REVIEW

CNS Neuroscience & Therapeutics

Medicinal Plants and Dementia Therapy: Herbal Hopes for Brain Aging?

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SUMMARY

An escalating "epidemic" of diseases like Alzheimer's has not yet been met by effective symptomatic treatments or preventative strategies. Among a few current prescription drugs are cholinesterase inhibitors including galantamine, originating from the snowdrop. Research into ethnobotanicals for memory or cognition has burgeoned in recent years. Based on a multi-faceted review of medicinal plants or phytochemicals, including traditional uses, relevant bioactivities, psychological and clinical evidence on efficacy and safety, this overview focuses on those for which there is promising clinical trial evidence in people with dementia, together with at least one other of these lines of supporting evidence. With respect to cognitive function, such plants reviewed include sage, *Ginkgo biloba,* and complex mixtures of other traditional remedies. Behavioral and psychological symptoms of dementia (BPSD) challenge carers and lead to institutionalization. Symptoms can be alleviated by some plant species (e.g., lemon balm and lavender alleviate agitation in people with dementia; St John's wort treats depression in the normal population). The ultimate goal of disease prevention is considered from the perspective of limited epidemiological and clinical trial evidence to date. The potential value of numerous plant extracts or chemicals (e.g., curcumin) with neuroprotective but as yet no clinical data are reviewed. Given intense clinical need and carer concerns, which lead to exploration of such alternatives as herbal medicines, the following research priorities are indicated: investigating botanical agents which enhance cognition in populations with mild memory impairment or at earliest disease stages, and those for BPSD in people with dementia at more advanced stages; establishing an ongoing authoritative database on herbal medicine for dementia; and further epidemiological and follow up studies of promising phytopharmaceuticals or related nutraceuticals for disease prevention.

Introduction

Dementia

Dementia in the elderly is an epidemic of unprecedented proportion and crisis in modern medicine. Cost estimates exceed a billion Euros in Europe alone. Alzheimer's disease (AD) accounts for the majority, followed by vascular (VaD) and Lewy body types of dementia (LBD—dementia with Lewy bodies and Parkinson's disease (PD) dementia (PDD)), mixed pathologies being more common than not. Licensed drugs for dementia are still few: cholinesterase inhibitors (four drugs developed to inhibit acetylcholinesterase (AChE)) and for some, also butyrylcholinesterase (BuChE) and memantine (a glutamate NMDA receptor antagonist). A range of other drugs often prescribed incidentally include antipsychotics, antidepressants, tranquillizers, and hypnotics.

Symptoms include a range of cognitive impairments (notably memory—particularly the ability to form new memories, attention, and executive function). Equally important, as they primarily lead to institutionalization in the absence of stabilizing cognitive therapies, are behavioral and psychological symptoms of dementia (BPSD). These include psychosis, agitation, anxiety, sleep disorders, and depression. With respect to psychosis, there is limited efficacy of neuroleptics (drugs developed for schizophrenia not dementia) with multiple adverse effects including stroke and reduced mortality in people with dementia [1]. Depression is associated with worse quality of life, greater disability, faster cognitive decline, high rate nursing home placement, higher mortality, more depression, and burden in caregivers [2], and yet according to Bains et al. (2002) [3], there is little evidence that antidepressants are an effective treatment for patients with depression and dementia.

Since underlying causes are not yet identified (with the exception of hereditary AD and vascular risk factors for VaD), associated pathologies (potential therapeutic targets) are manifold: so-called "core" pathologies such as β-amyloidosis and abnormal tau (AD),

angiogenic and ischemic lesions (VaD) and α-synucleinopathy (LBD); neurotransmitter abnormalities, predominantly cholinergic but also others such as glutamatergic and serotonergic; inflammatory mechanisms; oxidative damage; apoptosis; and attenuated neuroplasticity (synaptic and dendritic proteins, trophic factors, and neurogenesis). Of these pathologies enhancing cholinergic function by inhibiting AChE activity still continues to be the first drug treatment option. Although, not unexpectedly, individual response is variable, there is some evidence for positive effects on disease progression [4,5] and while controversial, some data support cholinergic dysfunction as an early stage pathology [6].

The Phytochemical Approach

Scientific research into medicinal plants or herbs for dementia began about 15 years ago, although a more empirical form of enquiry dates back hundreds or thousands of years as cultures explored which plants were useful for what conditions (ethno–or archao–pharmacology) and passed information on species, preparation, and dose through the ages. This longstanding use, as for traditional Chinese medicine (TCM) and European herbal medicine up to the present time, provides an invaluable database on the safety and efficacy of numerous species. Because of their continued survival as medicines, it can be assumed that properly used (plant part, preparation, and dose), safety and tolerability may be predicted. Because of the complexity of chemical content (in terms of both diverse classes and multiple analogues within any class) and variety of bioactivities, herbal medicine offers the prospect of the kind of "built in" poly-pharmacology that is increasingly apparent for orthodox drugs. Added to this lure is the prospect of new drug discovery; amongst numerous examples of drugs originating from plants that have central nervous system (CNS) effects are ephedrine (*Ephedra sinica* Stapf), hyoscine (*Hyoscyamus niger* L.), morphine (*Papaver somniferum* L.), physostigmine (*Physostigma venenosum* Balf.), and galantamine from species of *Galanthus* and *Narcissus*. Precedents for the continuing discovery of plants or phytochemicals in other areas of medicine include numerous oncology medicines [7,8], potential drugs for infectious diseases (e.g., antibacterials and antivirals) [7], for analgesia [9], and for immunological and inflammatory diseases [7].

How phytochemicals could relate to complex cerebral functions such as memory or mood is presumably associated with their biosynthesis to deter predators or attract pollinators or disseminators by targeting the nervous system; this action has also been exploited to develop insecticides such as the pyrethrins, derived from *Chrysanthemum* species, which target sodium channels [10]. Converging themes underpin expectations that plant medicines will provide new treatments for dementia: realization of escalating problems and costs of dementia; a disappointing pace of new synthetic drug development in part due to stringent requirements for clinical evidence and licensing but also the complexities of dementia pathologies; and a wider acceptance of concepts of complementary or alternative medicine [11].

This review does not include all herbal or phytochemical approaches to dementia therapy since research in this area from ethnobotany, through pharmacology and chemistry to clinical evidence has extended long enough to generate other comprehensive reviews. Adams et al. (2007) [12] collected information on over 150 plant species in various preparations and mixtures for age-related cognitive disorders (mainly from European herbals from the 16th and 17th century, alongside traditional Chinese and Indian medicinal works). The broad range of plant extracts and compounds with AChE inhibitory activity has recently been reviewed [13,14], as has evidence for promising species such as sage (*Salvia* species), lemon balm (*Melissa officinalis* L.), *Huperzia serrata* (Thunb.) Trevis., and combinations of other traditional Chinese medicinal herbs, in addition to ginkgo (*Ginkgo biloba* L.) [15,16] (for which there is an extensive review of literature—see below).

Neuroprotective effects of phenolic compounds, such as resveratrol from grapes and red wine, curcumin from turmeric (*Curcuma longa* L.) and epigallocatechin from green tea (*Camellia sinensis* Kuntze) (relevant to oxidative mechanisms) [17,18] and research data mainly from *in vitro* or *in vivo* models on novel plant extracts and their bioactivities with antiamnesic effects on different neurotransmitter systems have also been reviewed [19]. Man et al. (2008) [20] concluded from a review of controlled clinical studies that herbal medicines "Can be a safe, effective treatment for Alzheimer's disease" and according to a meta-analyses by May et al. (2009) [21] "There is overall positive evidence for the effectiveness and safety of certain herbal medicines for dementia management."

This review is limited to plant extracts or chemicals with some promising clinical evidence in people with dementia, in conjunction with one or more other supporting lines of evidence (ethnobotanical, psychological effects in the normal or other populations, and mechanistic including effects on *in vitro* or *in vivo* models relevant to clinical symptoms and/or pathologies associated with dementia), but will also briefly consider future areas of natural product research relevant to dementia.

Cognitive Function

Natural Products Derived from European Plants (Table 1)

Galantamine

Licensed for the treatment of AD and now synthesized, this selective reversible and competitive inhibitor of AChE was originally derived from snowdrops. Together with other galantamine containing plants such as *Narcissus* species, these were not traditionally used for age-related cognition or memory [22]. Such chemicals are no doubt biosynthesized to deter predators, and if ingested cause severe gastrointestinal effects. Accordingly, side-effects of the drug include nausea, vomiting, and diarrhea. The identification of numerous other naturally derived AChE inhibitors (see above) was motivated by the hope of finding compounds that might selectively target brain areas affected in dementia. While not yet tested in humans, new sources of natural AChE inhibitors continue to be discovered, and recently include some lycopodane-type alkaloids from the Icelandic club moss *Lycopodium annotinum* ssp. *alpestre* [41] and a monoterpene diglycoside, (β-cyclogeraniol diglycoside) from *Nelumbo nucifera*, a plant used traditionally in Asia for nervous conditions [42].

Table 1 European plants and their constituents with relevance for dementia: cognition

Plant name*, part, and phytochemicals associated with biological activities	Traditional uses	Relevant bioactivities	Clinical effects/observations in humans
Snowdrop *Galanthus* species **Daffodil/narcissus** *Narcissus* species *Leucojum aestivum* L. (Amaryllidaceae) Bulbs Alkaloids: particularly galantamine	*Galanthus* and other Amaryllidaceae species: not commonly used as medicines in Europe; more recently (approx. last 40 years) used to alleviate various neurological conditions in Europe, particularly Bulgaria [22].	Galantamine is a well-documented AChE inhibitor and a positive allosteric modulator of nicotinic receptors [16]. Numerous synthetic galantamine derivatives have been developed including derivatives of 6-*O*-demethylgalantamine; some heterodimeric alkylene linked bis-galantamine derivatives inhibit AChE more potently than galantamine [16]. In animal models of amnesia, a prodrug of galantamine (Memogain®) improves cognition more effectively, with fewer side-effects, than galantamine [23]. Other alkaloids from *Narcissus* species inhibit AChE: 11-hydroxygalantamine, epinorgalantamine, assoanine, and sanguinine [16].	Numerous multi-center, RCTs show galantamine is well-tolerated and significantly improves cognitive function in AD patients [14,24]. Galantamine may also be of some therapeutic value in LBD and VaD [16].
Lemon balm/melissa *Melissa officinalis* L. (Lamiaceae) Aerial parts Essential oil; rosmarinic acid and derivatives	Reputed in European medicine to treat melancholia, neuroses, and hysteria; acclaimed for promoting long life and restoring memory [16].	An ethanolic extract, the essential oil, and some oil components (citral) weakly inhibit AChE; rosmarinic acid and derivatives are also associated with AChE inhibition [16]. Other activities: antioxidant, possible estrogenic, binding to muscarinic M_1, nicotinic, 5-HT_{1A}, 5-HT_{2A}, histamine H_3, and $GABA_A$ receptors; essential oil inhibits GABA-induced currents in rat cortical neurons [16,25,26].	Improved cognitive performance in healthy participants in RCTs following treatment with cholinergically active *M. officinalis* dried leaf or a standardized extract; cognitive improvements observed in AD patients treated with *M. officinalis* extract for 4 months in a double-blind RCT [15,16].
Sage *Salvia* species, in particular: *S. officinalis* L. and *S. lavandulifolia* Vahl. (Lamiaceae) Aerial parts Monoterpenoids including 1,8-cineole and α-pinene	Used traditionally in European medicine for memory disorders; its use is quoted in 16th and 17th century English herbals [15].	Various CNS effects reported for different *Salvia* species including memory enhancing, neuroprotective, and antiparkinsonian activities [27]. Extracts and oils from *S. officinalis* and *S. lavandulifolia* are antioxidant, antiinflammatory, and inhibit AChE; the latter activity is associated with oil monoterpenoids (1,8-cineole and α-pinene) [24,28,29].	A standardized oil extract of *S. lavandulifolia* produced significant effects on cognitive ability (immediate word recall scores improved) in healthy young adults (RCT) [30]. A similar study showed positive modulation of mood and cognition in healthy young adults given standardized essential oil of *S. lavandulifolia* [31]. *S. officinalis* extract enhanced secondary memory performance in adults (> 65 yr age, RCT) [32]. In a pilot trial (11 patients with mild to moderate AD) *S. lavandulifolia* oil significantly improved cognitive function, reduced neuropsychiatric symptoms, and improved attention [33]. In a multi-center RCT, AD patients treated with *S. officinalis* extract had significantly better outcomes in cognitive function [34].

Table 1 Continued

Plant name*, part, and phytochemicals associated with biological activities	Traditional uses	Relevant bioactivities	Clinical effects/observations in humans
Lesser periwinkle *Vinca minor* L. (Apocynaceae) Aerial parts Alkaloids: vincamine	A folk medicine used for loss of memory and circulatory disorders [35].	Vincamine and derivatives (vincanol and vinpocetine) show cerebral vasodilator/nootropic activity, block voltage-gated Na^+ channels, and are neuroprotective [36,37]. Vincamine modulates brain circulation and neuronal homeostasis and is antihypoxic [35]. However, alkaloid fractions extracted from aerial parts are cytotoxic *in vitro* [35].	Double-blind studies have assessed efficacy of vinpocetine in dementia but quality of methods is limited; a 16-week double-blind RCT (203 patients: mild to moderate dementia) showed significant benefit in the vinpocetine treated group [38]. Although a lack of evidence to support clinical use of vinpocetine in cognitive disorders [39], it improved cognitive status and cerebrovascular reserve capacity in patients with ischemic stroke and MCI in a pilot study [40].

*Common and Latin names (plant family).

Galantamine is effective in AD with respect to cognition and also behavioral symptoms and activities of daily living (the requisite triad for drug licensing) and at all stages of the disease tested [43], but not for mild cognitive impairment (MCI) [44]. While it is generally assumed the main biological outcome of treatment is to elevate the level of acetylcholine (ACh), other unexpected effects of cholinesterase inhibitor (ChEI) agents of unknown impact include far greater sensitivity of another enzyme, aryl acylamidase, compared to AChE [45].

Sage

With a longstanding reputation in European herbal encyclopedias for improving memory, *Salvia officinalis* L. or *S. lavandulifolia* Vahl. have a range of relevant neurobiological activities: *in vitro*—anti-AChE [28,29] and anti-BuChE activities [46]; antiinflammatory and estrogenic activities [47]; antioxidant effects [24]; antiamylodogenic activity [48]; and *in vivo*—anti-AChE [49]; and memory enhancement [50]. In both young and elderly normal volunteers sage enhances memory (including accuracy of immediate recall) [30,32] and there is one open label trial [33] and one randomized controlled trial (RCT) in AD [34] indicating positive cognitive and behavioral effects. In another condition, MCI in PD, a pilot RCT in 25 patients, did not demonstrate significant differences in cognitive outcome between test and placebo, both groups responding significantly from baseline [51].

Lemon Balm

As for sage, this European herbal medicine is reputed to enhance memory and to possess calming and antidepressant properties. Neurobiological activities of *Melissa officinalis* extracts, distinct from sage include: nicotinic [52,53] and muscarinic receptor binding [26,53]; 5-HT_{1A}, 5-HT_{2A} and $GABA_A$ binding activity of the essential oil [26]; physiological effects of the essential oil on $GABA_A$-mediated transmission and reducing spontaneous synaptic transmission implying novel channel actions [25,54]. Psychologically, it improves memory in normal young adults and measures of calm; also increasing cognitive function under experimental stress, and reduces anxiety in normal young adults [15]. In one RCT *M. officinalis* reduced cognitive impairment in AD [15].

Periwinkle

Lesser periwinkle (*Vinca minor* L.) is reputed to improve blood flow to the brain and there are supportive data on this and neuroprotective effects of a synthetic derivative of the vincamine alkaloid, vinpocetine [37]. Vinpocetine has provided some promising clinical trial data on cognitive enhancement in people with dementia although according to a Cochrane review [39], not sufficient to support its use, although it enhanced memory and learning in VaD [40].

Natural Products Derived from Traditional Chinese Medicines (Table 2)

Ginkgo

There are far more mechanistic and clinical data on *Ginkgo biloba* relevant to dementia than for any other plant species. This may reflect the widespread use of ginkgo for many conditions other than memory (e.g., tinnitus, premenstrual tension, intermittent claudication), the availability of standardized extracts, and few indications of significant side-effects. As with any drug there are, however, interactions between ginkgo and other drugs (Table 2).

Table 2 Plants used in TCM and their constituents with relevance for dementia: cognition

Plant name*, part and phytochemicals associated with biological activities	Traditional uses	Relevant bioactivities	Clinical effects/observations in humans
Ginkgo/maidenhair tree *Ginkgo biloba* L. (Ginkgoaceae) Leaves Many studies have focused on a standardized extract of *G. biloba*: EGb 761 (contains flavonoid glycosides and terpenoid lactones amongst other constituents)	TCM use dates back for centuries; Pharmacopoeia of the People's Republic of China includes seeds as a remedy for cough and asthma [55]. In Europe, leaf preparations were used to treat circulatory disorders in the 1960s; now a popular herbal remedy reputed to alleviate memory problems [56].	EGb 761: Favorable effects on cerebral circulation, neuronal cell metabolism, the cholinergic system; has antioxidant activity, reduces apoptosis, and is neuroprotective against NO- and β-amyloid-induced toxicity; the latter effect is associated with the flavonoids [16,56]. Other extracts improve cognition in young and old rats, short-term memory in mice, and spatial learning and memory in rats with aluminum-induced brain dysfunction; reduce cognitive impairment and hippocampal damage after ischemia and attenuate scopolamine-induced amnesia in rats [16,56]. Cognitive activities may be due to effects on cholinergic function and/or by modulation of the glutamatergic system, and/or possibly via histaminergic mechanisms [19].	Clinical efficacy of extracts (including EGb 761) has been extensively evaluated in numerous RCTs with both AD and healthy subjects [16,19,56,57]. A meta-analysis of RCTs demonstrates clinically relevant positive results with *G. biloba* in AD patients [58]. Many trials indicate *G. biloba* can modestly improve cognitive ability, but trial outcomes are not consistently based on objective methods of analysis. One RCT in multiple sclerosis patients (120 mg extract twice daily) showed *G. biloba* to produce no significant improvement in cognition, but it was suggested to influence some cognitive processes (e.g., mental flexibility) [16]. Generally, oral administration is well-tolerated with no serious adverse effects [16]. The use of *G. biloba* with antiplatelet or anticoagulant medicines may increase the risk of hemorrhage [59].
***Huperzia serrata* (Thunb.) Trevis.** (Lycopodiaceae) Moss Alkaloids: huperzines A and B	Used in TCM as a treatment for memory loss [56].	Huperzine A: Improves cognitive processes in cognitively impaired and chronically hypoperfused rats, and in gerbils following ischemia [56]. Reversibly inhibits AChE *in vitro* and *in vivo*; more potent than huperzine B [14]. Is eight-fold more potent than donepezil and two-fold more potent than rivastigmine in increasing cortical ACh levels, with a more prolonged action [19]. Is neuroprotective against β-amyloid peptide, oxygen-glucose deprivation, free radical-induced cytotoxicity, and glutamate; also an NMDA receptor antagonist in the cerebral cortex [56]. Attenuates apoptosis by inhibiting the mitochondria-capase pathway and has neurotrophic effects [56]. Numerous synthetic analogues of huperzines A and B; include huprines X, Y, and Z which inhibit AChE more potently than huperzine [14]; a dimer derivative of huperzine B potently inhibits AChE, is neuroprotective against β-amyloid, and improves scopolamine-induced spatial performance deficits in rodents [4,14].	In phase IV clinical trials, huperzine A improved memory in elderly, AD, and VaD patients, with few adverse effects [16]. Clinical efficacy of huperzine A also demonstrated in other RCTs in AD patients with improvements in cognition, behavior, and mood [19]. A pro-drug of huperzine, Debio 9902 (ZT-1), was safe and effective when administered once daily to AD patients in a phase IIa clinical trial; further trials are in progress [7]. One small trial (14 VaD participants) showed no significant beneficial effect of huperzine A on improvement of cognitive function [60].

Table 2 Continued

Plant name*, part and phytochemicals associated with biological activities	Traditional uses	Relevant bioactivities	Clinical effects/observations in humans
Ginseng *Panax ginseng* C.A.Mey. (Araliaceae) Other species of *Panax* are used for similar indications Root Triterpenoid saponins: ginsenosides	Used in TCM as a general tonic and reputed to invigorate the body and to prolong life [61].	Numerous *in vivo* studies show individual ginsenosides to reduce or prevent memory deficits associated with cholinergic function; activation of estrogen receptors also suggested to explain effects on learning processes [61,62]. Ginsenosides, Rg_1 and Rb_1 in particular, improve learning and memory in various memory-impairment models [63] and enhance ACh levels in the CNS, by increasing choline acetyltransferase (ChAT) activity or by inhibiting AChE activity [19]. Extracts and ginsenosides are neuroprotective; ginsenoside Rg_3 inhibits NMDA receptors [18,19,64].	Studies in healthy volunteers show improved abstract thinking, attention, information processing, cognitive performance, auditory reaction time, social functioning, and mental health with a standardized ginseng extract (> 4% ginsenosides per oral dose); other studies in healthy volunteers show no quantifiable effects on memory; conflicting trial data are considered to be due to compositional differences in ginsenosides [62]. A review of RCTs using any type of *P. ginseng* to treat patients with AD focused on two trials assessing the effectiveness of ginseng as an adjunct to drug therapy on cognitive function compared with conventional drug therapy; results (MMSE and Alzheimer's Disease Assessment Scale) were significantly in favor of ginseng; due to methodological limitations, evidence for efficacy of ginseng in AD is inconclusive [65].
***Polygala tenuifolia* Willd. (Polygalaceae)** Root Only some cinnamic acid derivatives and onjisaponins have shown some relevant activities *in vitro* [16]	Used in TCM for cardiotonic and cerebrotonic effects [16]; Pharmacopoeia of the People's Republic of China: a remedy to anchor the mind and for forgetfulness [55]. Used in traditional Japanese medicine as a mixture with 12 other prescription components (kami-utan-to (KUT)), to treat psycho neurological diseases.	Extracts reverse scopolamine-induced cognitive impairment, are neuroprotective against glutamate, and APP *in vitro* and dose-dependently inhibit AChE activity *in vitro* [16,66]. Numerous studies on a TCM prescription (DX-9386**), which ameliorates memory impairment *in vivo* [24,56]. KUT increases nerve growth factor secretion *in vitro*, improves passive avoidance behavior, and induces ChAT activity in the cerebral cortex of aged rats and in scopolamine-induced memory impaired rats; activities are mainly attributed to the *P. tenuifolia* content of the prescription [16].	An extract (BT-11) enhanced some cognitive functions including memory in elderly humans in a RCT [66]. In a 12-month RCT (seven AD patients treated with KUT) the rate of cognitive decline was significantly slower than patients receiving no medication for AD, with efficacy most obvious at 3 months [67]. In a 12-week trial, KUT combined with donepezil produced benefits on cognition and brain perfusion in AD patients, compared to donepezil monotherapy [68].
Saffron *Crocus sativus* L. (Iridaceae) Stigmas Carotenoids: crocin	Used in TCM to treat disorders of the nervous system [24].	An extract and crocin improve learning behavior *in vivo*; crocin suppresses TNF-α-induced apoptosis of neuronally differentiated PC12 cells *in vitro* [24]. Extract and carotenoids inhibit β-amyloid aggregation and are antioxidant [69].	In a 22-week double-blind trial, AD patients treated with saffron showed comparable improvements in cognition compared to donepezil [70].

*Common and Latin names (plant family).

**Composition: *Polygala tenuifolia*, *Panax ginseng*, *Acorus gramineus* [Soland.] (Acoraceae), *Poria cocos* (Schwein.) F.A. Wolf (Fomitopsidaceae) (ratio 1:1:25:50).

Mechanistic effects relevant to dementia (summarized in Table 2) have been recently reviewed by Kaschel (2009) [71] and include: endothelial protection; inhibiting low-density lipoprotein oxidation; reducing mitochondrial DNA damage; reducing stroke damage; reducing β-amyloid aggregation and deposition (also promoting clearance and protection against toxicity); also genomic effects—increasing transthyretin expression [72].

Clinical data while profuse still remain surprisingly equivocal for AD. In 2002, a Cochrane review claimed improvement in cognition and activities of daily living [73] but a subsequent similar type of review [74] indicated either no or inconsistent and unreliable evidence for predictable clinical benefit. Not unexpectedly, given its high profile and intense marketing for cognition, research continues. Kaschel (2009) examined psychological data from 29 pooled RCTs which indicate significant positive effects versus placebo on selective attention and executive function in people with dementia [71]. With respect to non-AD types of dementia, Napryeyenko et al. (2009) observed similar positive effects in AD and VaD with fewer side-effects than placebo (in a secondary RCT analysis) [57]. Whether ginkgo may be more appropriate as a cognitive enhancer in normal populations as early reports indicated [58] remains to be established.

Ginseng

While relevant mechanistic data are extensive for this antiaging "panacea" [59,61] (summary of relevant activities in Table 2), clinical data relating to dementia are positive but not yet strong. Reported trials in AD or MCI have mostly been either open label or single blind and although there is evidence for improved cognition in AD patients, overall evidence for efficacy in AD is limited [65]. In a recent review of two RCTs of *Panax ginseng* in people with AD, Lee et al. (2009) concluded results suggested significant effect in favor of ginseng but that both were "burdened with serious methodological limitations" [65]. Studies involving healthy volunteers also show improvements in cognitive performance but efficacy has not been consistent [59,62]. It may be that, as for other traditional plant medicines for cognition, efficacy is greater for those that have not yet developed dementia.

Huperzine

The moss *Huperzia serrata* has been used in TCM for treating and preventing dementia. It contains huperzine A, a potent anti-AChE alkaloid, which is neuroprotective [16], effects related to its ability to attenuate oxidative stress, regulate the expression of apoptotic proteins, protect mitochondria, and modulate amyloid precursor protein (APP) metabolism [75]. Relevant activities of huperzines A and B, and derivatives are summarized in Table 2.

In 1996, the drug "Shuangyiping," a tablet formulation of huperzine A, was developed in China and used for symptomatic treatment of AD; huperzine A is also marketed in the USA as a dietary supplement as powdered *H. serrata* for memory impairment [16]. The only clinical evidence available is from studies conducted in China. In a meta-analysis of RCTs, Wang et al. (2009) noted improved cognition (Mini-Mental State Examination: MMSE) with minimal adverse effects [76], which, if verified, would advocate for the superiority of natural products with traditional uses relevant to dementia.

Other Traditional Chinese and Japanese Herbal Medicines

In TCM combinations of herbs are frequently prescribed, multiplying complexity and interpretation in mechanistic studies. The TCM mixture ba wei di huang wan (includes *Alisma orientale* (Sam.) Juz. rhizome and *Rehmannia glutinosa* Steud. root) improves scopolamine-induced memory impairment and has muscarinic receptor effects [77,78], and in an eight-week RCT with mild to severe dementia patients, MMSE significantly improved in the treated group [77]; although a small sample size ($n = 33$), the therapeutic potential of this mixture and the individual components warrant further study. Another TCM tonic luweidihuangtang (contains some of the same components as ba wei di huang wan) enhanced cognitive ability in normal human subjects in a double-blind placebo-controlled trial and, consequently, further clinical studies in dementia patients are suggested [79]. Other TCMs have been evaluated for potential efficacy in dementia, with a Cochrane database review for one decoction (zhiling; consists of 15 components) concluding that further evidence is required for efficacy in VaD [80], although a modified sanjiasan decoction improved on MMSE and IQ scores compared to control in patients with VaD [81]. It is apparent that there is some preliminary evidence for efficacy of some TCMs in dementia, although, as with other promising natural products including *G. biloba* [74], further controlled trials are required.

Yokukansan (Chinese: yi gan san) is a traditional Japanese medicine consisting of seven components (listed in Table 3), developed in the 16th century as a remedy for restlessness and agitation in children. Amongst a range of mechanistic studies, it reverses learning deficits in an AD transgenic mouse [82] and reduces glutamate toxicity [83]. Despite this, but consistent with traditional use, this mixture does not enhance cognition [84] but ameliorates BPSD (see below and Table 3). Another Japanese remedy, kami-utan-to (KUT), has shown promising effects on cognition in dementia patients (Table 2).

Behavioral and Psychological Symptoms

BPSD as a Whole (Table 3)

For galantamine, clinical evidence while supportive of effects of this and other ChEIs on behavioral measures such as the Neuropsychiatric Inventory (NPI), is not definitive for BPSD since trials have not involved patients primarily affected by BPSD [114]. There is, in contrast, more substantial evidence for ginkgo. In meta-analyses of RCTs, Scripnikov et al. (2007) found the largest drug-placebo differences in favor of EGb 761 were for apathy/indifference, anxiety, irritability/lability, depression/dysphoria, and sleep/night time behavior [115], and Hoerr (2003) also reported significant improvement for BPSD as a whole [94]. With respect to other TCMs, Shinno et al. (2007, 2008) noted in small open label trials that yokukansan improved BPSD, including psychiatric symptoms and sleep structure in LBD and AD

Table 3 Plants and their constituents with relevance for dementia: behavioral and psychological symptoms

Plant name*, part, and phytochemicals associated with biological activities	Traditional uses	Relevant bioactivities	Clinical effects / observations in humans
Cannabis *Cannabis sativa* L. (Cannabaceae) Aerial parts Cannabinoids: Cannabidiol (CBD), Δ^9-tetrahydrocannabinol (THC)	One of the oldest psychotropic drugs; known in China since around 4000 BC [85].	Modulation of the cannabinoid system by cannabinoids may regulate glutamate production, oxidative stress, and neuroinflammation [86]. CBD: antioxidant and neuroprotective *in vitro* [87]; sedating and antagonizes psychotropic effects of THC [88]. THC: stimulates appetite but also impairs learning and memory [88]. Biphasic effects of cannabinoids on anxiety are reported; both anxiolytic and anxiogenic effects occur *in vivo*; CBD is anxiolytic *in vivo* [89].	Nabilone (synthetic cannabinoid) improves anxiety in patients compared to placebo [88]. THC improves behavioral disturbances including agitation and stimulates appetite in AD patients and alleviates nocturnal agitation in dementia [87,88]. Assessment of the efficacy of cannabinoids (any dose) in the treatment of dementia in all double-blind and single (rater)-blind RCTs found no evidence that cannabinoids are effective in improving disturbed behavior or other symptoms in dementia [86].
Ginkgo/maidenhair tree *Ginkgo biloba* L. (Ginkgoaceae) Leaves Refer to Table 2	Refer to Table 2	EGb 761 restores decreased cerebral 5-HT_{1A} receptors and increases 5-HT uptake *in vivo*, and is antidepressant and antistress in behavioral models [90,91]. Ginkgolic acid conjugates and ginkgolide A are anxiolytic *in vivo* [92,93].	Studies with dementia patients with BPSD show EGb 761 to improve BPSD compared to placebo [94]. RCT with 400 patients (AD or VaD) for 22 weeks: EGb 761 was superior to placebo on NPI scale and an activities-of-daily-living scale [57]. RCT with AD patients showing neuropsychiatric features: treatment with either donepezil or EGb 761, or combined, significantly improved cognitive performance and neuropsychiatric symptoms [95].
St John's wort *Hypericum perforatum* L. (Clusiaceae) Herb Anthraquinone derivatives: hypericin Prenylated phloroglucinols: hyperforin	Reputed uses: sedation, excitability, neuralgia, neurosis, anxiety, depression [59].	Numerous studies *in vitro* and *in vivo* show antidepressant activity—precise mechanisms are unclear. Extracts show affinity for adenosine, $GABA_A$, $GABA_B$, benzodiazepine and MAO_A and MAO_B receptors; inhibit MAO_A and MAO_B activities; also inhibit 5-HT, dopamine, and noradrenaline uptake. Antidepressant components are considered to be hyperforin, hypericin, and flavonoids; hyperforin inhibits 5-HT, dopamine, noradrenaline, GABA, and L-glutamate uptake [59].	Over 40 RCTs in patients with different types of depression; placebo RCTs indicate *H. perforatum* is comparable in efficacy to conventional antidepressants; generally, evidence for efficacy is inconsistent and complex—this may reflect variation in *H. perforatum* products tested [59,96]. Limited evidence for efficacy in anxiety disorders in humans [97].
Lemon balm/melissa *Melissa officinalis* L. (Lamiaceae) Aerial parts Essential oil components	Traditional uses include: sedative and for nervousness [59]. Indicated for "all complaints supposed to proceed from a disordered state of the nervous system" and "to chase away melancholy" [15].	Extracts are sedative *in vivo* [59]; the essential oil (oral dose) prolongs hexobarbital-induced sleep *in vivo* [15]. Essential oil binds to muscarinic M_1, 5-HT_{1A}, 5-HT_{2A}, histamine H_3 receptors, and $GABA_A$ receptors [26] and reversibly inhibits GABA-induced currents in rat cortical neurons [25].	*M. officinalis* combined with *Valeriana officinalis* extracts improve sleep quality in healthy volunteers and patients with insomnia in RCTs [59]. *M. officinalis* essential oil aromatherapy treatment for 4 weeks (RCT) with dementia patients reduced agitation and improved quality of life [15].

Table 3 Continued

Plant name*, part, and phytochemicals associated with biological activities	Traditional uses	Relevant bioactivities	Clinical effects / observations in humans
Kava *Piper methysticum* G.Forst. (Piperaceae) Rhizome Kava lactones	Traditionally used in Pacific Island cultures for relaxing effects [97].	Kava lactones bind to GABA receptors but studies investigating different kava lactones have shown conflicting results; anxiolytic action of extracts and kava lactones observed in experimental models for anxiety [59,97].	Meta-analysis of RCTs shows a significant reduction in anxiety in kava treated patients, but has been implicated in cases of hepatotoxicity, thus is prohibited in unlicensed medicines in the UK and some other countries [59,97].
Lavender *Lavandula angustifolia* Mill. (Lamiaceae) Aerial parts Essential oil components, including linalool	Traditional uses: sedative and antidepressant [98].	Reported to act similarly to benzodiazepines and enhance the effects of GABA [98]. Oil inhibits radioligand binding to muscarinic M_1, 5-HT_{2A}, histamine H_3 receptors, and $GABA_A$ receptors *in vitro* [26]; electrophysiological studies show it reversibly inhibits GABA-induced currents [54]. Oil is anxiolytic *in vivo* [99]; a separate study *in vivo* did not associate anxiolytic effects of linalool with $GABA_A$ receptor modulation [100]. Linalool inhibits ACh release and is sedative; linalool and linalyl acetate (absorbed transdermally) cause CNS depression; linalyl acetate has narcotic actions [98].	In small-scale trials, lavender oil decreases anxiety (Hamilton rating), increases mood scores, and is a possible antidepressant; when applied as a massage to intensive care patients in a clinical study it significantly improved perceived anxiety compared to non-treated patients [101]. Oral administration of lavender oil to adults with anxiety disorder (RCT) showed it to be as effective as lorazepam [101]. Topical application of three oils including lavender to dementia patients improved feelings of well-being, increased alertness, decreased aggression and anxiety, and improved sleeping patterns [98]. Other RCTs also associate lavender aromatherapy with reducing agitation in dementia patients [102–104]; administration via inhalation was not associated with efficacy suggesting topical application may be required [105].
Valerian *Valeriana officinalis* L. (Valerianaceae) Rhizome/root Iridoid valepotriates; essential oil	Traditionally used to treat hysterical states, excitability, insomnia and cramp [59].	Extracts show affinity for $GABA_A$ and 5-HT_{5a} receptors; they potentiate GABA release from hippocampal slices and inhibit synaptosomal GABA uptake [59]. CNS depressant effects observed *in vivo* with valepotriates [59].	Several (but not all) RCTs describe a hypnotic effect for valerian in patients with insomnia [59]. There are few controlled trials on valerian efficacy in anxiety; a combined treatment of valerian with St John's wort reduced anxiety more effectively than diazepam in a randomized double-blind study [59,97].

[116,117]; Iwasaki et al. (2005), in a study of people with mild to severe dementia treated for a month, reported significant improvements in behavior and daily living in the treatment group [118]. Monji et al. (2009) noted reduced NPI and reduced antipsychotic medication in yokukansan treated compared to the control AD group [84]. Relevant activities and other studies for these species are summarized in Table 3.

Agitation (Table 3)

Essential oils have been tested for effects on agitation (and related symptoms like aggression) in people with dementia in the context of aromatherapy. Numerous controlled clinical trials using lavender and/or melissa (up to 6 weeks treatment) have been conducted [102–105,119]; all except Smallwood et al. (2001) [119]

Table 3 Continued

Plant name*, part, and phytochemicals associated with biological activities	Traditional uses	Relevant bioactivities	Clinical effects / observations in humans
Yokukansan – composed of: *Atractylodes lancea* DC. rhizome *Cnidium* species rhizome *Uncaria* species twig / branch *Angelica* species root *Bupleurum* species root *Glycyrrhiza* species root The fungus: *Poria cocos* (Schwein.) F.A. Wolf	Traditional Japanese remedy	In thiamine-deficient rats yokukansan ameliorated memory disturbance, anxiety-like behavior, the increase in aggressive behavior, the decrease in social behavior, and neurological symptoms and, inhibited the degeneration of neuronal and astroglial cells in the brain stem, hippocampus, and cortex [106]. Yokukansan has a partial agonist effect on $5HT_{1A}$ receptors *in vitro*, attributed to the *Uncaria* component [107]; this activity is suggested to explain the ameliorating action of yokukansan on social and aggressive behavior of *p*-chloroamphetamine-injected rats [108]. Treatment of aged rats with yokukansan enhanced serotonergic and dopaminergic transmission in the prefrontal cortex and produced anxiolytic effects [109]; anxiolytic action is also suggested to be mediated by the benzodiazepine system [110].	Twelve weeks of yokukansan treatment significantly improved BPSD in AD patients, without serious adverse effects or cognitive decline [84]. In patients with AD (including mixed-type dementia) or LBD, yokukansan treatment improved BPSD including delusions, hallucinations, agitation/aggression, depression, anxiety, and irritability (assessed with NPI and MMSE) [111]. In one small trial ($n = 14$), patients with PD and PDD were treated with yokukansan; significant improvements in behavioral and psychological symptoms, particularly the incidence and duration of hallucinations, were observed in most patients after 4 weeks treatment, without worsening cognitive function or parkinsonism [112]. In five cases of frontotemporal dementia, behavioral symptoms were improved by yokukansan (assessed using NPI and Stereotypy Rating Inventory (SRI)) [113].

*Common and Latin names (plant family).

report significant reductions in agitation and related symptoms like aggression. The study of Ballard et al. (2002) [103], the only study cited in the Cochrane review of Thorgrimsen et al. (2003) [120] (as being possible to assess up to that time), showed melissa lotion applied twice daily reduced not only agitation, but also neuropsychiatric symptoms and social withdrawal, and increased constructive activities compared to a control lotion. In a follow up RCT of melissa including a donepezil-treated group, the only positive trend was an improved quality of life [121], although the placebo effect was unexpectedly high, compliance was less than in previous trials and, interestingly, donepezil significantly increased agitation. Mechanistic data to support the clinical effects of these agents are summarized in Table 3.

While cannabis (*Cannabis sativa* L.) is frequently associated with psychosis, Passmore (2008) suggested that the synthetic cannabinoid receptor agonist nabilone could be appropriate for the treatment of dementia-related agitation [122]. Walther et al. (2006) reported that Δ^9-THC was effective in an open label study in reducing night time agitation and motor activity in people with severe dementia [123]. Another cannabinoid, CBD, present in cannabis (but not in the "skunk" bred for psychoactive potency) is progressively being reported to have antipsychotic effects in normal people. CBD has a pharmacological profile similar to antipsychotic drugs and reduces schizophrenia-like features in open label trials [124]. In an open label study in PD, CBD reduced psychosis [125] (a notable feature of LBD and PDD).

Herbals Relevant to BPSD Symptoms in Non Demented Populations (Table 3)

There are a number of natural products that show efficacy in some behavioral and psychological symptoms such as depression in the normal population. It is therefore logical to consider these natural products for potential application to alleviate BPSD, and rational to suggest that their efficacy and safety could also be assessed in dementia patients. For major depressive disorder there are substantial RCT data for the efficacy of St John's wort (*Hypericum perforatum* L.). Rahimi et al. (2009), in a meta-analysis of 13 RCTS comparing selective serotonin reuptake inhibitors (SSRIs) and *H. perforatum*, noted that *H. perforatum* does not differ from SSRIs with respect to efficacy and adverse events in major depressive disorder [126]. Less withdrawal due to adverse events with *H. perforatum* indicated an advantage in management. In a Cochrane review of placebo RCTs, Linde (2009) found *H. perforatum* to be superior to placebo for major depression and similarly effective, but with fewer side-effects, than standard antidepressants [96]. Pharmacological data support the relevance of this

herb for depression (Table 3). In planning clinical trials in people with dementia, numerous drug interactions via cytochrome P450 enzymes (e.g., theophylline, warfarin, protease inhibitors) and pharmacodynamic interactions (e.g., triptans and SSRIs) need to be considered.

For generalized anxiety, plant species worth considering for people with dementia on account of some clinical data in non-demented populations, supported by relevant pharmacological data, include kava (*Piper methysticum* G.Forst.) [127], passionflower (*Passiflora incarnata* L.), and St John's wort [97]. For sleep disorders (which include both night and day time disturbances) there are both traditional and some limited evidence in normal individuals that lavender, valerian (*Valeriana officinalis* L.), and chamomile (*Matricaria recutita* L.) enhance sleep [59,128].

In addition to BPSD, ameliorating side-effects of antidementia drugs is an unexplored area for herbal usage. Limiting gastrointestinal effects of ChEIs would impact on problems of tolerability and compliance. Peppermint (*Mentha* x *piperita* L.) oil [129], and ginger (*Zingiber officinale* Roscoe) [59] have potential in this area.

Disease Prevention/Stabilization

Since the safety of some herbals has been established through traditional use and toxicity data are available (e.g., for many used in the food industry), these may be particularly relevant to long-term, potentially prophylactic use. Among extracts, derived preparations or phytochemicals for which there is both mechanistic neuroprotective and some positive clinical evidence are ginkgo, curcumin, coffee, tea, red wine, and nicotine (Table 4).

By far, the greatest investment of time and resources has been in the trials of ginkgo in non-demented populations followed up to assess the development of dementia. The NIH ginkgo evaluation of memory (gem) RCT followed 3069 non-demented individuals over 8 (median 4.1) years [142]. The results were negative: dementia rate was 3.3 per 100 person-years in the test group and 2.9 per 100 person-years in the placebo group. Other studies investigating the effect of ginkgo on dementia development have yet to establish any protective effect (Table 4). The French GUIDAGE study of ginkgo (2800 non-demented with memory loss) is still in progress [149]. It is important to consider if ginkgo extracts investigated (and other natural products investigated for their clinical effects) are of the appropriate quality, with respect to their chemical profiles and levels of active constituents, and are taken at an appropriate dose. These factors can influence both efficacy and safety and, thus, trial outcomes. A monograph for the quality control of ginkgo is described in the European Pharmacopoeia [59]; however, for many plant species no official standards for their quality control exist.

Curcumin from turmeric (*Curcuma longa* L.) has multiple, especially antiinflammatory, properties, including reducing amyloid in Alzheimer's transgenic animal models ([140] and Table 4). Despite the lack of RCT evidence, there is epidemiological evidence to suggest curry consumption is associated with better cognitive performance in non-demented elderly Asians [150]. In 1010 60–90 year olds, frequent/occasional curry consumers had significantly higher MMSEs compared to non/rare consumers. This is consistent with a lower prevalence of AD (accounting for longevity) in India compared to Western countries, although this comparison is more anecdotal than scientific.

With respect to tobacco and nicotine, early epidemiological data indicating a protective effect of smoking for AD were followed by many studies indicating the reverse. For PD, the meta-analysis by Elbaz (2009) reiterates the long established reverse association between smoking and PD [151], although whether this extends to cognitive risks (the development of LBD or PDD) is not clear. Numerous data support the neuroprotective effects of nicotine relevant to mechanisms of AD but smoking risks complicate the issue for VaD [144].

Coffee or caffeine are associated with disease modifying effects including reduction of β-amyloid [135]; other mechanisms associated with coffee alkaloids are shown in Table 4. There is some epidemiological data supporting reduced (65%) dementia risk in coffee drinkers [136]. A similar conclusion was reached by Barranco Quintana et al. (2007) [152], but not by Ritchie et al. (2007) [153] or Laitala et al. (2009) [154].

The concept of wine to protect against disease is ever popular and dementia is no exception with epidemiological studies indicating that wine reduces the risk [155,156]. Panza et al. (2009) reviewing this subject suggest that evidence needs to be analyzed in conjunction with potentially interactive factors such a smoking and ApoE4 status [157]. The mechanisms that might explain a preventive effect of wine, particularly the polyphenolic component resveratrol, are summarized in Table 4 and have been reviewed by Kim et al. (2010) [140].

The borderline between plants as pharmaceuticals or nutraceuticals is blurred and numerous fruits and vegetables have bioactivities, in addition to nutritional purposes, such as antioxidant, antiinflammatory, and as increasingly apparent, also anticholinesterase activities. Epidemiology indicates fruit and vegetable juices delay the onset of AD [158] and daily consumption of fruits and vegetables is associated with a decreased risk of all causes dementia [159]. Since AD and VaD are associated with systemic risk factors such as cardiovascular disease and diabetes, there is as yet unexplored potential for investigating numerous plant medicines that reduce these risks in normal populations for effects on the development of dementing diseases. Adherence to a traditional Mediterranean diet (characterized by high intakes of vegetables, fruits, nuts, legumes, cereals, and oils containing unsaturated fatty acids) is associated with lower overall mortality, mortality from some diseases (e.g., cardiovascular), and is suggested to reduce AD risk [160,161]. Evidence also suggests that high intakes of mono- and poly-unsaturated fatty acids, such as those occurring in olive (*Olea europaea* L.) oil, protect against cognitive decline; fatty acid intake may influence AD and dementia risk, although the level of any protective effect remains unclear [161,162].

Conclusions

Expectations for the potential of medicinal plants or phytochemicals for dementia therapy have been met by an impressive literature on clinical and scientific studies for a surprisingly long list of agents. Cognition enhancing effects in dementia populations are not any more (and in some instances less) substantial than for prescription drugs. Given that plants traditionally used for

Table 4 Plants and their constituents with relevance for dementia: disease prevention

Plant name*, part, and phytochemicals associated with biological activities	Traditional uses	Relevant bioactivities	Clinical effects/observations in humans
Tea/green tea *Camellia sinensis* Kuntze (Theaceae) Leaves Catechins	Used in TCM for antiaging effects and for nervous system disorders [130].	Green tea extract containing catechins: inhibits β-secretase [18]. Catechins including epigallocatechin-3-gallate: antiinflammatory, antioxidant, protect hippocampal neurons exposed to β-amyloid; phenolics including catechins are neuroprotective in animal models of AD and PD, and improve memory [18,131].	Epidemiological evidence suggests green tea polyphenols improve age-related cognitive decline [18]; cross-sectional data (1003 subjects, age > 70 yr) associates high green tea consumption with a lower incidence of cognitive impairment [131]. Epidemiological study (2,500 participants): associated tea drinking with a reduced risk of dementia [132].
Coffee *Coffea arabica* L. (Rubiaceae) Seeds Alkaloids: caffeine, trigonelline	Stimulant drink or paste in Ethiopia [133].	Caffeine: neuroprotective, reverses cognitive impairment, decreases brain β-amyloid levels *in vivo* [134,135]; a CNS stimulant [136]. Trigonelline: increases neurite outgrowth, inhibits AChE *in vitro*, improves memory retention *in vivo* [137,138].	Coffee intake at midlife is associated with a decreased risk of dementia/AD in later life, compared with no or low coffee intake (1409 participants age 65–79 yr, average follow-up: 21 yr) [136]. High caffeine intakes inversely associated with AD risk when AD patients compared with age-matched non-AD controls over 20 yr [134].
Tumeric *Curcuma longa* L. (Zingiberaceae) Rhizome Curcuminoids including curcumin	Used in traditional Indian medicine for various disorders (e.g., rheumatism, cough, inflammation, and wounds) [139].	Curcumin: antioxidant, antiinflammatory (including COX-2 inhibition), neuroprotective, inhibits β-amyloid formation [18,139,140]; protective effects of curcumin observed in animal models of AD [18,140].	Lower prevalence of AD in some populations has been suggested to be due to a curcumin-rich diet [140].
Ginkgo/maidenhair tree *Ginkgo biloba* L. (Ginkgoaceae) Leaves Refer to Table 2	Refer to Table 2	EGb 761: antioxidant and a radical scavenger, reduces apoptosis, is neuroprotective, inhibits β-amyloid aggregation [56,71]; in preclinical studies it protects the brain from ischemic/hypoxic damage and protects mitochondria [71].	A prospective longitudinal study showed no association between *G. biloba* use and dementia risk, although other epidemiological studies suggest a protective effect on cognition [141]. A 3.5 yr trial of *G. biloba* in 118 persons > 85 yr found a protective effect in compliant patients, but no significant effect on cognitive decline overall [141]. In a 12-week RCT in healthy volunteers, treatment with *G. biloba* combined with *Panax ginseng* improved memory quality, but in a separate 4-month trial (*G. biloba* + nutrient supplement) no cognitive improvements were reported [141]. *G. biloba* extract did not reduce dementia incidence in 3069 elderly individuals (normal cognition or MCI) in a RCT (follow up: 6.1 yr) [142].

memory are based on populations that did not generally develop dementia (longevity being less), such medicinal plants may be more relevant in normal elderly populations, those with MCI or at the earliest stages of disease. In this context a number of herbs and their constituents with promising effects in normal and/or elderly persons excluded in this review should be pursued.

In contrast to cognition and particularly in view of the lack of safe effective drugs, medicinal plants for BPSD appear more

Table 4 Continued

Plant name*, part, and phytochemicals associated with biological activities	Traditional uses	Relevant bioactivities	Clinical effects/observations in humans
Tobacco *Nicotiana* species (Solanaceae) Leaves Alkaloid: nicotine	Used traditionally in North America for stimulant effects [143].	Nicotine: enhances cognition, stimulates nicotinic receptors, inhibits ß-amyloid formation and the neurotoxic effects of glutamate, upregulates nerve growth factor pathways, inhibits apoptosis, reduces oxidative stress [16,144].	A link between smokers and a lower incidence of AD is reported; administration of nicotine to AD patients and to healthy (non-AD) elderly people improved cognitive function; some cohort studies report smoking shows either no association with AD risk, or moderately increases AD risk [16,144]. Most epidemiological studies and meta-analyses show smokers have a lower risk of developing PD; some studies have not confirmed this inverse relationship [144].
Grapes: wine *Vitis vinifera* L. (Vitaceae) Fruit Polyphenolic compounds including resveratrol	Ancient cultures including Ayurveda used red wine for various beneficial health effects [145].	Red wine and resveratrol improve memory in different behavioral studies *in vivo* [145]. Resveratrol: protects against β-amyloid toxicity *in vitro*, is antioxidant, modulates inflammatory processes, suppresses AChE activity [140,145]. Other red wine polyphenols: neuroprotective *in vivo* and *in vitro*, inhibit β-amyloid fibril formation *in vitro* [146].	Longitudinal and cohort studies (19 studies over a 10 yr period) and 25 cross-sectional or case-control studies show over half of the risk factors for cognitive decline or dementia were lower in moderate consumers of alcohol compared with abstainers [147]. Light to moderate alcohol consumption is associated with a reduced risk of AD, VaD, and other types of dementia [148]. Epidemiological studies show moderate red wine consumption in particular may attenuate clinical dementia in AD [145].

*Common and Latin names (plant family).

promising in general. Traditional use favors such agents for symptoms such as anxiety, aggression, depression, and sleep disturbances irrespective if concomitant dementia. With respect to disease prevention (the most important long-term objective in today's aging population), epidemiological data for some agents are promising enough to warrant prospective intervention studies, costs of such far outweighed by future costs to society of dementia.

Complexities associated with plant extracts as opposed to isolated chemicals, not discussed in this review, include: agreement on the best ways to "take the medicine" (i.e., dose and formulation, beverage or food); regulatory and quality control issues such as standards for herb cultivation and preparation so that different clinical trials can be more directly compared. Standardization of herbal medicines to known active constituents is an essential but challenging aspect for their therapeutic use. Relatively few plants that modify cognitive functions have been extensively studied to determine the compounds responsible for the observed activities, their modes of action, and appropriate clinical doses. There is also a comparative lack of officinal monographs (such as those in the European and United States Pharmacopoeias) describing methods for the quality control of herbal medicines. Consequently, research to identify active phytochemicals, their pharmacological effects, and the concentrations required to achieve therapeutic doses must continue, to enable standardized herbal medicines of the appropriate quality and safety to be used to produce more reproducible and reliable clinical data.

Two of the four main drugs currently licensed to treat cognitive symptoms in dementia are derived from plant sources (galantamine and rivastigmine). Thus, natural products are a potential source of other single active constituents that may be developed as drugs for dementia. Indeed, there have been numerous attempts to modify the chemical structures of naturally derived AChE inhibitors to improve efficacy and minimize adverse effects, as recently reviewed [14]. Although the development of new drugs as single chemical entities for dementia is one aim, the use of plant extracts can still be valuable. If more than one constituent in a plant is responsible for the clinical effects, it may be too simplistic to conceive that a single phytochemical has the same effect or efficacy. It is under these circumstances that the appropriate qualitative and quantitative chemical profiles of the herbal products must be investigated to ensure their safety and efficacy. It should also be considered that the development of natural products as pharmaceuticals may be restricted by a reluctance from industries to invest in the cost of extensive trials and by issues of patenting

natural products to achieve exclusivity. An alternative approach would be to register appropriate herbal medicinal products under the 2004/24/EC Directive, introduced by the European Medicines Agency for EU member states (if the product meets the specified requirements, which include evidence for traditional use, clinical particulars, and safety data).

We suggest the following clinical priorities for taking the prospect of much needed new standardized natural products for dementia forward: investigating cognitive enhancing effects less on established dementia populations and more on elderly normal, MCI or at the earliest stages of disease; initiating trials of standardized herbals that ameliorate individual symptoms in the BPSD spectrum; establishing an authoritative database available to practitioners and carers providing information on species with promising clinical trial evidence, types of herbal preparations, dosage, reputable commercial sources that adhere to quality control standards, safety issues and herb-drug /herb-herb interactions; and pursuing epidemiological or follow up studies on potentially disease protective botanicals with long term safety records.

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Conflict of Interest

The authors have no conflict of interest.

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