

The Role of Natural Products in Pharmacotherapy of Alzheimer's Disease

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Abstract

Alzheimer's disease is characterized by forgetfulness, disturbance in memory and loss of mental abilities. The final outcome of the disease is loss of personality and intellectual functions. Alzheimer's disease is common cause of dementia particularly after the age of 70 years. Cholinesterase inhibitors are used for the treatment of Alzheimer's dementia, but due to unpleasant side effect; these groups of drugs can not be used for long term treatment. Phyto drugs are being investigated for possible cure of Alzheimer's disease. A number of constituents like Galanthamine, Huperzine, Hyperforin, & Desoxy-peganine have shown promising result. Some Ayurvedic herbs like *Bacopa monneria* (Bacosides) have recently gained attention because of memory enhancing activity. The article deals with latest findings in phytotherapy of Alzheimer's disease.

Keywords: Alzheimer's disease, Dementia, Natural Products, Medicinal Herbs.

Alzheimer's disease is a leading cause of dementia in developed countries. Alzheimer's disease is a progressive, degenerative disease characterized by memory loss, language deterioration, impaired visuospatial skills, poor judgment, indifferent attitude, but preserved motor function (1). Alzheimer's disease usually begins after age 65, however, its onset may occur as early as age 40, appearing first as memory decline and, over several years, destroying cognition, personality, and ability to function.

Confusion and restlessness may also occur. The type, severity, sequence, and progression of mental changes vary widely. The early symptoms of Alzheimer's disease, which include forgetfulness and loss of concentration, can be missed easily because they resemble natural signs of aging (2). Similar symptoms can also result from fatigue, grief, depression, illness, vision or hearing loss, the use of alcohol or certain medications, or simply the burden of too many details to remember at once. The course of the disease varies from person to person (3).

There is no cure for Alzheimer's disease and to slow the progression of the disease. Tacrine has shown positive results in improving mental functions in patients in the early or middle stages of Alzheimer's disease (4). Reversible acetylcholinesterase inhibitors are used for the treatment of mild to moderate dementia of the Alzheimer's disease (5). Although acetylcholinesterase inhibitors have shown promising results, an effective therapeutic answer for Alzheimer's disease is still eluding the scientific research.

Natural products are significant source of synthetic and traditional herbal medicines (6). In rural areas natural products are still the primary healthcare systems. The alternative systems of medicine include Ayurveda, Siddha, Homeopathy, Unani and Traditional Chinese Medicine (TCM) and all have roots in natural products (7). The use of natural products is limited not only to herbs but marine, animal and mineral preparations have been purified by the traditional healers for medicinal use (8). Alternative medicine is becoming popular and increasing number of patients are visiting alternative medicine healers (9).

The natural products are often crude in original state. Today standardised extracts are used in herbal practice and with the help of procedures like chromatography it is possible to study the chemical composition of plants. Alzheimer's disease is the area, where natural products have not been exploited to their potential (10). Some institutions are carrying out preclinical trials with isolated constituents like Huperzine, Bacosides, Hyperforin, & Desoxy-peganine.

Bacopa monniera (Nir-brahmi) is a medicinal herb used in ancient system of medicine, Ayurveda. Recent clinical research has highlighted the cognition enhancing activity of the herb. Saponins (Bacosides) are the active principles of the herb and classified as Bacoside- A & B. A standardised extract containing Bacosides content upto 2.5-3.0% is recommended (11). In a double blind placebo-controlled study the herb (300-mg) was tested for cognition enhancing activity. Neuropsychological testing was conducted pre- (baseline) and at 5 and 12 weeks post drug administration. *Bacopa monniera* significantly improved speed of visual information processing measured by the IT task, learning rate and memory consolidation measured by the AVLT ($P < 0.05$), and state anxiety ($P < 0.001$) compared to placebo, with maximal effects evident after 12 weeks (12).

Withania somnifera (Ashwagandha) is important medicinal plant of Ayurveda. Animal studies have shown that *Withania somnifera* may alternate concentrations of neurotransmitters at brain levels. A methanolic extract of *Withania somnifera* root inhibited the specific binding of [3H] GABA and [35S] TBPS, and enhanced the binding of [3H] flunitrazepam to their putative receptor sites. The extract inhibited [3H] GABA binding by 20 +/- 6 per cent whereas a concentration of 1 mg of the extract produced 100 per cent inhibition. The extract (5-100 micrograms) produced 20 +/- 4 to 91 +/- 16 per cent enhancement of [3H] flunitrazepam binding. In functional studies using ³⁶Cl-influx assay in mammalian spinal cord neurons, *W. somnifera* root extract increased ³⁶Cl-influx in the absence of GABA. This effect on ³⁶Cl-influx was blocked by bicuculline and picrotoxin; and enhanced by diazepam. The results suggest that the *Withania somnifera* extract contain an ingredient, which has a GABA-mimetic activity (13).

In another study, Sitoindosides VII-X, and Withaferin-A (Withanolide), isolated from aqueous methanol extract from the roots of *Withania somnifera* induced increase in cortical muscarinic acetylcholine receptor capacity. This may be a possible mechanism behind the cognition-enhancing and memory-improving effects of extracts from *Withania somnifera* observed in animals and humans (14).

Latest research investigations have proved *Ginkgo biloba* to be effective in the treatment of cerebral insufficiency, dementia (including Alzheimer's disease), arteriosclerosis and depression. *Ginkgo* has shown to increase production of adenosine triphosphate, resulting in increased cerebral glucose metabolism *Ginkgo's* effect contains a group of flavonoids called ginkgolides, which act by dilating micro-capillaries, thereby increasing oxygen levels in cerebral tissue (15). A standardized extract containing 24% *Ginkgo* flavonglycosides of 40 mg three times daily is recommended by many practitioners.

Hyperforin, the acylphloroglucinol derivative of *Hypericum perforatum*, commonly known as St. John's wort, has recently gained attention of researchers as a United States Patent has been filed by Chatterjee, et al for use of Hyperforin and Hyperforin based extracts in the treatment of dementia (16). Although standardised extracts of *Hypericum perforatum* are used in the treatment of mild to moderate depression, but Chatterjee, et al. have developed a method for stabilization of Hyperforin, as it is a highly unstable compound (17). An international patent has also been filed by Dr. Willmar Schwabe for the use of pure Hyperforin and Hyperforin containing salts for treatment of dementia.

Deoxypeganine (an alkaloid) present in *Peganum harmala* has been reported to be helpful in treating Alzheimer's dementia. Deoxypeganine has been investigated in detail in the former Soviet Union and its pharmacological actions have been intensively researched. Pharmacological studies in America have revealed that Deoxypeganine has activity similar to reversibly acting cholinesterase inhibitors. Deoxypeganine inhibits acetylcholinesterase and monoamine oxidase, thereby preventing the degradation of acetylcholine and dopamine. Deoxypeganine is known to cross the blood-brain barrier.

Huperzine, an alkaloid isolated from highly concentrated and purified extract of *Huperzia serrata* (previously known as *Lycopodium serrata*) has shown usefulness in Alzheimer's disease. Huperzine A has been evaluated in placebo-controlled clinical trials in China both as a treatment for Alzheimer's disease as well as a treatment for memory loss (18). In these studies, the Huperzine was well-tolerated and significantly improved memory and cognitive performance (19). Huperzine A readily crosses the blood-brain-barrier. Scientific studies have shown that Huperzine A inhibits acetylcholinesterase activity in the brain and increases the acetylcholine levels for up to 6 hours (20).

Vinpocetine an alkaloid isolated from Madagascar periwinkle, *Vinca alba*, has demonstrated significant nootropic

activity (21). Vinpocetine, improves blood flow to the brain, makes it easier for the brain to use glucose and oxygen, and allows the brain to survive longer and better after periods of oxygen deprivation. In another double-blind study (22), elderly patients with central nervous system degenerative disorders were treated with Vinpocetine or placebo. Patients receiving 10 mg of Vinpocetine three times a day for 30 days, then 5 mg three times a day for 60 days scored consistently better in all evaluations. CGI Vinpocetine group at day 30; 77% at day 90; improvement seen in 77% at day 30 and 87% at day 90. The improvement in 59% Vinpocetine-treated patients was rated good to excellent. No serious side effects were reported (22).

An acetone extract of *Lawsonia inermis* has shown nootropic effect in animal models. The active constituent of *Lawsonia inermis* has not been studied (23). *Salvia officinalis* has been reported to have cholinergic activities (10). *Melissa officinalis* has been reported to have interaction with nicotinic receptors in the Central nervous system (24). Nicotinic receptor activation is associated with protection against beta-amyloid- and glutamate- induced cytotoxicity. Cholinergic activity in the GI tract might explain the use of lemon balm to treat functional GI complaints; however, the actions of lemon balm on the GI tract are unclear.

Galantamine is an alkaloid, which was isolated from *Galanthus nivalis* L by D. Paskov and L. Ivanova in 1956 (25). Now a day's synthetic version of Galantamine is available for the treatment of Alzheimer's dementia. Several multicenter clinical trials have shown usefulness of Galantamine in the treatment of dementia. Studies have revealed that Galantamine interacts with nicotinic cholinergic receptors. In a 6-month double-blind phase, 1289 patients were randomized to treatment with 24 or 32 mg/day of Galantamine vs. placebo, followed by a 6 month open-label phase, in which all patients received 24 mg/day. The group on Galantamine was benefited more than placebo in terms of Dementia scale (26). So far seven studies have been done and it has been concluded that the pharmacological activity of Galantamine is similar to acetylcholinesterase inhibitors.

The efficacy of certain herbal products is beyond doubt, common examples being Vincristine, Vinblastine, and Morphine & Digoxin. Artemesinin, Taxol & Silymarin have been recently developed from plant source and are reputed drugs in their respective segments. Scientists are exploring natural products for effective answer for Alzheimer's disease and isolated fractions of some medicinal herbs have shown promising results. Ethical phytochemical screening and large-scale trials are required for further scientific validation of these remedies.

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