increased the dopamine level. (27) 2. . AR enhanced the brain-derived neurotrophic factor (BDNF) and ERs up-regulation which may be	Enhanced BDNF and reduced the Oxidative stress.
Patha *(Cissampelos Pareira* Linn.)	1.*Patha* reduced the age related cognitive decline . (29) 2. Patha showed significant results in comparison with the Daizepam for the anxiety-like behaviour in adult albino rats. (30)	Protects from cognitive decline and exerts the anxiolytic behaviour.
Shigru *(Moringa oleifera Lam)*	Leaf extract showed potent nootropic activity.(31)	Nootropic and antidepressant activity.
Trikatu *(Zinziber officinale* Roscoe*, Piper nigrum*(L.), *Pippali, Piper longum* L. *)*	1.*Piperine* protected from mitochondrial integrity via reducing oxidative stress and improving mitochondrial membrane potential and neuronal survival in a cerebral ischemia rat model. (32) 2. Piperine exhibited the antioxidant and cognitive enhancement in streptozotocin (STZ)-induced dementia in Male Wistar rats. (33)	Improved mitochondrial membrane potential and neuronal survival.
Triphala *(Emblica officinalis Gaertn, Terminalia bellerica (Gaertn) and Terminalia chebula* Retz.*)*	1.*Triphala* polyphenols reduced the stress induced cognition deficit.(33) 3.*Triphala* enhanced the memory functions in the AD (34)	Improved the cognition deficiency and the memory functions

Discussion

Ghrita is included under *Chatushasneha*, along with *Taila,Vasa and Majja*. The quality to imbibe the features of the coalesced ingredients and the unique ability to reach within the deepest tissue in a *ghrita* dosage form makes this oily preparation significant from the rest of the lipid fractions. It is used as food as well as for therapeutic purposes. *Acharya Kashyapa* has

mentioned, various herbs that are utilized in conjunction with *ghrita* to strengthen *Medha* given in the concept of *Jatakarma Samskara*. *Kashyapa* also mentioned various formulations i.e. *Abhaya Ghrita* which contain herbs which have nootropic effect. *Acharya Charaka* has also mentioned various *ghrita* such as *Brahmi ghrita, Kalyanka ghrita, Mahakalyanaka ghrita* etc. which is recommended in *Unmada* and *Apasmara*. It can be utilized not only for the growth and development of young children but also for older adults due to its abilities to support memory, cognition, and bodily functions that are necessary for the body to function properly.

In conventional science *ghrita* can be regarded as a lipophilic dairy product containing lipid, water and less than of non-fat substances. It is rich in Polyunsaturated fatty acid (PUFA) of omega-6 and omega-3 series, especially Docosahexaenoic acid (DHA) and Arachidonic acid (AA) which is responsible for the development and maintaining the function of the brain since childhood and throughout life. Another constituent Butyric acid (BA) was found to combat the *Porphyromonas gingivalis* and *Fusobacterium nucleatum* that leads to periodontitis. This was by preventing the apoptosis rate, accelerating the SOD, CAT enzymes and preserving the mitochondrial status. (35) The neurons utilize the oxygen to generate Reactive Oxygen Species (ROS) that directly depletes the anti-oxidant enzymes which are also seen in age old conditions or when disease pathogenesis encroaches the body. The above mentioned herbals constituents exhibit the anti-oxidant and anti-inflammatory activity besides the antiepileptic, antidepressant, nootropic activity, etc. The active component of these herbs could be the main reason for the pharmacological activity in the brain through different pathways. *Ghrita* as main ingredient not only act on the brain and perform different functions i.e. neural development, nerve cell differentiation and migration, myelinations and synaptogenesis, but also act as target-delivery agent for the active chemical constituent of these herbs through synergistic effect.

Memory loss is an initial symptom of neuronal degeneration other than confusion, irritation, behavioural changes and other cognitive deficits. In the most common Scopolamine related models the Akt, MAPK and ERK pathways are found to be affected. This muscarinic receptor antagonist models targeted the acetylcholinesterase inhibitor research. The methanolic extract of AC rhizome are found in many such induced model for such inhibitory activity. The aqueous and dichloromethane extracts were showing the dose related deviations and (36) α-Asarone is the major compound isolated acting upon the cortex, hippocampus and the striatum regions. The acetylcholine preservation at the synaptic sites are found to be the reason inferred from these models. CP exerted the activity in the cortex and the hippocampus regions of male Wistar rats. (37) BM carries the phytochemicals like quercetin, apigenin, wogonin, and bacopaside X, which were showing the affinity towards the Acetylcholinesterase (AChE) with weak hydrogen bonds and vander walls force of attraction for the inhibition via anionic sub-active site of AChE which is same as the mechanism shown by Donepezil. (38) AR exerted the evidence of AchE inhibition on the hippocampal and the prefrontal cortex of the charles foster male albino rats by the steroidal saponin content. (39) Tinosporide and 8-hydroxytinosporide isolated from TC were the other phytomolecules with this synaptic inhibition of the AChE. (40) The combined effects of Triphala or Trikatu are not much explored in this aspect even though individual drugs like Emblica officinalis is reported with this activity. (41)

The L –glutamate and the ROS induced neuronal cell death are the other target specified pharmacological models with confined effects on the NMDA receptors. These are the glutamate receptors that influence the synaptic plasticity along with the memory and learning. α-Asarone of AC was exerting the protection on the hippocampal cells against Endoplasmic Reticulum stress with the phosphorylation of the protein kinase RNA-like ER kinase (PERK). (42) An in-vitro model on mice hippocampal cell line (HT22 cell line) exhibited the protective model activity with the hexane extract from BM. (43)

In similar fashion the serotonin transmission and synthesis is also necessary for the proper psyche. The Selective Serotonin reuptake inhibitors are regarded as one of the effective anti-depressant medicines. BM has been found to increase the tryptophan hydrolase activity which is the enzyme needed for Serotonin synthesis. This increases the levels of serotonin synaptic activity by the drug. (44)The same upregulation can be seen in the SERT (Serotonin Transport Proteins), which are the transport proteins for the further metabolism which creates the contrast activity but indicates the adaptability of neuronal fraction to the available phytochemicals. (45) . But AC has seen only to increase the serotonin levels. (46). Whereas the CP and TC can regulate the dopaminergic and the serotonergic pathways.

The lipid fractions of *ghrita* like DHA along with these herbal contents can improve the synaptic transmission. The passive diffusion of DHA might be facilitated due to the concentration of the neuronal grey matter, synopsis, mitochondria and microsomal factors embedded with such lipid fractions. (47) Many in-vivo models also report the high DHA diet and synaptic improvement of the DHA levels. There are evidences for less neuronal cognitive decline in regions consuming the heavy DHA embedded diets. (48)

Conclusion

We can conclude that *ghrita* base formulation is a special product in terms of both as a food and medication which is beneficial to all age groups particularly from the time of birth for the development of brain. *Ghrita* carries the better bio-availability, when processed with nootropic herbs increasing the potency and have better absorption and transportation of phyto-constituents. More researches have to be conducted to determine the pharmacodynamic and pharmacokinetics characteristics of these formulations.

Abbreviations:
AA : Arachidonic acid
Aβ : Amyloid beta peptide
ACh : Acetylcholine
AChE : Acetylcholinesterase
AD : Alzheimer's disease
AR : *Asparagus racemosus*
BA : Butyric acid
BM : Bacopa monnierie
BDNF: Brain-derived neurotrophic factor
CAT :Chloramphenicol acetyltransferase
CNS : Central Nervous System
CP : Conculvulus pluricauli
DHA : Docosahexaenoic acid
GABA : Gamma-aminobutyric acid
IL-1β : Interleukin-1β
NMDA receptor : N-methyl-D-aspartate receptor
TC : *Tinospora cordifolia*
TNF-α :Tumor necrosis factor alpha
STZ : streptozotocin
PUFA : Polyunsaturated fatty acid
SOD : Superoxide dismutase
ROS : Reactive oxygen species

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