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EVIDENCE BASED ANTI-DEMENTING ACTIVITY OF SARASWATA GHRITA "A NOOTROPIC COMPOUND FROM AYURVEDA

Obed Ahmed Ansari, J.S. Tripathi and Sayema Ansari

Division of Manas Chikitsa (Psychosomatic Medicine and Neuropsychiatry), Department of Kayachikitsa, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

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Correspondence to Author:

Obed Ahmed Ansari

M. D. Scholar Final year, Division of Manas Chikitsa (Psychosomatic Medicine and Neuropsychiatry), Department of Kayachikitsa, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

E-mail: obi2712@gmail.com

ABSTRACT: Life expectancy is increasing as a result of advancement in medical science and the availability of better healthcare services. As the risk of dementia increases with increasing age, the number of persons with dementia in the general population is also rising. Alzheimer's disease is the most common form of dementia, accounting for approximately 70% of the dementia cases. So far, efforts to find a cure for Dementia have been disappointing, and the drugs currently available to treat the disease address only its symptoms and with limited effectiveness. Apart from genetic susceptibility, chronic exposure to other toxins, free -radical damage, Diabetes, high blood pressure, and high cholesterol, high homocysteine level are the major risk factors for Alzheimer's and stroke-related dementia. Reducing oxidative stress by anti-oxidants, protecting brain inflammatory lesions using anti-inflammatory drugs and facilitation of brain cholinergic neurotransmission with anti-cholinesterase are some positive approaches to management for dementia especially in Alzheimer's disease. *Saraswata ghrita*, a polyherbal medhya compound drug used in traditional medicine for cognition and memory related problems is blended with the drugs, which exert a variety of pharmacological actions including anti-inflammatory, anti-amyloidogenic, anti-cholinesterase, hypolipidemic, and antioxidant properties. This paper encompasses the brief descriptive information of different scientific studies on various ingredients of *Saraswata ghrita*.

INTRODUCTION: Life expectancy is increasing as a result of advancement in medical science and the availability of better healthcare services. The proportion of elderly persons in the general population is therefore rising.

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Dementia is a syndromic representation of different pathologies of brain – usually of a chronic or progressive nature – characterized by disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement without any impairment in consciousness.

Alzheimer's disease is the most common form of Senile dementia and possibly contributes to 60–70% of cases. Other major contributors include vascular dementia, Dementia with Lewy bodies,

and a group of diseases that contribute to Frontotemporal dementia. The boundaries between subtypes are indistinct and mixed forms often co-exist [1]. Due to increasing life expectancy the number of people suffering from Senile dementia would increase rapidly in both developed and developing countries. More than 25 million people suffered from Senile dementia in 2000. By 2030, that is expected to rise to 63 million, 65% of whom in less developed countries [2].

Senile dementia is one of the major causes of disability in later life. So far, efforts to find a cure for dementia have been disappointing, and the drugs currently available to treat the disease address only its symptoms and that too with limited effectiveness. It is believed that therapeutic interventions that could postpone the onset or progression of dementia would dramatically reduce the number of cases in the next 50 years [3].

Apart from genetic susceptibility chronic exposure to other toxins, free -radical damage, Diabetes, high blood pressure, and high cholesterol, high homocysteine level are the major risk factors for Alzheimer's and stroke-related dementia [4]. Reducing oxidative stress by anti-oxidants, protecting brain inflammatory lesions using anti-inflammatory drugs and facilitation of brain cholinergic neurotransmission with anti-cholinesterase are some positive approaches to management for dementia especially of Alzheimer's type [5].

Through the ages, many medicinal herbs have been used to improve memory and cognitive function and to treat neurodegenerative diseases in traditional medicine. Pharmacological effects of some plants have also been reported[6]. Ayurveda, the Indian system of medicine, is gaining greater attention and popularity in many parts of the world.

The disease preventive and health promotive approach of Ayurveda, which takes into consideration the whole body, mind and spirit while dealing with the maintenance of health promotions, now enjoys increasing acceptability. Ayurveda had developed certain dietary and therapeutic measures to delay ageing and rejuvenating whole functional dynamics of the body organs.

This revitalization and rejuvenation is known as the 'Rasayana chikitsa' (rejuvenation therapy) [7]. Ayurveda claims that several plants, the "Medhya" plants (intellect promoting) which have been found beneficial in cognitive disorders [8].

Saraswata ghrita, an Ayurvedic polyherbal drug, described in ayurveda classics is a unique combination of Medhya drugs having high content of *Brahmi*, which is a well-known drug for its Nootropic and Memory enhancing properties through various researches and clinical studies [9-11]. The Ghrita also contains *Haridra*, *Amlaki*, *Haritaki*, *Pippali*, *Vidanga*, *Kushta* and *Vacha* like drugs which are having a variety of pharmacological action including anti-inflammatory, anti-amyloidogenic, anti-cholinesterase, hypolipidemic, and antioxidant effects.

Ingredients at a glance:

Hindi Name	Botanical Name
Brahmi	*Bacopa monnieri*
Termeric	*Curcuma longa*
Amalaki	*Embellica officinalis*
Kustha	*Saussurea lappa*
Nishotha	*Operculina terpethrum*
Haritaki	*Terminalia chebula*
Pippali	*Piper longum*
Vidanga	*Embelia ribes*
Vacha	*Acorus calamus*
Saindhava	*Rock Salt*
Goghrita	*Clarified Butter*

Critical Review of Scientific studies on ingredients:

Brahmi (*Bacopa monnieri*): *Brahmi* (also known as Bacopa) is a bitter-tasting creeper plant found in damp and marshy areas and is commonly used in Ayurvedic medicine as a nerve tonic, diuretic, and cardiotonic and as a therapeutic agent against epilepsy, insomnia, asthma, and rheumatism [12]. The principal constituents of *Bacopa monnieri* (BM) are saponins and triterpenoid, bacosaponins that include bacopasides III to V, bacosides A and B, and bacosaponins A, B, and C [13]. Traditionally, BM was used to improve memory and cognitive function [14]. The BM extracts have been investigated extensively for their neuropharmaco-logical effects and their nootropic actions [15].

Vollala *et al* [16] examined the effect of *Bacopa monnieri* (*Brahmi*) extract (20, 40 and 80mg/kg) on learning and memory in rats employing spatial learning (T-maze) and passive avoidance tests. The results showed improvement in spatial learning performance and enhanced memory retention in rats treated with extract. The probable mechanism was attributed to its action on the repair of damaged neurons, neuronal synthesis, and the restoration of synaptic activity with ultimately effect on nerve impulse transmission.

In another study investigated by Saraf *et al* [17], *Bacopa monnieri* significantly alleviated Nω-nitro-L-arginine methyl ester (L-NAME) (a nitric oxide inhibitor) induced amnesia in mouse model of morris water maze study. Nitric oxide synthase (NOS) mediated pathway was supposed to plays a more dominant role in *B. monnieri*–mediated reversal of amnesia.

BM also inhibited cholinergic degeneration and displayed a cognition-enhancing effect in a rat model of AD [18]. Based on animal study results, bacosides were shown to have antioxidant activity in the hippocampus, frontal cortex and striatum[19]. Animal research has shown that the BM extracts modulate the expression of certain enzymes involved in generation and scavenging of reactive oxygen species in the brain [20]. It was suggested that the adaptogenic properties of the herb would be beneficial in the management of stress related conditions as BM showed the potential to be effective in stress in a study on rats [21].

BM extract has shown neuroprotective effect against aluminium-induced oxidative stress in the hippocampus of rat brain [22]. Yet another study suggested that BM extract reduces amyloid levels in PSAPP mice and can be used in the therapy of Alzheimer's disease [23].

Turmeric (*Curcuma longa*): Turmeric is a rhizomatous herbaceous perennial plant of the ginger family, Zingiberaceae. Derived from the rhizome and root, *Turmeric* is used as a spice and colouring agent and in traditional medicine in Asia. The active constituents are thought to be Turmerone oil and water soluble Curcuminoids, including Curcumin [24]. Curcumin is the principal curcuminoid and is responsible for the yellow colour of the *Turmeric* root [25].

The molecule is known to possess antimicrobial, anti-inflammatory, antihypertensive, anti hyperlipidemic, antitumor, anticancer, anti-phlogistic, antidiabetic, antipsoriasis, anti-thrombotic, antihepatotoxic and many other useful properties [26]. Besides its protective action in peripheral organ disorders, the molecule is known to possess neuroprotective properties as well [27].

Reviewers suggest *Curcumin* may be a promising therapy for Senile dementia especially in AD because it has at least 10 neuroprotective properties, including anti-inflammatory, antioxidant, inhibition of βA formation, clearance of existing βA, and copper and iron chelation [28-30]. Animal studies have indicated that *Curcumin* can enhance the adult hippocampus neurogenesis process by increasing the number of newly generated cells in the dentate gyrus region of hippocampus [31].

Moreover, it is a potent inhibitor of reactive astrocyte expression and thus, prevents hippocampal cell death induced by kainic acid[32]. In one of the recent studies, low doses of *Curcumin* has shown to effectively disaggregate beta amyloid as well as prevents fibril and oligomer formation and thus found to be protective in treating Alzheimer's disease [33]. Epidemiologic studies show a 4.4-fold lower incidence of AD in Southeast Asian countries where *Turmeric* is commonly used as a dietary spice [34].

Curcumin also enhances the level of neurotrophic factors such as brain derived neurotrophic factor (BDNF) [35]. Apart from its neutoprotective action *Curcumin* has also shown powerful antioxidant and anti-inflammatory properties [36]. In addition, a low dose of *Turmeric* (160 parts per million, or ppm) reduced proinflammatory cytokine levels that are linked to the neuroinflammatory cascades involved in neuritic plaque pathogenesis [37]. *Curcumin*'s *in vitro* ability to inhibit lipid peroxidation and neutralize reactive oxygen species may be several times more potent than that of vitamin E [38].

Amla (*Embellica officinalis*): The fruit *Emblica officinalis*, syn: *Phyllanthus emblica* (Euphorbiaceae), Emblic myrobalan locally known as *Amla* is one of the important herbal drugs used in Unani (Graeco-Arab) and Ayurvedic systems of medicine.

Emblica officinalis (*E. officinalis*) is used both as a medicine and as a tonic to build up lost vitality and vigor. *Amla* is a richest source of Ascorbic acid (Vitamin C) [39]. *Amla* as well as Ascorbic acid has been shown to be effective as memory enhancers in our earlier studies [40-42]. On similar lines, all formulations in which *Amla* or Ascorbic acid are used as a base (or principal constituent) would produce beneficial effects on memory performance by virtue of their Ascorbic acid content. Vitamin C in *Amla* accounts for approximately 45-70% of the antioxidant activity [43].

Rats were examined for the antioxidant properties of *Amla* extracts and its effect on the oxidative stress in streptozotocin-induced diabetes was also reported. The extracts showed strong free radical scavenging activity. *Amla* extracts orally administered to the diabetic rats slightly improved body weight gain and also significantly increased various oxidative stress indices of the serum of the diabetic rats. Moreover the decreased levels of albumin in the diabetic rats were significantly improved with this drug. It also significantly improved the serum adiponectin levels. Thus, *Amla* can be used for relieving the oxidative stress and improving glucose metabolism in diabetes [44].

Flavonoids derived from *Amla* exhibit maximum beneficial action by eliciting highly potent hypolipidaemic and hypoglycaemic activities. In addition to this, flavonoids were found to be effective in elevating the haemoglobin levels in rats[45]. In another study, *Amla* churna has been found very effective for hypercholesterolemia and prevention of atherosclerosis [46].

Kushta (*Saussurea lappa*): *Saussurea lappa* is costus plant from the family of Compositae. It is founds in himalyan region and the root is widely used for various diseases due to its broad medicinal property. This plant contain active principles like Saussurine, Costunolide, Lactones and the pharmacologial activity of this plant has demonstrated for its hepatoprotective, hypo-glycemic, antidiabetic, hypotensive and vaso-relaxation effects [47]. Ethanolic extract of *Saussurea lappa* at a dose range of 50–200 mg/kg, p.o. was studied for the acute and chronic inflammation induced in both mice and rats. The extract showed considerable values for anti-inflammatory activity through carrageenan-induced paw oedema and peritonitis animal models which showed the anti-inflammatory activity in a dose dependent manner [48].

Saussurea lappa was found most effective for obese, diabetes in a recent clinical study on potent hypoglycaemic plants of different regions from India was undertaken to find antidiabetic plants used in Indian folklore and by different tribes [49]. An immunostimulant activity of Inuline (isolated from costus root) has been also reported in an experimental study [50].

Nishotha (*Operculina terpethum*): *Nishotha* (*Operculina turpethum* syn. *Ipomoea turpethum*) is commonly used since centuries in Ayurvedic system of Medicine to treat fevers, edema, ascites, anorexia, constipation, hepatosplenomegaly, intoxication, haemorrhoids, fistula, anemia, obesity, abdominal tumors, ulcers/wounds, worm infestation, pruritus and other skin disorders [51].

The root extract of *Operculina turpethum* has been used as an anti-inflammatory, purgative and hepatoprotective agent [52]. In a clinical study Ethereal, alcoholic and aqueous extracts of roots of *Operculina turpethum* (Nishoth) have been screened for their anti-inflammatory activities [53].

The antidiabetic potential of the methanolic extract of *O. turpethum* stem (MEOTS) and methanolic extract of *O. turpethum* root (MEOTR) was also evaluated in the Streptozotocin (STZ) - induced type 2 diabetic models. The dose 100 mg/kg of MEOTS and MEOTR were administered to normal, glucose loaded and experimental diabetic rats for 21 days. The significant reduction in fasting blood glucose levels were observed in the normal rats at 3 h as well as in the treated diabetic animals at 21 days [54]. This shows the strong hypoglycaemic action of *Operculina terpethrum*.

In another type of experimental study the Antioxidant activity of methanolic extract of *Operculina turpethum* stems (MEOT) on 7, 12 dimethylbenz(*a*)anthracene (DMBA) induced breast cancer was investigated in female Sprague–Dawley rats. Oral administration of MEOT remarkably reduced the lipid peroxidation activity and increased the antioxidants level in drug treated animals and decreased the tumour weight significantly [55].

Haritaki (*Terminalia chebula*): *Haritaki* (*Terminalia chebula*, family combretaceae) commonly called as Black myrobalan, Ink tree (or) Chebulic myrobalan is a moderate tree used in traditional medicines The dried ripe fruit of *T. chebula* is an important Indian herb used extensively in the indigenous system of medicine (Ayurveda) for its homeostatic, antitussive, laxative, diuretic, and cardiotonic activities [56]. The antioxidant and free radical scavenging properties of *Haritaki* have been well proven in different studies. The leaves, bark and fruit of *T. chebula* possessed high antioxidant activity and phenolics were found to be responsible for this activity [57].

Strong antioxidant activity of aqueous extract of *T. chebula* was observed by studying the inhibition of radiation induced lipid peroxidation in rat liver at liver microsomes at different doses [58] and methanolic extract was also found to inhibit lipid peroxide formation and to scavenge hydroxyl and superoxide radicals *in vitro* [59]. Cytoprotective effect on oxidative stress and inhibitory effect on cellular aging of *Teminalia* fruits have also been documented in some studies [60].

Hypolipidemic activity of *T. chebula* extract against experimentally induced athersclerosis has been documented [61]. It also possessed hypocholesterelomic activity against cholesterol-induced hypercholesterolemia and atherosclerosis in rabbits [62]. *T. chebula* in a polyherbal formulation (Aller-7) exhibited a dose dependent anti-inflammatory effect against Freund's adjuvant induced arthritis in rats [63]. *T. chebula* fruit and seeds exhibited dose dependent reduction in blood glucose of streptozotocin induced diabetic rats both in short term and long term study and also had renoprotective activity [64, 65].

Pippali (*Piper longum*): *Piper longum* popularly known as *Pippali* belonging to the family Pipperaceae, an important medicinal plant is used in traditional medicine in Asia and Pacific islands especially in Indian medicine [66]. It is a common Indian dietary spice which has been shown to possess a wide range of therapeutic utilities in the traditional Indian medicines. Piperine is the major and active constituent of long pepper (*Piper longum*) which is responsible for it pungent smell and has been found to possess a number of therapeutic properties [67].

The effect of Piperine, have been investigated, on memory performance and neurodegeneration in animal model of Alzheimer's disease, showed that Piperine significantly improved the memory impairment and neurodegeneration in hippocampus [68]. Piper extracts and Piperine possess inhibitory activities on prostaglandins, leukotrienes, as well as on NF-κB activation, and thus exhibit anti-inflammatory activity [69]. In a different animal study, an aqueous suspension of *P. longum* root powder demonstrated weak opioid but potent NSAID type of analgesic activity [70].

Oral administration of dried fruits has been demonstrated significant anti-hyperglycemic, antilipidperoxidative and antioxidant effects in diabetic rats comparable to that of the standard reference drug glibenclamide in Alloxan induced diabetic rat [71]. The different bio chemical constitution of *Piper longum* fruits showed potent Hypochoesterolaemic activity in rat model [72, 73]. *Pippali* also possess weak hypertensive effect as intravenous administration of piperine showed dose dependent (1 to 10mg/kg) decrease in mean arterial pressure in normotensive anaesthised rat [74].

The antidepressant activity of piper longum has been also reported in some studies [75, 76]. Apart from all these activity, *Pippali* is known to have a potent bio-enhancer activity. Piperine an major alkaloid of *Pippali* was found to enhance the bioavailability of structurally and therapeutically diverse drugs, possibly by modulating membrane dynamics due to its easy partitioning and increase in permeability of other drugs [77].

Vidanga (*Embelia ribes*): *Embelia ribes*, commonly known as *Vidanga*, is a large woody climbing shrub that belongs to the family, Myrsinaceae, which is widely distributed in India, Sri Lanka, Malaysia and South China. Embelin is the main bioactive molecule responsible for its various pharmacological and medicinal properties [78]. It is highly valued in Ayurveda as a powerful anthelmintic [79].

Various preparations of the plant are also known to be used as brain tonic and for treating mental disorders [80]. In a preliminary study, Tripathi [81] has demonstrated the blood glucose lowering activity of the decoction of the *Embelia ribes* fruits in glucose-fed albino rabbits.

Bhandari *et al*., [82, 83] have reported the antidiabetic, dyslipidemic and antioxidant activity of *Embelia ribes* Burm in streptozotocin-induced diabetic rats, using gliclazide as a positive control drug.

In a recent study, the aqueous extract of *Embelia ribes* treatment enhanced the antioxidant defence against methionine-induced hyperhomo-cysteinemia, hyperlipidemia and oxidative stress in rat brain [84]. The Embelin also showed anxiolytic activity in different animal model. Free radical scavenging and antioxidant activity of Embelin have been also reported in some studies [85].

Vacha (*Acorus calamus*): *Acorus calamus* (Family: Acoraceae) is a semi-evergreen perennial medicinal plant with scented rhizomes, arching tapered reed-like leaves and minute yellow-green flowers. It is known as *Vacha* in Ayurveda and the rhizome of this plant has been used in Indian and Chinese system of medicine for hundreds of years to cure diseases especially the central nervous system (CNS) abnormalities [86]. The rhizomes are considered to possess anti-spasmodic, carminative and antihelmintic properties and also used for treatment of epilepsy, mental ailments, chronic diarrhea, dysentery, bronchial catarrh, intermittent fevers and tumors [87].

Apart from these, *Acorus calamus* also possesses anticholinesterase and neuroprotective activity [88]. The ethyl acetate extract of *Acorus calamus* was found to be potent antioxidant by inhibition of 1, 1-diphenyl-2-picrylhydrazyl (DPPH) free radical [89]. Administration of the 50% ethanolic extracts (100 and 200 mg/kg) as well as saponins (10 mg/kg) isolated from the root extract of *Acorus calamus* demonstrated significant hypolipidemic activity [90].

The whole formulation is in *Ghrita* form. Ayurveda has traditionally considered ghee to be the healthiest source of edible fat, with many beneficial properties. According to Ayurveda, ghee promotes longevity and protects the body from various diseases.

Ghee has been heavily utilized in Ayurveda for thousands of years for its health-promoting properties. It is administered alone and is used in conjunction with herbs to treat various disorders. There are 55-60 types of medicated ghee described in the Ayurvedic texts [91].

Ghee carries the therapeutic properties of herbs to all the body's tissue. The lipophilic action of ghee facilitates transportation to a target organ and final delivery inside the cell since the cell membrane which also contains lipid. Ghrita can also be used as a bio enhancer for the drugs which have poor bio availability like *Curcumin* [92]. Many of Ghrita formulation have been proved for their Nootropic and memory enhancer properties [93].

CONCLUSION: In traditional system of medicines, various plants and their isolated phytochemicals have been used for treatment of various disorders related to learning and memory. *Saraswata ghrita* has great potential to show activities relevant for their use in the disorders like Alzheimers disease and Dementia.

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