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**File: ■ Alzheimer's Disease  
■ Ethnobotany**

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**RE: Review of Promising Ethnobotanical Treatments for Alzheimer's Disease**

Howes M-JR, Houghton PJ. Ethnobotanical treatment strategies against Alzheimer's disease. *Curr Alzheimer Res.* 2012;9(1):67-85.

The challenges involved in successfully pursuing ethnobotanical leads are cogently summarized: accurately translating traditional usage into Western medical ideology, characterizing herbal preparations and their chemical constituents, and shifting focus from "the" active ingredient to polyvalence.

In this review, plants and their phytochemicals are discussed for their relevance in targeting current mechanisms considered to be involved in the pathology of Alzheimer's disease (AD), including cholinergic dysfunction,  $\beta$ -amyloidosis, inflammatory pathways, tau hyperphosphorylation, and oxidative pathways; and targeting symptoms, including cognitive impairments and behavioral and psychological symptoms of dementia. Many of the plants included in this study were selected because they have been investigated in a number of published animal and clinical studies.

#### *Bacopa (Bacopa monnieri)*

All parts of the small herb bacopa, formerly known as (syn.) *B. monniera* and *Herpestis monniera*, have been used in Ayurvedic medicine for centuries. It is known in Sanskrit as *brahmi*. One of its traditional uses is for improvement of memory and cognition. Bacosides A and B, and bacopaside XI (saponins), are the major compounds thought to be responsible for its activity, although alkaloids and flavonoids have also been isolated. In vivo and in vitro studies suggest that bacopa may reduce memory loss via the following mechanisms of action: modulation of cholinergic function, general antioxidant effects, preventing accumulation of  $\beta$ -amyloid (A $\beta$ ), and affecting the nitric oxide (NO) pathway. Some clinical studies have been conducted in the last ten years, with most studies using a crude aqueous or aqueous alcoholic extract, rather than purified constituents. Most clinical results appear to support the traditional use when compared to placebo. Safety studies reported few adverse events (AEs), with mild gastrointestinal (GI) disturbance being the most common.

#### *Gotu kola (Centella asiatica)*

Gotu kola is an Ayurvedic remedy reputed to restore memory and longevity. In vivo and in vitro studies have demonstrated that gotu kola may reduce memory loss via antioxidant mechanisms, an anti-A $\beta$  effect, neuroprotection against A $\beta$  and glutamate-induced toxicity, neuronal dendritic growth, neuronal repair, and acetylcholinesterase (AChE) inhibition.

Randomized controlled trials (RCTs) with normal middle-age and elderly subjects demonstrated that gotu kola extract improved cognitive functions and mood compared to placebo. The authors conclude that based on available data, gotu kola is a candidate for clinical assessment in AD.

#### Saffron (*Crocus sativus*)

Saffron is from the stigmas of *Crocus sativus*, and it is used traditionally to treat emotional disorders, mania, and depression. These symptoms can also be associated with dementia. Although some RCTs indicate saffron extract may alleviate mild-to-moderate depression, most RCTs have focused on the efficacy of saffron extracts on cognition. RCTs indicated that saffron may be efficacious for improving cognition in patients with AD. The authors point out that despite in vitro and in vivo evidence supporting neuroprotective and memory-enhancing effects of crocins (the constituents to which some extracts are standardized), crocins have poor intestinal absorption in rodents and are hydrolyzed to crocetin in the GI tract. The authors conclude that extracts standardized to crocetin content, or perhaps other as yet unidentified constituents, should be investigated. Given the high cost of saffron, it is also noteworthy that crocus petal extracts have been shown to exert antidepressant effects compared to fluoxetine and placebo in 2 RCTs (although these extracts were not chemically characterized or standardized).

#### *Epimedium* species

*Epimedium koreanum* is used in traditional Korean medicine, and *E. brevicornum* is used in China for memory improvement. Most of the research has been conducted on an isolated flavonoid constituent called icariin. Although icariin appears to improve learning and memory in vivo, no RCTs have been conducted with patients who have dementia using icariin or *Epimedium* extracts.

#### Ginkgo (*Ginkgo biloba*)

Ginkgo has been popular around the world for the past 35 years in the treatment of declining cognition and memory. Constituents considered to contribute to activity (and used for standardization) include flavonoids and terpenoid lactones, including ginkgolides A, B, and C, and bilobalide. Ginkgo relies on several constituents for its beneficial polyvalent effect, rather than a single entity. A Cochrane review published in 2009 concluded that, "There is no convincing evidence that *G. biloba* is efficacious for dementia and cognitive impairment." The authors point out that although some studies question ginkgo's promise as a treatment of AD symptoms, there are many studies using standardized extracts that show a positive response. *G. biloba* has vasodilatory and antithrombotic effects, is antioxidant, inhibits A $\beta$  production and damage, and may modulate neurotransmitter release; all of these are relevant to influencing pathological processes and symptoms of AD. AEs are mild and include nausea, headache, GI disturbances, and occasional allergic skin reactions. Ginkgo has been associated with hemorrhage reactions, and thus should be used with caution for those on anticoagulant or antiplatelet therapy; although, it has recently been concluded that standardized ginkgo extracts may not increase bleeding risk.

#### Lemon balm (*Melissa officinalis*)

Lemon balm is one of the few plants traditionally claimed to improve memory that has been evaluated in clinical studies. One RCT reported improvement in cognition and a reduction in agitation in patients with AD after 4 months of oral treatment with an extract of lemon balm. Other studies have investigated the effects of lemon balm oil applied to the skin on agitation in AD. A Cochrane review published in 2003 concluded that lemon balm could reduce agitation, neuropsychiatric symptoms, and social withdrawal, and it could increase constructive activities compared to placebo in patients with dementia. The authors conclude

that additional studies are needed to assess effects of lemon balm oil and extracts on cognition and other symptoms of AD, and on the most appropriate route of administration.

#### *Polygala (Polygala tenuifolia)*

*Polygala (yuan zhi)* root is used in traditional Chinese medicine (TCM) for forgetfulness. It is often combined with other TCMS. In vivo and in vitro studies show an improvement in memory, neuroprotection, AChE inhibition, and inhibition of some inflammatory mediators. Two RCTs conducted in healthy, elderly subjects demonstrated that polygala improved cognition; however, there have been no RCTs conducted in patients with AD.

#### *Muirapuama (Ptychopetalum olacoides)*

The root of muirapuama, a small tree found in the Amazon basin of Brazil, is also known as marapuama or marantã. Root extracts are used in Brazil for central nervous system (CNS)-related ailments. In vivo studies show that an extract improved memory and that the active constituents are considered bioavailable when taken orally. The authors conclude that RCTs are needed before efficacy claims in humans can be made.

#### *Salvia species*

In traditional European herbal medicine, sage (*Salvia* spp., especially *S. officinalis* and *S. lavandulifolia*) has been described as treating brain and memory disorders. In vivo and in vitro studies demonstrate that these *Salvia* species improved memory retention; inhibited AChE; had antioxidant, anti-inflammatory, and estrogenic effects; and were neuroprotective against A $\beta$ . In RCTs, they improved cognition in healthy volunteers and in patients with AD. Due to the high thujone content, concerns have been raised that *S. officinalis* essential oil and large doses of extract may cause seizures. The authors emphasize the need for effective quality control to produce standardized and safe extracts for therapeutic use.

Extracts from *S. miltiorrhiza* root show in vivo efficacy for ischemia-induced memory impairments, but RCTs are needed to investigate efficacy and safety more extensively. *S. miltiorrhiza* has been reported to induce cytochrome P450, suggesting a potential for drug interactions, and hemorrhagic risk was increased when it was administered to patients taking warfarin.

Although there are many plants with the potential to help patients with AD, few have been thoroughly investigated. The authors conclude that even if the scientific studies do not provide definitive proof of efficacy, many of these plants have been used for a long time in their original context and will continue to be used, regardless of the views of scientific medicine. They call for more RCTs evaluating well-characterized and standardized herbal products.

—Heather S. Oliff, PhD

The American Botanical Council has chosen not to reprint the original article.

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