

# Alzheimer's disease prevention and treatment using herbal agents

## Abstract

The prevalence of Alzheimer's disease (AD) is increasing secondary to genetic and environmental factors. There are some medications available in the market that slow down the disease progress, however, none of the approved medications treat AD without adverse effects. There are many herbal agents or natural medicines that have proven effective to prevent or manage various neuropsychiatric conditions. This article reviews herbal agents available in the market that have proven effective and discusses the possibility of standardizing dosage and formulation of herbal agents through Federal Drug Administration (FDA) regulations.

**Keywords:** neurodegenerative disorders, caprylic acid and coconut oil, curcumin, ashwagandha, bacopamonniera, centellaasiatica, resveratrol

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Roy Sebastian,<sup>1</sup> Tony L Brown<sup>2</sup>

<sup>1</sup>Baylor Scott and White Hospital, Texas Regional Medical Center at Sunnyvale

<sup>2</sup>Harvard University, USA

**Correspondence:** Brown Tony L, Harvard University, USA, Tel 813-405-1474, Email [cbrown@psot.harvard.edu](mailto:cbrown@psot.harvard.edu)

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## Introduction

Alzheimer's disease causes serious memory loss, especially in the elderly population over 70 years of age. It causes significant financial burden on the society, and an emotional burden on family members and caregivers of the AD. According to the Center for Disease Control, AD affects approximately 5% of people 65 to 74 years of age and almost 50% of people older than 85 years old, at an annual cost of about \$148 billion in the U.S. alone. An estimated 5.3 million persons in the U.S. have AD. This figure is projected to grow to 13.2 million by 2050 (Center for Disease Control).

Patients typically present with loss of episodic memory that progresses to progressive dementia over the years. In the amnesic type of AD, imaging studies show atrophy of medial temporal lobes of the brain in the early stages, then spreads to the lateral temporal, parietal and frontal lobes (Klunk, Engler, Nordberg, et al., 2004). Microscopically, the affected area of the brain demonstrate the presence of neuritic plaques containing amyloid beta ( $A\beta$ ), neurofibrillary tangles (NFTs) and  $A\beta$  accumulation in blood vessel walls of the cortex and leptomeninges.<sup>1</sup>

## Discussion

In the early stages of amnesic AD, the first sign of memory loss may go unnoticed or be ascribed to benign age-related forgetfulness. Once the memory loss becomes apparent to the patient and family members, standardized tools to assess cognitive function may be used for objective data. If the results fall 1.5 standard deviations or more outside the normal distribution on standardized memory tests, the term mild cognitive impairment (MCI) is applied. Eventually, the cognitive problems begin to interfere with daily activities, following instructions on the job, driving, shopping, and housekeeping.

In the middle stages of AD, the patient may be unable to work, easily confused, and require daily supervision. Impairment of language skills becomes evident—first naming, then comprehension, and finally fluency and loss of judgment. Delusions are common, usually simple, with themes of theft, infidelity, or misidentification.

The aging process and neurodegenerative processes are inextricably linked to oxidative stress. Interventions that can counteract the oxidative stress mechanisms will decrease or prevent the detrimental effects of oxidative damage and thus improve or maintain the healthy

state of the cells especially neurons in this context. It would lessen the risk of neurodegenerative disorders and increase the lifespan of older adults. Developing healthy lifestyle interventions is the key component of many types of research that will help the elderly population to maintain physical and cognitive health, and reduces the burden on society and economy related to the care of aging population.

Cognitive dysfunction is a major health problem in the current century, and many neuropsychiatric disorders and neurodegenerative disorders, such as schizophrenia, Alzheimer's dementia, and Parkinsonism, can be severely functionally debilitating in nature. Researchers have identified neurotransmitters and signaling molecules as therapeutic targets. Various studies for newer therapeutic agents have targeted neurotransmitters and signaling molecules.

Current medical management of AD includes medications such as acetylcholinesterase inhibitors and NMDA receptor antagonists. Literature review has shown that the effectiveness of the conventional drugs is statistically significant but clinical significance is limited to the slowing, rather than reversal of the disease.<sup>2</sup>

## Phytochemicals

Phytochemicals are the chemical molecules contained in plants not usually processed for pharmacological purposes. Phytochemicals influence the function of various receptors for both excitatory and inhibitory neurotransmitters in the brain and thus can maintain or alter the chemical balance of the brain. This knowledge was used in the traditional practice of medicine after several plants were identified to have medicinal properties to treat cognitive disorders. A growing number of herbal remedies are available in the market claim to be effective as mood enhancers, memory boosters or agents to slow down or prevent Alzheimer's disease and related dementias. There are few objective measures to evaluate the safety and effectiveness of these products. The effectiveness of these drugs is based largely on tradition and a rather small body of scientific research. Law for the marketing of dietary supplements does not require the rigorous scientific research and clinical trials by the U.S. Food and Drug Administration (FDA) for the approval.

## Caprylic acid and coconut oil

Caprylic acid is a medium-chain triglyceride (fat) and is the key ingredient of Axona - a medical food marketed for Alzheimers disease

produced from the coconut or palm kernel by processing. Caprylic acid is converted to ketone bodies when metabolized, and the ketone bodies can function as the alternate energy source in the brain<sup>3</sup> when the neurons are not able to use glucose as the energy source because of the disease process and histological changes in Alzheimer's disease. Glucose is the chief energy source of a normal brain. GLUT1 is the carrier protein that transports glucose across the cell membrane and blood brain barrier. According to a recent study, reduced expression of GLUT1 worsens Alzheimer's disease<sup>4</sup> suggesting that GLUT1 may act as a therapeutic target for Alzheimer's disease vasculo-neuronal dysfunction and degeneration. GLUT1 deficiency in mice also has shown overexpression of amyloid  $\beta$ -peptide (A $\beta$ ) precursor protein,<sup>4</sup> the pathognomic histological finding in Alzheimer's disease.

### Curcumin

Curcumin is an anti-inflammatory molecule in the turmeric root family. Turmeric has a typical yellow color and it been used for thousands of years as to prepare herbal medicines to preserve and color food items. Curcumin, also known as diferulomethane, was isolated as the major yellow pigment in turmeric. It has a polyphenolic molecular structure that has been attributed to its medicinal properties and health benefits, e.g., one study found that curcumin might help the macrophages to remove the amyloid plaques found in Alzheimer's disease.<sup>5</sup> Macrophages, the principal components of the innate immune system, facilitate the removal of foreign proteins, microbes and abnormal protein build-ups via phagocytosis. Macrophages help the body to clear abnormal amyloid proteins in AD. They help the body to fight against foreign proteins and then effectively remove them. In a study, blood was taken from nine volunteers; six AD patients and three healthy controls with no disease.<sup>5</sup> Macrophages were treated with curcumin and beta amyloid was introduced to the blood. The blood of the AD patients treated with curcumin demonstrated increased beta-amyloid protein clearance compared to the untreated blood. Curcumin-treated macrophages demonstrated improved phagocytosis of amyloid plaque. Thus, curcumin may support the immune system to clear the amyloid protein.<sup>5</sup>

### Ashwagandha

Withaniasomnifera (WS), also known as Ashwagandha, is an agent that promotes cognition and memory. Beta-amyloid plaques are considered toxic to neurons in the brain and when they accumulate in people with various neurodegenerative diseases.<sup>6</sup> Since these tests were conducted in test tube samples, more studies in animals and clinical trials in human beings were recommended. A study in mice demonstrated that after 30 days of administration of a semi-purified extract of Ashwagandha root, the behavioral deficits of the mice were reversed and amyloid plaques were eliminated in the cortex and hippocampus of the mice. It also improved the cognitive functioning of the mice significantly.<sup>7</sup>

Another study was specifically carried out to evaluate the effects of Withaniasomnifera on cognitive and psychomotor performance in healthy human participants.<sup>8</sup> After 14 days of treatment with Withaniasomnifera, outcomes showed significantly improved reaction time in five of the six psychomotor performance tests, with no sedative effects, when compared to placebo and baseline testing.

The mechanism of action of Withaniasomnifera in humans is not clear. Animal studies have shown that the Sitoindosides VII-X and Withaferin A (glycowithanolides) are the active phytophenols, responsible for the mechanism of increased cortical muscarinic acetylcholine capacity, with a modulation of cholinergic

neurotransmission.<sup>9</sup> These studies indicate the use of Withania somnifera can cause significant changes in neurological baseline functions. Researchers postulate that it can be applied clinically in prevention, and possibly repair, of central nervous system disorders.

### Bacopamonniera

Bacopamonniera (Brahmi) in the Ayurveda system of Indian Herbal Medicine has been used for centuries. Traditionally, Ayurvedic medical system has been using it for anxiety relief, as a tonic for the brain to enhance learning and memory development, and prevention of epilepsy.<sup>10</sup> Aging leads to various degenerative changes in the body, and the quantity and quality of these changes depend on upon the anatomy and physiology of the tissue. The factors that contribute to these changes are oxidative damage to the DNA and hormonal deficiency. Normal stress response requires synchronized functioning of various hormones and neurotransmitters. Bacopa contains many alkaloids, such as abrahmine and herpestine, saponins, d-mannitol, hersaponin and monnierin that are responsible for the medicinal value. Other active constituents include betulinic acid, stigmastanol, beta-sitosterol, numerous bacosides, and bacopasaponins.<sup>11</sup> The bacosides enhance kinase activity, neuronal synthesis, and restore synaptic activity.<sup>12</sup> These neuronal repair actions are valuable in AD management.

### Resveratrol

Resveratrol is a phytophenol present in high amounts in red grapes. It has high antioxidant activity. More recent studies showed that resveratrol enters the CNS rapidly following peripheral administration, and can protect neurons in the brain and spinal cord against ischemic injury.<sup>13</sup> In an experimental study using rats, ischemic damage to the brain and spinal cord neurons after a cerebrovascular and mechanical insult was prevented by administering resveratrol.<sup>14</sup> It can protect against nitric oxide-mediated oxidative stress-induced death in cultured neurons.<sup>15</sup> Similarly, resveratrol protected dopaminergic neurons in midbrain slice cultures against metabolic and oxidative insults.<sup>13</sup> It is an important outcome of the study relevant to Parkinson's disease.<sup>16</sup> In models relevant to Alzheimer's disease, resveratrol protected neuronal cells from being killed by amyloid  $\beta$ -peptide and promoted amyloid  $\beta$ -peptide clearance from cultured cells.<sup>13</sup>

### Centellaasiatica

Centellaasiatica (CA) is a psychoactive medicinal plant used for centuries in Ayurvedic system of medicine as an ingredient of medhyarasayna. It has been shown to decrease the oxidative stress on the brain.<sup>17</sup> Major bioactive compounds of this plant contain highly variable triterpenoidsaponins, and related saponins.<sup>18</sup> It also contains triterpenoid acids. However, the exact mechanism of action of triterpenoid acids in the treatment and management of neurological disorders has not been fully elucidated.

There are many herbal agents available on the market found to be effective in preventing, and managing many neurodegenerative disorders. Caprylic acid, for example is converted to ketone bodies in the body, and the ketone bodies can function as the alternate energy source in the brain when the neurons are not able to use glucose as the energy source because of the disease process and histological changes in Alzheimer's disease. Curcumin may support the immune system to clear the amyloid protein and prevent amyloid plaque build-up. Sitoindosides VII-X and Withaferin A (glycowithanolides) are the active phytophenols, responsible for the mechanism of increased cortical muscarinic acetylcholine capacity, with a modulation of

cholinergic neurotransmission. Bacopa contains many alkaloids that enhance kinase activity, neuronal synthesis, and restore synaptic activity. These neuronal repair actions of Bacopa are valuable in Alzheimer's disease management. Resveratrol has demonstrated its ability to protect against nitric oxide-mediated oxidative stress-induced death in cultured neurons. Centella asiatica has been shown to decrease the oxidative stress on the brain and may be beneficial in preventing AD.

### Concerns about herbal agents

Although some of the herbal remedies may be valid candidates for treatments, there are concerns about using these drugs as an alternative or in addition to modern medicine: Effectiveness, safety, purity, and possible drug interactions are unknown. Laws for the marketing of dietary supplements do not require the rigorous scientific research needed by the FDA for the approval of a prescription drug. The manufacturer of a dietary supplement doesn't have to provide the FDA with the evidence of safety and effectiveness. Unfortunately, this may lead to the presence of toxic contaminants in the supplement. Under the current FDA regulation, including the Dietary Supplement Health and Education Act of 1994, the FDA has the authority to remove products from the market if it can prove that such products are adulterated (e.g., that the product is unsafe) or misbranded (e.g., that the labeling is false or misleading). Dietary supplements may cause serious interactions with prescribed medications if not used carefully. For the best benefits of the people, if FDA mandates clinical trials and strict quality checks for herbal agents before introduction to the market, the purity and safety can be assured. The post-market study also should be encouraged for any adverse effects. Everyone should be advised to consult with a pharmacist or Physician before taking herbal supplements by labeling requirements.<sup>19-22</sup>

### Conclusion

Phytochemicals and other herbal medicines are found to be useful in preventing or treating many neurodegenerative conditions, especially Alzheimer's disease. Studies have shown that the herbal agents contain many potential alkaloids, and they can counteract oxidative stress on the nervous system and act as anti-inflammatory agents on aging brain. Many herbal agents in the market have demonstrated beneficial effects in patients with AD, and either improved cognitive functions or reversed cellular level damage to the neurons. It is also important to watch for drug interactions especially when taken with other medications. If FDA implement rules and regulations to ensure the purity and quality of herbal agents, it would be beneficial for the public to take them while minimizing the risks. Standardization of herbal medicines and integration of herbal medicines in United States Pharmacopeia (USP) will change the way the herbal medications are manufactured, marketed, and prescribed so that potential adverse effects, and drug interactions can be eliminated. Adding herbal agents to the standard treatment regimen may lead to improved clinical significance.

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### Conflicts of interest

Herbal agents for prevention and treatment of Alzheimer's Disease: The authors hereby certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock

ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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