



Review Article

Herbal Medicine for the Mind: Traditionally Used Medicinal Plants for Memory Loss from the Indian Subcontinent



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Abstract

Memory loss is a symptom of several neurological disorders, including dementia and Alzheimer's disease (AD). It can significantly impact individuals, their loved ones, and society as a whole. Current pharmaceutical interventions have shown some improvement in individuals' quality of life, but more needs to be done to reduce the burden of memory loss and AD. This paper investigates herbal remedies for memory loss, with a particular focus on the mechanisms underlying their effects. By consulting several South Asian printed books, numerous traditionally used medicinal plants with memory-enhancing properties were identified. A review of published studies showed that many of these plants have reported properties related to memory enhancement and the treatment of AD. Some of the relevant mechanistic actions reported for these plants include acetylcholinesterase inhibition, anti-inflammatory activity, antioxidant effects, and neuroprotective properties. There is also evidence that some plants exhibit a combination of different mechanisms, making them especially promising as therapeutic agents for memory loss. Our review shows the existence and potential of medicinal plants in addressing memory loss. Additionally, some reports provide a scientific basis for the use of these plants in conditions characterized by memory decline, such as AD. This study underscores the importance of further research to evaluate the efficacy of traditionally used medicinal plants in the management of memory loss.

Introduction

Human life expectancy has been steadily increasing.¹ With this rise in lifespan, the prevalence of chronic illnesses has also grown.^{2,3} Chronic diseases such as Alzheimer's disease (AD), dementia, diabetes, cancer, and heart disease are now more common than ever before.^{4,5} The prevalence of these conditions is expected to continue increasing over the next decade.⁶ Neurocognitive disorders such as AD and dementia are projected to affect 152 million people worldwide by 2050.⁷ These disorders are characterized by cognitive decline and memory loss. They impact not only the patients but also their loved ones and society at large.⁸ Numerous mechanisms can contribute to neurocognitive and memory disorders, including chronic inflammation,⁹ oxidative stress,¹⁰ and vascular insufficiency,¹¹ all of which can lead to neuronal cell death.¹²

While certain pharmacological treatments exist for these disorders,¹³ they are often limited by issues of affordability, accessibility, efficacy, and tolerability.¹⁴ Consequently, there is a growing interest in holistic and herbal alternatives that may offer comparable efficacy to pharmaceuticals, while potentially reducing costs and adverse effects.¹⁵

Traditional herbal medicine has long been a mainstay of treatment throughout human history, especially in Asia and the Indian Subcontinent.^{16,17} Recently, traditional medicine practices have gained popularity in other parts of the world, especially among individuals seeking alternatives to conventional pharmaceuticals.¹⁸ This paper sought to identify plants traditionally used in the Indian Subcontinent to manage memory impairment and to evaluate whether any of these plants have been experimentally studied for this purpose. Memory loss is a symptom seen in several different conditions, including dementia. Common symptoms of dementia include memory loss as well as problems with judgment, language, and reasoning. Dementia itself can result from a variety of underlying conditions, including Alzheimer's disease, Lewy body dementia, and vascular dementia.

The first phase of this study involved surveying South Asian medicinal plant books to identify as many plants as possible believed to have beneficial effects on memory loss. Several local books and sources were consulted.^{19–34}

The second phase of the study involved a literature search using

Keywords: Acetylcholinesterase; Alzheimer's disease; Herbs; Memory; Plants; South Asia; Traditional medicines.

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Table 1. List of plants traditionally used for their memory-enhancing effects in South Asia

Botanical name	Family	Local name (Hindi)	English name	Part used	References
<i>Acacia nilotica</i>	Mimosoideae	Babul, kikar	Gum Arabic tree	Gum	27
<i>Acorus calamus</i>	Aracaceae	Waj, bach	Sweetflag	Roots	33
<i>Anacardium occidentale</i>	Anacardiaceae	Kaju, kaja	Cashew nut	Nuts	33
<i>Boswellia glabra</i>	Burceraceae	Kundar, Salai loban	Indian olibanum	Gum, resin	33
<i>Celastrus paniculatus</i>	Celastraceae	Malakanguni	Staff tree	Seed, leaf, oil	23
<i>Centaurea behen</i>	Compositae	Safed bahman	Behen, centaurea	Roots	33
<i>Coriandrum sativum</i>	Umbelliferae	Dhania	Coriander	Fruit, leaf	23
<i>Evolvulus alsinoides</i>	Convolvulaceae	Shankapushpi	Dwarf morning-glory	Whole herb	23,24
<i>Hydrocotyle asiatica</i>	Umbelliferae	Khulakudi	Indian pennywort	Whole plant, leaf	23
<i>Panax ginseng</i>	Araliaceae	Jenseng, tapmari	Ginseng	Roots, tea of leaf	33
<i>Salvia officinalis</i>	Labiatae	Salbia sefakuss	Common sage, garden sage	Leaves (dried)	20
<i>Withania somnifera</i>	Solanaceae	Asgandh, ashvagandha	Winter cherry, withania	Roots	33
<i>Zingiber officinale</i>	Zingiberaceae	Adrak, zinjibeel, sonth	Ginger	Rhizomes	25,33

The search was performed using several South Asian books.

databases such as PubMed and Google Scholar to determine whether any of the identified plants have been scientifically shown to possess memory-enhancing properties. Given the various pathways and mechanisms contributing to memory loss, additional reported properties—such as anti-inflammatory, antioxidant, neuroprotective effects, and impacts on cerebral blood flow—were also recorded.³⁵

Memory-enhancing medicinal plants

A total of 13 traditionally used plants from local South Asian texts were identified as having memory-enhancing properties (Table 1).^{20,23-25,27,33} As stated, all these texts are local books from South Asia (India and Pakistan). The terms we searched for in the plant descriptions within these books were “memory” and “forgetful-

ness.” This led to the identification of these plants, which are traditionally known in local customs as those that can help individuals with memory issues. Table 1 also shows the plant families they belong to, their local names (usually in Hindi or Urdu), their English names, and the parts of the plants used for this specific memory-enhancing effect. The books did not provide further details on the manner of use or any mechanisms behind these plants’ effects. These books are not research- or science-based but instead present a collection of information based on folk knowledge and culture. The only information provided was the indication that the plants listed in Table 1 have traditionally been used to benefit people with memory loss. These plants belong to different plant families, although two of them are members of the Umbelliferae family (Fig. 1). Several studies have shown that plants from this family have beneficial effects on memory.³⁶⁻³⁸ The most commonly used parts of these plants for this benefit are the leaves and roots (Fig. 2).

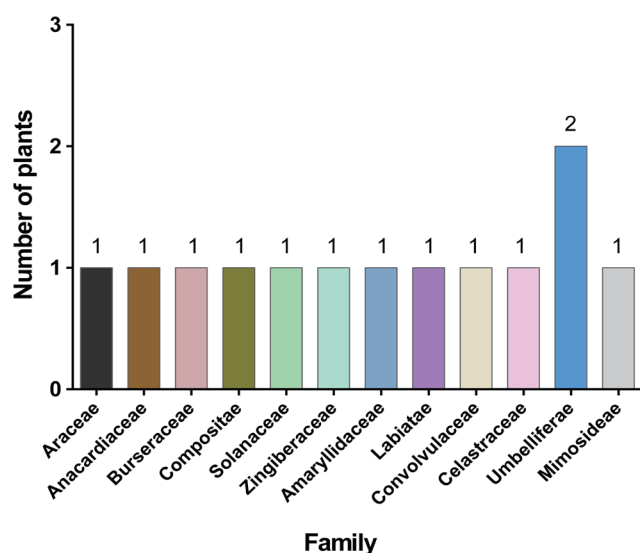


Fig. 1. Graph showing the different plant families represented by the memory-enhancing plants.

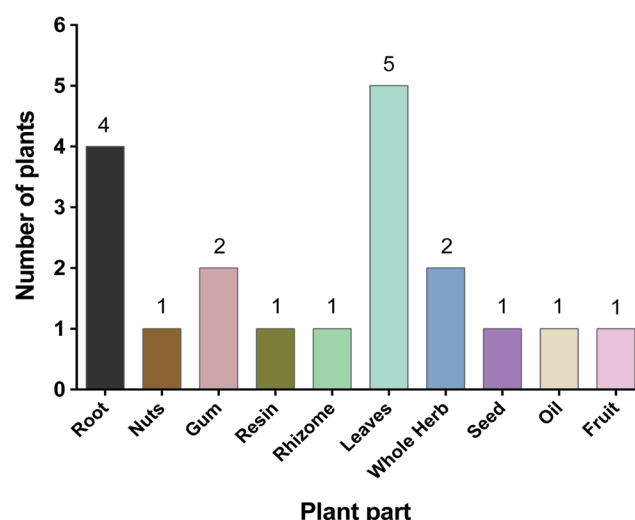


Fig. 2. Graph showing the different plant parts traditionally used for enhancing memory from the discussed medicinal plants.

After reviewing the published studies, we found that the roots and leaves of many different plants have been scientifically proven to be effective against memory loss.^{39,40}

Scientific evidence to back these plants

The second phase of the study involved investigating whether the plants listed in Table 1 have any scientific evidence supporting their memory-enhancing effects. This was done through a literature review of these plants on databases such as PubMed and Google Scholar. Several plants from Table 1, when searched through these databases, were found to have been reported with evidence supporting their memory-enhancing effects (Table 2).^{41–126} Of the 13 plants, only *Boswellia glabra*, *Centaurea behen*, and *Hydrocotyle asiatica* were not found to have any published data on this aspect of their pharmacology. While searching the databases, we used the following terms to help find relevant information: memory, dementia, Alzheimer's disease, and cholinesterase (ChE), one of the main mechanisms through which chemicals can benefit memory deficits.

Mechanism of action involving acetylcholinesterase inhibition

Table 2 shows all the plants with reported activities on memory enhancement. The table also details the primary mechanisms proposed in those studies for their memory-enhancing effects, the experimental models used, and the potential chemicals in the plants responsible for these activities. For all the plants listed in Table 2, the predominant mechanism proposed for their memory-enhancing effects is the inhibition of ChE enzymes, namely acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). The exact pathogenesis of AD is not clearly defined, but there is a consensus on the role of acetylcholine (ACh) and its excitatory contribution to nerve conduction.¹²⁷ Conversely, the central hydrolyzing enzyme AChE can break down ACh, leading to a deficit in ACh levels. This is why most clinically used AD drugs (donepezil, rivastigmine, and galantamine) are AChE inhibitors, which can inhibit the AChE enzyme and increase ACh levels in the brain,¹²⁸ helping with the memory symptoms of AD. The AChE inhibitory activity of these plants has been investigated using both *in vitro* and *in vivo* methods. This points to the abundance of natural chemicals that could contribute to drug discovery in this area via the pathway of AChE inhibition. As all the plants in Table 2 have shown ChE inhibitory activities, there is a need for more advanced studies to investigate these plants and their components further to develop them into clinically useful medications for patients with memory loss due to AD.

Mechanism of action involving N-methyl-D-aspartate (NMDA) antagonism

In addition to AChE inhibitor drugs, memantine is another drug clinically used in AD that works through a separate pathway by blocking NMDA receptors. This receptor plays a key role in the central nervous system, particularly in cases where abnormal NMDA receptor function or expression levels are associated with several neurodegenerative diseases, including AD.¹²⁹ Table 2 shows that several plants have activities reported in modulating NMDA receptor function, specifically plants like *Celastrus paniculata*, *Withania somnifera*, and *Zingiber officinale*. This suggests that plants could also be a valuable source for new NMDA receptor ligands, in addition to ChE ligands.¹³⁰ Memantine was approved by the U.S. Food and Drug Administration over 20 years ago. More research should be focused on this area, and additional

NMDA antagonists need to be approved for use in AD. Plants present a viable option for discovery in this area of interest.

Additional mechanisms for memory enhancement

The studies listed in Table 2 also show that anti-inflammatory and antioxidant mechanisms are common among these plants used for memory loss in AD.¹³¹ Neuroinflammation is not typically linked to the onset of AD, but it can exacerbate the disease by elevating abnormalities caused by amyloid-beta (A β) and tau proteins. When immune cells release inflammatory cytokines, it further triggers the immune system and increases inflammation levels.¹³² In people with AD, immune cells are often overly active, which leads to an increased buildup of A β and tau proteins. This excessive activity can also result in the loss of synapses, damage to the blood-brain barrier, and overall brain degeneration.¹³³ Similarly, there is a risk of imbalance between the production and breakdown of A β . This imbalance causes elevated levels of A β to accumulate in the brain.¹³⁴ A β can create oxidative stress, which in turn can further increase A β production. Neurons are particularly vulnerable to oxidative stress because they have low levels of antioxidants, and their membranes are rich in fatty acids that are easily damaged.¹³⁵ This highlights the importance of these mechanisms and their relevance in drug discovery for AD research. Much has been published in this regard, as evident from Table 2, and further efforts are needed to bring this to fruition in terms of developing newer AD drugs.

From the findings of this review, it is also evident that some plants exhibit not only one mechanism of action but multiple mechanisms contributing to their efficacy in addressing memory loss in AD. For instance, *Acorus calamus*, *Anacardium occidentale*, and *Salvia officinalis* are reported to have AChE inhibitory, cholinomimetic, and antioxidant properties^{47,52,54–57,102,112}; *Celastrus paniculatus* has AChE inhibitory, antioxidant, and NMDA antagonist activities^{69,70}; *Coriandrum sativum*, *Evolvulus alsinoides*, and *Withania somnifera* exhibit antioxidant, anti-inflammatory, and AChE inhibitory effects^{113–115}; while *Zingiber officinale* exhibits cholinomimetic, antioxidant, BuChE inhibitory, and Ca²⁺ antagonist activities.^{121,122} Among the pure compounds, 6-gingerol, a known constituent of ginger rhizome, is recognized for having multiple properties, including Ca²⁺ antagonist and BuChE inhibitory effects. This suggests that 6-gingerol could potentially target AD from multiple angles, much like the ginger rhizome from which it is isolated.¹²¹ The potential of plants and their pure compounds to benefit disease conditions and target different pathways is promising for discovering and designing new therapeutic entities for AD.

Integrative medicine is a healthcare approach that combines conventional medicine with complementary and alternative therapies.¹³⁶ This collaboration involves the use of traditional therapies, including medicinal plants. As demonstrated in this study, there is a wide range of age-old medicinal plants with potential benefits for memory loss and other cognitive issues. The scientific literature reveals the diverse mechanisms within these plants that support brain health. By merging folk knowledge with contemporary medical science, a more holistic approach can be offered to patients, thereby improving patient care and outcomes in the field of cognitive health.

Data from clinical trials in humans

Human clinical trials are pivotal in the drug discovery process, including for drugs derived from plant sources. While experiments

Table 2. Published data related to memory improvement and potential use in Alzheimer's disease for plants traditionally used for their memory-enhancing effects in South Asia

Plant name	Proposed mechanism	Experimental model	Chemical responsible	References
<i>Acacia nilotica</i>	AChEi, BuChEi, anti-inflammatory	<i>In vitro</i>	Heptacosane, niloticane	41
	AChEi	<i>In vitro</i>		42,43
<i>Acorus calamus</i>	Prevention of mitochondrial damage in hippocampus	Mice	α -Asarone	44
	AChEi	Rats		45
	Low memory deficit via antioxidant & anti-inflammatory effect	Rats		46
	Antioxidant, AChEi	Rats		47
	Antioxidant, $\downarrow$ Na-K-ATPase	Rats		48
	AChEi	<i>In vitro</i>		49–51
	$\uparrow$ Cholinergic system, antioxidant	Mice		52
	Antioxidant, $\downarrow$ cell death	<i>In vitro</i>		53
	Antioxidant, anti-inflammatory	Rats		54
	Prevention of oxidative stress, neuroinflammation & neurobehavioral changes	Rats		55
<i>Anacardium occidentale</i>	Antioxidant, effects on Cholinergic & GABAergic system	Rats	Anacardic acid, Phenolic lipids, cardanol, cadol	56
	AChEi	<i>In vitro</i>		57–62
<i>Celastrus paniculatus</i>	$\uparrow$ Behavioral outcomes, AChEi, $\downarrow$ neuroinflammation, $\uparrow$ synaptic plasticity, $\uparrow$ cognitive functions	Rats	Triterpenoid (ursolic acid, oleanolic acid, lupane); polyphenols (catechin, quercetin, kaempferol)	63
	Improved behavior, $\downarrow$ oxidative stress, AChEi	Mice		64
	Improved behavior, oxidative stress	Rats		65
	Improved cognitive functions	Rats		66
	Memory enhancement seen on elevated plus maze and passive avoidance tests	Mice		67
	AChEi	Rat		68
	Antioxidant, AChE independent effect	Rat		69
	NMDA $\downarrow$, antioxidant	Rat		70
	Antioxidant	Rat		71
	Reversed scopolamine-induced task performance deficit	Rat		72
	Involvement of aminergic system	Rat		73
	Aluminum induced neurodegeneration and oxidative stress	Rat		74

(continued)

Table 2. (continued)

Plant name	Proposed mechanism	Experimental model	Chemical responsible	References
<i>Coriandrum sativum</i>	↓ Oxidative stress, AChEi	Zebrafish		75
	Neurogenesis and synaptogenesis	<i>In vitro</i>		76
	Barnes maze test performance	Mice		77
	Oxidative stress	Rat		78
	Antioxidant	Rat		78
	AChEi	Mice		80
	AChEi	<i>In vitro</i>	Linalool, γ-terpinene, α-pinene	81
	↓ Oxidative stress via protecting cell death, ↓ ROS production, preventing cell apoptosis, modulating sirtuin longevity	<i>In vitro</i>	Linalool, linalyl acetate, geranyl acetate	82
	Antioxidant, anti-inflammatory, ERK inhibitory	Drosophila		83
	Antioxidant, AChEi	<i>In vitro</i>	Tannins, flavonoids, phenols	84
<i>Evolvulus alsinoides</i>	Antioxidant, anti-inflammatory, AChEi, memory enhancing	<i>In vitro</i> , rat	Steroid (stigmasterol, betulinic acid); coumarin (scopoletin); flavonoid (β-carotene, chlorogenic acid)	85
	↓ Streptozotocin induced cognitive impairment by ↓ oxidative stress, ↑ cholinergic function, ↓ rho kinase expression	Rat		86
	Antioxidant	<i>In vitro</i>		87
	Prevention against scopolamine induced amnesia	Mice		88–91
	Improvement against radial arm maze task and Barnes maze test	Rat		92
	Effect on elevated plus-maze	Rat		93,94
	Improved memory	Humans		95
	↓ β-amyloid production via ↑ capacitative Ca ²⁺ entry	Mice	Ginsenoside	96
	Different memory tests	Rat		97
	↑ Neurogenesis and synaptogenesis through the CREB/BDNF signaling pathway	Mice	Ginsenoside	98
<i>Panax ginseng</i>	↓ Neuroinflammation and inhibits neurotoxicity of Aβ deposition and Tau phosphorylation	Rat	Ginsenoside	99
	AChEi	<i>In vitro</i>	Homopanaxynol, homopanaxydol	100
	AChEi, BuChEi, antioxidant, ↓ amyloid-beta Aβ	<i>In vitro</i> ; Nematode (Globodera pallida)		101
				(continued)

Table 2. (continued)

Plant name	Proposed mechanism	Experimental model	Chemical responsible	References
<i>Withania somnifera</i>	↓ β-amyloid deposition, ↓ oxidative stress, AChEi	Rat	Methyl carnosate, carnosic acid, carnosol, rosmanol, salvianolic acids	102
	Improved perceived exertion, working memory, and reaction time	Humans		103–107
	Modulation of Brain-derived Neurotrophic Factor	<i>In vitro</i>	benzyl 6-O-β-D-apiofuranosyl-β-D-glucoside	108
	Effect on Morris water maze via CaM kinase II protein expression	Mice		109
	Antioxidant	Rat		110
	AChEi	Mice		111
	Activation of cholinergic system	Rat		112
	↑ Cognitive function and mood	Humans		113
	Anti-inflammatory	Rat		114
	Antioxidant	<i>In vitro</i>		115
	Protection from glutamate induced neurotoxicity	Rat		116
	Protection from neurotoxicity and neuroinflammation	mice		117
	↑ executive function, attention, short-term/working memory	Humans		118
	↑ memory and focus, psychological well-being, sleep quality, ↓ stress levels,	Humans		119
	AChEi, BuChEi, Ca ²⁺ antagonist	<i>In vitro</i> , rabbit	Withanolides	120
<i>Zingiber officinale</i>	Muscarinic agonist, Ca ²⁺ antagonist, BuChEi	Rodent, <i>in vitro</i>	6-Gingerol	121
	Antioxidant	Mice		122
	↓ cognitive deficits via blocking PERK/CHOP-dependent ER stress pathway and apoptosis	<i>In vitro</i>	Zerumbone	123
	↓ ethanol-induced cognitive impairment via modulation of expression of NMDA and GABA receptors, ↓ oxidative damage	Rat		124
	↑ Memory and behavior post lipopolysaccharide exposure	Rat	6-shogaol	125
	↓ Oxidative stress	Rat		126

AChEi, acetylcholinesterase inhibition; AD, Alzheimer's disease; BDNF, brain-derived neurotrophic factor; BuChEi, butyrylcholinesterase inhibition; CHOP, CCAAT-enhancer-binding protein homologous protein; CREB, cAMP response element binding; ERK, extracellular signal-regulated kinase; GABA, gamma-aminobutyric acid; NMDA, N-methyl-D-aspartate; NMDAR, N-methyl-D-aspartate receptor; PERK, protein kinase RNA-like ER kinase; ROS, reactive oxygen species.

done on animals provide critical starting data on safety, efficacy, and biological effects, human trials confirm these findings and ensure that a drug works safely and effectively in people. Human trials also provide important information regarding dosage, adverse effects, and how the human body processes the drugs. This is especially important because plants contain hundreds of active chemicals, and the response observed in lab animals may not always extrapolate directly to humans. Additionally, genetics and individual response variations among humans make clinical trials necessary to fully understand the biological effects of the drugs and to help with the approval of the drug for widespread human consumption.

With this in mind, we examined the data in Table 2 and observed that three of the plants mentioned have been the subject of human trials: *Panax ginseng*, *Salvia officinalis*, and *Withania somnifera*. For *Panax ginseng*, the referenced study tested a ginseng extract called ThinkGIN™ to assess its potential for improving memory in older adults with subjective memory impairment.⁹⁵ A 12-week clinical trial was conducted with 80 participants aged 55 to 75. Half of the participants took ThinkGIN™ daily, while the other half took a placebo. After 12 weeks, the ThinkGIN™ group showed significant improvements in memory and cognitive function compared to the placebo group. Safety tests showed no serious side effects.

Multiple human trials have been performed on *Salvia officinalis* (sage). One crossover, randomized, double-blind trial with 26 volunteers assessed the effects of sage supplementation two hours before a fatiguing cycling task.¹⁰³ Results showed that sage improved cognitive functions, including perceived exertion, working memory, and reaction time in the athletes. In another randomized, double-blind trial,¹⁰⁴ sage was administered to 94 healthy individuals over a 29-day period. The study consistently showed significant benefits in working memory and accuracy in task outcomes. The study suggested that terpenes and phenolics in the herb were responsible for these benefits. Additionally, a double-blind, randomized pilot study involving 44 healthy human volunteers demonstrated that a combination extract containing sage improved delayed word recall in volunteers under 63 years of age.¹⁰⁵ A terpenoid-containing sage extract tested in 36 healthy volunteers showed improved performance on secondary memory and attention tasks, reduced mental fatigue, and increased alertness following oral administration.¹⁰⁶ Lastly, a randomized, placebo-controlled, double-blind, balanced, five-period crossover study involving 20 healthy older adults showed enhancement in secondary memory performance and improved accuracy in attention tasks.¹⁰⁷ The authors identified the ChE inhibitory mechanism of the extract as responsible for these beneficial effects.

Finally, *Withania somnifera* (ashwagandha) has also been studied in human volunteers. In one randomized, double-blind study,¹¹³ 59 healthy young human volunteers received an ashwagandha extract. Results showed improvements in multiple parameters of cognitive function, mood, and markers of health and safety. In another double-blind, placebo-controlled, crossover study,¹¹⁸ 13 healthy volunteers were administered an ashwagandha extract. The extract benefited executive function, improved attention, and enhanced short-term/working memory. Finally, a double-blind, randomized, placebo-controlled clinical trial examined the effect of a root extract of ashwagandha in 130 healthy adults.¹¹⁹ Over 90 days of testing, the extract not only improved memory and focus, psychological well-being, and sleep quality but also reduced stress levels. The administration of the extract was safe for the volunteers, and no adverse effects were noted.

The results from these human trials demonstrate the effectiveness of these medicinal herbs in improving cognition and memory.

Limitations

This review presents various South Asian medicinal plants traditionally used for memory loss. Although several plants have been identified and shown to have a scientific basis for use in memory loss, there are still a few limitations to this study:

Only a limited number of books were searched for this review article. Additional local books and printed literature might have yielded more plants traditionally used for memory loss.

This review and study could have been further strengthened if an in-person survey of local herbalists and traditional healers had been conducted. This would have provided actual, real-time data about the practical clinical use of medicinal plants by traditional healers in South Asia for patients with memory loss. This could be the next step in this direction.

Talking to actual patients about how they use these plants in real life would have also been more effective. Currently, the books used to reference the use of these plants only describe the plant parts used for medicinal benefit. Conversations with healers and patients would have provided more information on the process of preparing these plants for use in treating memory loss.

This study is just a review of plants traditionally used in South Asia. A broader study involving other cultures and nations would provide a much larger list of plants with this benefit. In the future, such an effort could be undertaken.

This review did not delve deeply into the medicinal chemistry aspect. A detailed exploration of the chemicals in plants with memory-enhancing benefits could provide more insights into drug design and discovery.

Conclusions

The initial effort to identify South Asian plants traditionally used for memory-enhancing effects yielded a list of medicinal plants. Most of these plants have been reported in the literature to have activity in improving memory, particularly memory loss associated with AD. Several mechanisms have been reported, such as AChE inhibition, modulation of NMDA receptors, and antioxidant and anti-inflammatory effects. Most of the studies cited tested these plants on animals. Our study highlights the existence of plants and chemicals that can target memory loss through multiple pathways simultaneously, emphasizing the need for more research in this area. Currently, only AChE inhibitors and NMDA receptor antagonists are available for clinical use in memory loss and AD. If extracts or chemicals with the ability to target disease via multiple pathways simultaneously were introduced, it could potentially be a medical breakthrough. There is also a need to gather data from human studies to assess safety, efficacy, and pharmacokinetics, so that more agents can be made available for clinical use.

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Conflict of interest

MNG has been an editorial board member of *Future Integrative Medicine* since February 2023. The authors declare that there is no other conflict of interest.

Author contributions

Conceptualization, investigation, data curation, writing—original draft, and writing—review & editing (FAS, AG, ZU, MNG). All authors have made significant contributions to this study and have approved the final manuscript.

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