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A SYSTEMIC REVIEW ON HERBS SHOWING NEUROPROTECTIVE EFFECTS AGAINST ALZHEIMER'S DISEASE

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ABSTRACT
Memory loss, personality changes, and decline in cognitive function were characteristic of Alzheimer's disease (AD), a multifactorial, progressive, neurodegenerative disease. A number of factors may contribute to AD progression, including lifestyle, diet, environment, and genetics, although the exact cause of AD remains unclear. There had been two main hypotheses suggested as causes of AD, the cholinergic hypothesis and the amyloid hypothesis. Furthermore, vascular disease, infections, and environmental factors play a role in the disease, including age, genetic factors, head injuries, and genetic factors. In the past decade, more than two hundred promising drug candidates have failed clinical trials, including that the disease and its causes may be extremely complicated. In addition to being complementary and alternative interventions, medicinal plants and herbal remedies were also valuable resources for developing drug candidates for Alzheimer's disease. An overview of herbal supplements that were anti-inflammatory, anti-oxidative, and cognitively enhancing was provided in this article. Cognitive decline associated with AD can be prevented and treated using medicinal plants. The aim was to identify safe and effective small molecules for AD using these medicinal plants in drug discovery programs.

KEY WORDS: Alzheimer's disease, medicinal herbs, *Withania somnifera*, *Ginkgo biloba*, Saffron, Shankhpushpi, Brahmi.

INTRODUCTION

Alzheimer's disease refers to a severe decline in cognitive ability that interferes with daily activities. Dementia in people over 65 was most often caused by Alzheimer's disease (AD), which accounts for at least two-thirds of dementia cases [1]. Neurodegenerative disease such as AD were characterized by their insidious onset and progressive impairment of behavioural and cognitive functions, such as memory, comprehension, language, attention, reasoning, and judgement. US deaths from this disease were sixth in the world. Less than 10% of Alzheimer's disease patients develop the disease before the age of 65 (early onset). In some cases, AD may be improved with medication, but there is no cure [2]. There are three stages of Alzheimer's disease, based on how much cognitive impairment a person has: preclinical, mild, and dementia-stage. Alzheimer's disease is classified differently in these stages than it is in the DSM-5. It is most commonly characterized by episodic short-term memory loss with sparing of long-term memory, which may occur even when not present as a symptom

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of the disease. There are several consequences associated with short-term memory loss, including difficulty solving problems, impaired judgment, impaired executive functioning and disorganization, which contributes to problems with multitasking and abstract thought. There is a wide range of severity of impairment in executive functioning in the early stages. Then a language disorder and a visual-spatial impairment follow. There are many neuropsychiatric symptoms associated with this disorder in the mid to late stages, including apathy, social withdrawal, disinhibition, agitation, psychosis, and wandering. There is late onset dyspraxia, olfactory dysfunction, sleep disturbances, extrapyramidal motor symptoms like dystonia, akathisia, and parkinsonian symptoms. As a result, children are left with primitive reflexes, incontinence, and total dependency on their caregivers [3]. There are two prominent pathologic hallmarks of Alzheimer's disease:

- Extracellular amyloid deposition
- Intracellular neurofibrillary tangles (NFT)

Accumulated A causes neurodegeneration that leads to clinical dementia in AD. [4] Despite the fact that amyloid deposits were poorly correlated with cognitive decline in the symptomatic phase of dementia, drug targets to alpha amyloid have still not be successful [5]. Tau is a microtubule-associated protein that forms intracellular neurofibrillary tangles in AD brains and involves aberrant folding and hyperphosphorylation [6]. In response to the failure of trials of amyloid-based drugs, new focus has been placed on therapies aimed at tau [7]. There is a lack of understanding of the complex pathophysiology of AD as evidenced by the recent failure of drugs targeting tau deposits [8]. This shows the importance of considering additional pathophysiological factors that contribute to AD [9], such as autophagy, neuronal injury, peroxidation, metal ion toxicity, neurotransmission leading to oxidative stress, gut dysbiosis, unfolded protein response, lipogenesis, insulin/glucose dysregulation, and infections [10]. There is an urgent need to pursue alternative therapeutic strategies to address all the above-mentioned pathophysiological entities in the face of repeated failure of drug therapies targeting amyloid or tau [11]. The first cases of cognitive decline reversal in AD and pre-AD circumstances, including mild cognitive deficits and subjective cognitive problems, were reported using a thorough, customised strategy [12].

- Optimizing the microbiome, identifying gastrointestinal hyperpermeability and repairing damaged guts
- Returning insulin sensitivity by identifying insulin resistance
- Glycation reduction
- Nutritional, hormonal, and trophic molecule imbalances are identified and corrected
- Diagnose and treat pathogens such as Borrelia, Babesia, and Herpes
- Detoxification involves identifying and reducing levels of metal toxins, organic toxins, and biotoxins. Individualized, precision therapeutic programs deliver sustained effects that are superior to monotherapies

It is unfortunate that few scientific studies have been conducted on herbs and herbal remedies despite their long history of traditional use and safety and efficacy [13, 14]. Traditional practice of medicine recommends a number of plants and their constituents to enhance cognitive function [15]. This is to relieve other symptoms of Alzheimer's disease, such as memory loss, depression, and poor cognition. It depends on the complexity of the condition whether a single herb or a mixture of herbs should be used [16]. There is a rationale for this, as the plant's bioactive principles act synergistically as well as modulating the activities of other plant constituents [17]. Historically, a single herb or a combination of two or more herbs has been recommended for a specific disease in Ayurveda, traditional Chinese medicine (TCM), and Native American systems of medicine [18]. Here we review a subset of herbs that were useful in treating AD from a mechanistic point of view, based on their properties, functional characteristics, and physiological effects [19].

These herbs were chosen for their medicinal properties,

- Traditionally used for memory-related disorders, including Alzheimer's, these herbs have a long history in traditional medicine.
- Research on the potential therapeutic effects of phytochemicals derived from these plants,
- Analyzing these herbs' neuropharmacological effects
- A pre-clinical study or clinical trial is necessary to confirm their reputed anti-dementia and cognitive-enhancing properties.

Medicinal herbs against AD

1. *Withania somnifera*

A prominent brain rejuvenator for AD is ashwagandha, commonly known as Indian ginseng or winter cherry. As a nerve tonic, it increases energy, improves overall health, and increases longevity. In addition to its antioxidant properties, Ashwagandha also scavenges free radicals and supports immunity. The compound withasomniferin – A, withasomnidienone, withasomniferols A-C, withaferin A, withanone and others in Ashwagandha were of great interest to researchers as they belong to the ergostane-type steroidal lactones group. Additionally, beta-sitosterol,

phytoindosides VII-X and sitoindosides VII-X were present as well as alkaloids [20]. There has been evidence that some of these components scavenge free radicals that were generated during the initiation and progression of Alzheimer's disease. It was observed that withanamides A and C bind unambiguously to the active moiety of Aβ25-35 and prevent fibril formation. Further the compounds prevented the death of PC-12 cells and rat neuronal cells induced by "amyloid" [21]. Human neuroblastoma cells treated with ashwagandha extract exhibited dose- and time-dependent neurite outgrowth. In a different experiment, the Aβ peptide caused axonal and dendritic atrophy as well as the loss of pre- and postsynaptic stimuli in cultured rat cortical neurons [22]. Cultured cortical neurons treated with withanolide A exhibited significant regeneration of their axons and dendrites, as well as the formation of new pre- and post-synapse junctions. Even after discontinuation of drug administration, the in vivo ameliorative effects remained. It may partly explain the cognitive enhancement and memory improvement effects of ashwagandha aqueous extracts in rats, as they increased acetylcholine (ACh) content and activity of choline acetyl transferase [23]. Middle-aged and elderly APP/PS1 animals treated with the root extract had increased levels of the protein associated to low-density lipoprotein receptors, which improved A clearance and corrected the AD pathology [24]. Using a *Drosophila melanogaster* AD model, researchers discovered that ashwagandha therapy reduced the toxicity of A while also promoting durability.

2. *Ginkgo biloba*

There has been a lot of attention paid to *Ginkgo biloba* due to the possibility that it can treat AD. GB may also have potential as a therapeutic agent for several other chronic and acute conditions [25]. Terpenoids and flavonoids were the main pharmacologically active groups. In almost all clinical studies, GB extract was used, which contains flavonoids, terpene lactones, and ginkgolides. Research has shown that GB extract can be used to treat AD, CVS, Cancer, tinnitus, and various other conditions associated with aging [26]. Several mechanisms have been proposed for the effect of GB extract, including anti-oxidant activity, platelet activating factor activity, and inhibition of peptide aggregation for the treatment of AD and stress management [27]. The use of Gb is popular for the treatment of early-stage Alzheimer's disease and vascular dementia. Gb extract decreases apoptosis both in vitro and in vivo and reverses -amyloid and NO-induced toxicity *in vitro* [28]. Rats both young and old benefitted from treatment with Gb extract [29]. Mice also showed improved short-term memory after receiving Gb extract treatment [30]. According to several studies, ginkgo is as effective at treating AD as cholinesterase inhibitors [31]. Several randomized, double-blind, placebo-controlled trials showed modest improvements in cognitive function in AD subjects [32]. Additionally, GB extract improves daily living skills for AD patients and has negligible side effects compared to other AD medications [33].

***3. Crocus sativus* (Saffron)**

In Iran, India, and Greece, saffron is widely cultivated. Saffron is also recommended for its medicinal properties, in addition to its use in textiles and cosmetics [65,66]. Safranal, a carboxaldehyde, is the most important component of saffron. Saffron contains phytochemicals that can inhibit inflammation, increase antioxidant capacity, and inhibit amyloid formation *in vitro* and *in vivo*. Researchers randomly assigned forty-six AD patients to receive saffron 30 mg/day or placebo in order to assess its efficacy in treating mild to moderate AD. There was a significant difference in cognitive performance between saffron and placebo after sixteen weeks (ADAS-cog and CDR scores). A double-blind, placebo-controlled trial found saffron to be safe and effective in mild to moderate Alzheimer's disease [34]. We compared the effects of saffron extract and memantine on cognitive defects in a safety and efficacy pilot study. The study consisted of 68 patients with moderate to severe AD who were randomized, double-blind, and compared across two groups. Over a twelve-month period, subjects received capsules containing either memantine (20 mg/day) or saffron extract (30 mg/day). Apart from showing a low rate of adverse effects, saffron extract also significantly reduced cognitive decline in patients with moderate to severe Alzheimer's disease [35]. Consequently, all the above-mentioned studies have demonstrated that saffron can improve cognitive function and daily living skills in people with Alzheimer's disease and mild cognitive impairment. Since saffron is natural and does not have adverse side effects, it can be used to treat patients with AD just as effectively as conventional treatments.

4. *Convolvulus pluricaulis* (Shankhpushpi)

In addition to regenerating nerves and improving memory, Shankhpushpi is known as *Convolvulus pluricaulis* (Cp) [36]. Triterpenoids, flavonol glycosides, anthocyanins, and steroids are the major chemical components that contribute to cognitive enhancement and memory enhancement [37]. The effects of Cp are similar to those of racetams. Adrenaline and cortisol are produced in the body in response to CP. When tested in vitro, an ethanolic extract of Cp demonstrated significant antioxidant activity, and rats showed significant improvement in learning and memory after administration of the extract. Neonate rat pups were improved in retention and spatial learning after receiving aqueous root extract of Cp. Additionally, their memory and learning were improved due to a significant increase in ACh content and activity [38]. In rats treated with Cp extract,

dendritic branching points and processes were significantly greater than those in age-matched saline controls, suggesting that Cp promotes dendritic arborization to enhance learning and memory [39]. Young and old mice both had dose-dependent increases in acetylcholine esterase activity following administration of Cp extract, although young mice retained more memory than old mice. The herb has not been clinically evaluated for its ability to prevent dementia despite extensive literature demonstrating its therapeutic properties *in vitro* and *in vivo* [40].

5. *Bacopa monnieri* (Brahmi)

It is a perennial creeping plant found in moist wetlands throughout southern and eastern India as well as Australia, Europe, Africa, Asia, and North and South America. Asthma, memory loss, epilepsy, insomnia, and mental stress were all treated with Brahmi in ayurvedic medicine. There are several bioactive phytochemicals found in this plant, including saponins, bacopasides III, IV, V, bacosides A and B, bacosaponins A to F, alkaloids, sterols, betulic acid, polyphenols and sulfhydryl compounds, which were thought to be responsible for its neuroprotective effects. Multiple studies had showed that these phytochemicals had anti-oxidant and free radical scavenging effects in the brain by inhibiting lipid peroxidation. Memory and intellect are also affected by Bm, according to numerous studies. BM showed that it enhanced cognitive function in healthy individuals over the age of 60. Researchers administered either 130mg of BM extract or a placebo to 40 individuals above 60 years of age for 3 months, followed by a four-week placebo duration. Participants underwent memory tests that can accessed general information, orientation, mental control, logical memory, digital forwards, digit forwards and backwards, visual reproduction, and paired association learning. By adding the scores from all subtests, a total score for memory was determined. At 8 and 12 weeks after the trial started, this extract treated patients showed significant improvements in mental control, logical memory, and paired association learning compared to the placebo group. In the study, Bacopa was found to be effective in treating age-associated memory impairments. One prospective, non-comparative study involved 104 subjects suffering from MCI, who received BM extract and astaxanthin, phosphatidylserine, and vitamin E for 60 days. A combination formula that was tested was well tolerated. The clock-drawing test and Alzheimer's disease assessment scale-cognitive subscale were validated instruments to assess cognitive and mnemonic performance [41]. Scores on the ADAS and CDT significantly improved. A statistically significant improvement was observed in ADAS-cog and CDT after 60 days as compared with baseline values. Focus and attention, neurotransmitters, hormones, trophic factors, cyclic AMP, ion channels, protein transcription, synapse formation, and nutrients were all important factors that impact memory. A combination of BM extract and other compounds can modulate some of these processes. BM is administered along with the other nutraceuticals and cognitive supplements in the above-mentioned study, similar to our therapeutic program for patients with SCI and MCI [42].

6. *Curcuma longa* (Turmeric)

The Indian subcontinent and Southeast Asia are native to turmeric, a flowering plant in the ginger family Zingiberaceae. Several polyphenolic compounds called curcuminoids contribute to the yellow-orange color of this rhizome plant. Traditionally, turmeric has been used for treating a variety of conditions including liver detoxification, preventing infection and inflammation, balancing cholesterol levels, treating allergies, stimulating digestion, and boosting immunity because of its anti-inflammatory, antiseptic, and antibacterial properties [80]. An anti-inflammatory property of curcumin is associated with a decreased risk of Alzheimer's disease [43]. Several times more potent than vitamin E, curcumin blocks lipid peroxidation and neutralizes reactive oxygen species *in vitro*. A significant reduction in plaque load was observed when curcumin was given orally to aged mice with advanced plaque deposits [44]. Moreover, curcumin reduced anti-amyloid pathology, inflammation, and oxidative damage in AD mouse models [45]. By injecting curcumin directly into the brain, plaque levels were reduced as well as plaque further development was blocked. A number of studies have examined the effect of curcumin on cognitive function in animal models of AD. As well as curcumin's anti-inflammatory and antioxidant properties, researchers attribute the improvement to its ability to lower plaque levels [46]. Furthermore, curcumin reduces Aβ deposits, possibly by promoting autophagy. As curcumin's bioavailability is low, its metabolism is rapid, and its BBB penetration is poor, several analogues of curcumin have been tested for their bioavailability and effects on AD. Various animal models of AD can also be reversed by curcumin. Curcumin is more effective when given at higher doses than at lower doses, regardless of how it is administered, and improvements in cognition were greater when curcumin was combined with piperine, which has numerous pharmacological effects, especially against chronic diseases. There is significant evidence that curcumin forms strong complexes with metals, preventing toxicity and inflammation induced by metals.

Route of administration of herbs

The BBB prevents numerous potential therapeutic agents from entering the brain, which is the biggest challenge to drug delivery. In spite of oral administration being a common way to administer the herbs, no clear studies have demonstrated that herbal

components reach the CNS. This method bypasses the BBB, which allows direct access to the central nervous system, and is non-invasive, rapid, and non-invasive. The direct administration of herbs in the form of powders or oils is possible using this route of delivery. It is common for medicinal oils to contain a mix of lipophilic and lipid-soluble molecules to ensure synergistic interactions between constituents of the herb. As a result of INA, systemic side effects are minimized, brain injury is avoided, and implantable devices are no longer necessary. A transgenic mouse model of Alzheimer's disease has been treated using this technique. There are contradictory results in research studies regarding the effectiveness of INA, limiting its usefulness in clinical settings [47]. In traditional systems, INS is an attractive strategy for treating CNS conditions. However, there are few clinical studies supporting INS use [48]. A medicated oil can be applied to the body and massaged gently or deeply into the affected area as another method of herbal administration [49]. In addition to reducing stress hormone levels, massage also stimulates brain circulation [50]. Researchers recently found that endothelial cells line the capillaries that deliver solutes from oil directly into the prefrontal cortex and frontal lobe [51].

CONCLUSION

The number of Americans suffering from Alzheimer's dementia is estimated at 5.8 million. In 2050, Alzheimer's and other dementias may affect 13.8 million people. According to reports, approximately USD 290 billion was spent in the United States alone in 2019 on healthcare expenses and lost wages for patients with Alzheimer's disease and their caregivers. According to predictions, USD 1.1 trillion will be spent on Alzheimer's disease in the United States by 2050. Finding novel medicines for the treatment and prevention of AD is thus urgently needed. While numerous innovative methods of disease-modifying therapy and symptomatic care are being developed for AD at the moment, however it is unclear when they will reach the market. Particularly for chronic and complex disorders like AD, a considerable transition from a mono-therapeutic approach to a comprehensive, customised, multi-therapeutic approach may be successful. The majority of the research suggests that herbal remedies have enormous promise and can be utilised to treat AD in a similar systems-based, customised way. It is necessary to conduct additional research into the biological mechanisms of the herbs and to carry out sizable multicenter clinical trials in order to validate the efficacy of both single herbal formulations and mixed formulations in treating Alzheimer's disease and pre-cognitive Alzheimer's compromise. To get over methodological restrictions such bad study design, relatively small sample sizes, subpar outcome measures, and inappropriate endpoint selection, more thorough research is required. Combinatorial sciences, high-throughput screening methods, and the historical knowledge base of traditional medical systems are expected to make it simpler to incorporate herbal ingredients and formulations into the drug development process and produce novel functional leads for AD.

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