Herbal Medicine in the Treatment of Alzheimer's Disease

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Abstract

Treatment strategies for AD will have to include a variety of interventions directed at multiple targets. So far, the outcomes with available approved medications for AD are often unsatisfactory, and there is a place for alternative medicine, in particular herbal medicine. Herbal medicines are being used by about 80% of the world population primarily in the developing countries for primary health care. They have stood the test of time for their safety, efficacy, cultural acceptability and lesser side effects. This review tries to summarize the studies regarding *Ginkgo biloba, Salvia officinalis, Melissa officinalis* and *Crocus sativus* in the treatment of Alzheimer's disease.

Keywords: **Alzheimer's disease, *Crocus sativus, Ginkgo biloba, Melissa officinalis, Salvia officinalis***

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Introduction

Alzheimer's disease (AD) is the most common form of dementia in the elderly [1]. This condition is characterized by a progressive loss of memory, deterioration of virtually all intellectual functions, increased apathy, decreased speech function, disorientation, and gait irregularities. It is also one of the best known and important of all degenerative diseases [2]. It is a condition that is associated with considerable psychological and emotional distress for patients and their families. It is estimated that 3.5% of the population in the United States between the ages of 65 and 74 years of age is in at least the initial stage of AD [1, 2]. Most individuals who have advanced disease are 85 years of age and older. Females are slightly more likely than males to develop Alzheimer's disease [1, 2]. Deposition of amyloid-β (Aβ) in the brain is a neuropathological hallmark of AD and a potential cause of neuronal damage [3]. Although a "magic bullet" for AD has clearly not as yet been found, certain medicines offer modest benefit, and these may be conveniently divided into three classes, according as to whether they may prevent the development of the disease, retard its progression once it has set in, or offer some symptomatic relief [4, 5].

New studies suggest novel strategies for AD therapy. The most viable of these at the moment is targeting the disruption of neurotransmitter systems. Counteracting overproduction of amyloid-β is attractive in theory and has spurred the development of secretase inhibitors as well as active and passive immunization techniques. Nevertheless, the present drugs' effects are quite limited [4, 5].

Herbal medicine is still the mainstay of about 75 – 80% of the world population, mainly in the developing countries, for primary health care because of better cultural acceptability, better compatibility with the human body and lesser side effects. However, the last decade has seen a major increase in their use in the developed world [6, 7]. Preliminary clinical evidence indicates that some herbal medicines can ameliorate learning and memory in patients suffering from mild-to-moderate AD [8]. Potential beneficial actions exerted by the active ingredients of these herbs are not limited to the inhibition of cholinesterase inhibitors and include the modification of Aβ processing, protection against apoptosis and oxidative stress, and anti-inflammatory effects.

Ginkgo biloba

Originally, *Ginkgo biloba* (Coniferae) has been traditionally used for respiratory disorders in China and to improve memory loss associated with blood circulation abnormalities [9]. This herb has been subjected to numerous investigations regarding its potential in cognitive disorders. Standardized extracts, particularly EGb 761, derived from the plants' leaves are successfully used as herbal drug for the improvement of cognitive and memory impairment [10]. EGb 761 represents a prototype of plant extracts for attenuating CNS disorders, due to the fact that both flavonoids and terpenic lactones, which are partly also

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present in numerous other plant extracts, have been identified as the active principles in *Ginkgo* extracts as well as the ample experimental evidence on EGb 761's protective efficiency *in vitro* and *in vivo*. The potential of EGb 761 to attenuate the cytotoxic effects of Alzheimer's related neurotoxic amyloid peptides when added to the culture medium was demonstrated not only in neuronal-like cell lines but also primary neurons, though with different efficiency [11-13]. The impact of *Ginkgo* extract has been largely attributed to its antioxidant activity [12]. The effects of oxidative stress were reduced in lymphocytes and brain cells derived of EGb 761-treated AD-transgenic and non-transgenic mice [14, 15]. Recent data, however, indicate that EGb 761 also affects the production of neurotoxic beta-amyloid peptides (Aβ), for example, by up regulating α-secretase activity both in cells and animals [15]. In a nutshell, many placebo-controlled clinical trials proved *G. biloba* to be a useful herbal remedy for attenuating symptoms in dementia, with efficiency comparable to those of standard drugs in AD treatment [15]. This notion has been confirmed in a recent 3-month study in comparison to donepezil [16]. Furthermore, EGb 761 has been suggested to prevent neurodegenerative pathologies [17]. The ongoing GuidAge study, a double-blind randomized trial, will shed further light on the efficiency of EGb 761 in the prevention of AD [18].

Salvia officinalis, Melissa officinalis* and *Crocus sativus

Salvia officinalis (Sage; Lamiaceae) traditionally used, e.g., in tea preparations as anti-inflammatory agent, recently attracts attention as beneficial in dementia [19]. Sage protects PC12 cells from $Aß_{1–42}$ induced neurotoxicity, which include reactive oxygen species formation, lipid peroxidation, DNA fragmentation caspase-3 activation, and tau protein hyper phosphorylation [20]. These *in vitro* findings may help to elucidate Sage's clinical effects: *S. officinalis* extract was tested in patients with mild to moderate AD in a double-blind, randomized and placebo controlled multi-center trial in Iran [21, 22]. At 4 months, *S. officinalis* extract produced a significant better outcome on cognitive functions than placebo [23]. Using comparable clinical settings Akhondzadeh et al. [24] also reported beneficial effects for the traditional used remedies *Crocus sativus* (Iridaceae), traditionally used to treat all varieties of gastrointestinal ailments and *Melissa officinalis* (Lamiaceae) traditionally used, e.g., as an anxiolytic or mild sedative agent [24, 25]. Recent screening assays identified rosmarinic acid from *M. officinalis* extracts to potently inhibit AChE [26, 27]. Saffron is the world's most expensive spice and apart from its traditional value as a food additive recent studies indicate its potential as an anti cancer agent and memory enhancer [28, 29]. The value of saffron (dried stigmas of *Crocus*

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sativus L.) is determined by the existence of three main secondary metabolites: crocin and its derivatives which are responsible for color; picrocrocin, responsible for taste; and safranal responsible for odor [30]. This plant belongs to the Iridaceae family and as a therapeutically plant, saffron it is considered an excellent aid for stomach ailments and an antispasmodic, helps digestion and increases appetite. It is also relieves renal colic, reduces stomach ache and relieves tension [8, 31]. The world's total annual saffron production is estimated at 205 tons per year, with >80% of this harvest originating from Iran, mainly from the South Khorassan province. Saffron is used for depression and dementia in Persian traditional medicine [32]. Indeed, it is a Persian herb with a history as long as the Persian Empire itself [33-35]. It has been shown that administration of extracts of *Crocus sativus* L. antagonized ethanol-induced memory impairment in the passive avoidance task in the mouse, and the constituent of saffron extracts, crocin, prevented ethanol-induced inhibition of hippocampal long-term potentiation (LTP), a form of activity - dependent synaptic plasticity that may underlie learning and memory [36]. In addition, it has also been reported that crocin counteracted ethanol inhibition of NMDA receptor-mediated responses in rat hippocampal neurons [37]. Low doses of *Crocus sativus* extract antagonized extinction of recognition memory in the object recognition test and scopolamine-induced performance deficits in the passive avoidance task [38].

In conclusion, these studies show that *Crocus sativus* stigmas extract has antioxidant and anti amyloidogenic activity, thus reinforcing ethnopharmacological observations that *saffron* has a positive effect on cognitive function [39]. Another study indicated the possible use of *Crocus sativus* stigma constituents for inhibition of aggregation and deposition of amyloid-β in the human brain [40]. Therefore, increasing evidence from Persian traditional medicine as well as recent basic and clinical studies confirms that saffron may have potential for treating AD.

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