A Combination of Natural Products to Treat Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a chronic neurodegenerative condition associated with old age. It is the most common cause of dementia, inflicting an increasing social and economic burden. Medications which are currently approved in the United States do not reverse or prevent disease progression. Therefore, we seek new therapies.

There has been abundant interest in natural products to treat Alzheimer's. A large number of preclinical studies have demonstrated that crude natural products have therapeutic potential. Clinical trials have been conducted on a few of these individual natural products. A number of traditional medicines which are combinations of natural products have been used to treat AD. In modern times, testing has been undertaken to scientifically verify the activities of these combinations, including some successful clinical trials. Ascertaining which constituents are responsible for the positive effects, what interactions may be involved, and what role synergism plays, are daunting combinatorial problems.

Prevailing theories of AD causation have focused on the observed biochemical abnormalities of the senile brain. Observations of amyloid-β plaques, cholinergic deficits, tau protein abnormalities, neuroinflammation and oxidative stress, and aberrant signalling cascades leading to neuronal apoptosis have partially elucidated the clinical picture but have failed to produce satisfactory pharmaceuticals. Natural products are rich in substances which target relevant pathways in AD. Some have even become FDA-approved treatments for AD.

Recent research has produced evidence that AD may be caused by fungal infection in the central nervous system (CNS). Many natural products which have been investigated for their potential to curb the biochemical abnormalities associated with AD also show promise as antifungal agents.

We review the available literature in an attempt to determine which natural products are the most promising candidates for AD therapy. Preferred candidates have success in clinical trial, wide safety margins and robust biochemical rationale. We propose a combination to be tested in a randomized, placebo-controlled clinical trial (RCT).

Contents

1 Background

Natural products have probably been used as medicine for over 60,000 years. From then until modern times, more than 200,000 natural products and compounds have been discovered. [1] In recent history, modern chemistry has allowed the chemical design of individual molecules for pharmaceutical applications. But, applying individual molecules to chronic neurodegenerative diseases, for instance, has brought scant success. Interest in natural medicine has sustained through the modern era. A large majority of drugs derive from natural products. There were no fully synthetic compounds approved as a drugs in the time frame between 1981 and 2002. [2] Of 175 small molecules used against cancer up to 2010, 74.8% were not completely synthetic and 48.6%, were directly derived from natural products. [3] Antibiotic and antifungal compounds have come from leads provided by nature. Antibiotic discovery has been dependent on metabolites produced by soil bacteria. [4] Ethnobotany still provides a rich resevoir of CNS-active pharmacological leads. [5, 6] Herbal compounds from traditional medicine represent a frontier in dementia pharmacology research. [7]

Traditional medicines from China, Japan and Korea invariably employ combinations of different materials from plants and fungi. A large number of active components have been identified. [8] Synergistic relationships have been shown between substances in traditional combinations. Multiple active components working together may be the key to future AD treatments. [9, 10]

Psycotropic medicines derived from natural products are particularly promising. [11] Significant evidence exists that suggests that NPs may be effective psychotherapeutics. [12] A wealth of NPs are candidates for the treatment of Alzheimer's in particular. [13] Many acetylcholinesterase(AChE) inhibitors with potential clinical relevance have been discovered from natural products. [14] NPs may play a role in inhibiting microglial neurotoxicity. [15] In addition to biochemical target activities, traditional medicines may provide improvements in cognitive impairment, fatigue, mood, and anxiety. [16] A review of RCTs of "herbal medicine" for dementia in 2009 found 13 trials and concluded that some herbal medicines were more effective than placebo and at least as effective as standard drugs. [17]

Some have recently concluded, through a review of the scientific literature, that western pure drugs can not replace the advantages of Chinese combinations in AD treatment. [18]

1.1 Alzheimer's Disease Etiology

AD is a disease of old age characterized by slow onset with a progressive loss of cognitive function and gradual decline into dementia. AD is the most common cause of dementia. The time from diagnosis until death is usually 8-10 years. The most notable pathological changes are plaques of misfolded proteins, neurofibrillary tangles, alterations in the microvasculature of the brain, inflammation and oxidative stress.

1.1.1 Amyloid-β (AB)

The cerebral deposition of amyloid-β protein in AD patients has been recognized for decades. These proteins, which begin to accumulate for years or even decades before the onset of dementia, have long been considered central to the pathology of AD. [19]

A popular hypothesis states that AB is the causative agent in AD, causing the cascade of abnormality observed. Genetic mutations which cause abnormal amyloid precursor protein (APP) are implicated. AB is neurotoxic and could lead to the neurofibrillary tangles and ultimately the death of neurons. [20]

Soluble AB was strongly correlated with AD severity. Measures of insoluble AB could distinguish AD

patients from controls but could not predict AD severity. AB is usually thought of as extracellular. However, soluble AB can be extracellular or intracellular. [21]

More recently, synaptotoxic AB oligomers have been implicated in AD biopathology, triggering the accumulation of reactive oxygen species (ROSs). This provides an explanation for the therapeutic action of memantine. [22]

1.1.2 Cholinergic

Long ago scientists observed deficits in cholinergic innervation and loss of cholinergic neurons in AD patients. [23, 24]

1.1.3 Microcirculation

An idea related to AB toxicity is that disturbed microcirculation in the brain causes AD. [25] One recent review stated that the AB hypothesis of AD causation has proven inadequate and that therapeutic strategies should focus on the microcirculation hypothesis and supporting normal angiogenesis. [26]

The microcirculation hypthesis states that the primary cause of AD is related to deficiencies in the microvasculature of the brain. These deficits may allow the inflow of neurotoxins into the brain and, perhaps more importantly, prevent the adequate outflows of neurotoxins such as AB.

Blood-brain barrier (BBB) dysfunction has been noted in AD patients, including leakage which may allow neurotoxins and infectious agents to enter the brain. However, this finding is controversial. Some studies failed to find additional leakage in AD brains when compared to age-matched controls. Other BBB dysfunctions observed in AD involve inadequate nutrient supply and inadequate clearance of toxic substances. In addition, altered proteins at the neuro-vascular unit may promote inflammation, oxidative stress and neuronal damage. [27]

1.1.4 Inflammation

Certainly AD pathology involves extracellular plaques involving AB, neurofibrillary tangles with abnormal tau protiens, vascular malfunction and cell death caused by ROS and inflammation. Some propose that inflammation and oxidative stress precede the development of the AB plaques, initiating the pathological cascade observed in AD. [28]

1.1.5 Infection

The idea that infections cause AD has been widely studied and has not been ruled out. In fact, a substantial amount of evidence suggests that AD may be caused by infection. Histopathological hallmarks of AD are known to occur in chronic infections, including those of the CNS. [29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40] In addition, evidence has emerged that AB is antimicrobial and may be produced as an innate immune response to infection. [41]

Inflammatory cytokines typical of immune response to infection are associated with the inflammation observed in AD. Elevated levels of interleukin-1, interleukin-6 and tumor necrosis factor-α have been observed. [42, 43, 44, 45]

Pathogens most commonly studied in AD etiology have been viral, bacterial and prional. These include HSV-1, *C. pneumoniae*, *B. burgdorferi*, *H. pylori*, and prions. One group has argues that HSV-1 initiates the pathological cascade. [46] Although, if HSV-1 is the primary cause of AD, how do some people without HSV-1 infection develop AD? Another group found that anti-HSV IgM was associated with double the risk of developing AD, indicating that reactivated HSV-1 infection increases the risk of developing AD. [47]

The possibility of fungal pathogenisis has been al-

most completely overlooked. [48]

Recently, a series of studies provided evidence that AD may be caused by fungal infection in the CNS [49, 50, 51]

1.1.6 Other theories of causation

Deficits in glucose metabolism including insulin resistance have been implicated as risk factors for AD. [27] Some have even proposed that these irregularities could play a role in the etiology of the disease. [28] Research has indicated that those who develop type 2 diabetes and those who develop AD share some genetic risk factors. [52]

One review found that AD may be related to sleep apnea. [53]

In addition to a number of possible environmental hazards, an epidemiological review found a number of genes which increased the risk of early-onset and late-onset AD. [54]

1.2 Traditions

1.2.1 Kampo

Kampo medicine, a traditional medicine of Japan, is a complex system of individualized diagnosis and treatment. An important component of Kampo is precise formulations of natural products based on older Chinese recipes. 148 or more combinations are covered by the national health insurance system in Japan. Of 135 published randomized controlled trials on Kampo combinations published between 1986 and 2007, 37 were available in English. As chronic degenerative diseases have become more prominent in an aging population, interest in Kampo has increased as has Kampo's integration into modern medical practice. A recent survey indicated that 70% of Japanese physicians prescribe Kampo formulations. Insurance-covered formulations include standardized extracts and crude decoctions. Applying Kampo formulations to conventional diagnoses is a challenge because in traditional Kampo, the same conventional diagnosis could result in the prescription of different formulations while different conventional diagnoses could result in the prescription of the same formulation. [55] However, Kampo may evolve based on new scientific evidence. [56]

The testing specfic individual formulations on a specific conventional diagnosis is useful for applying Kampo formulations in clinical practice in countries like the United States where expert Kampo practioners are few. Therefore, for the purposes of this review, the best evidence will be considered to be randomized, placebo-controlled clinical trials on specific formulations for the specific diagnosis of AD.

1.2.2 TCM

A review of Chinese Herbal Medicine for the management of vascular dementia (VD), a disease similar to AD, was conducted, highlighting the urgent need for more clinical trials of high quality. [**?**]

1.2.3 Mixtures Used in Other Countries

Korean traditional medicines are heavily influenced by Chinese and Japanese. Accordingly, the most commonly used mixtures used to treat dementia in Korea are formed from the same ingredients found in Kampo and TCM. [57]

Ayurvedic medicine, the traditional medicine of India, has had detailed written descriptions of Alzheimer's dementia for millenia. [58] Some of the ayurvedic pharmacopeia coincides with those of East Asia.

2 Evidence for Combinations of Natural Products

Many different traditional mixtures exist which are used treat AD. The mixtures have many overlapping components.

Table 1 shows the degree of overlap between individual natural products and some traditional mixtures. This table does not come close to showing the full breadth of what is used in Chinese medicine.

A review of traditional Chinese formulations identified 104 formulations used to treat senile dementia involving 147 kinds of Chinese medicine. The pair most used was *Ligusticum* and *Acorus*, present in 27.9% of the identified formulae. [59]

In a review of double blind clinical trials of Chinese medicine to improve cognitive function, the most commonly used ingredients found were Acorus, Panax, Polygala, and Poria.

Our review so far has found that Poria, Acorus, Citrus, Glycyrrhiza and Zingiberis are the most commonly found in traditional medicines used in Asia to treat AD.

Saussureae Radix (Saussurea lappa Clarke), Longanae Arillus (Dimocarpus longana), Gardeniae Fructus (Gardenia jasminoides Ellis). Saussurea, Dimocarpus, and Gardenia are unique to KKT.

2.1 Yokukansan (YKS)

Yokukansan is a mixture of seven crude natural products, Atractylodis lanceae rhizoma, Poria cocos sclerotia, Cnidii rhizoma, Angelicae radix, Bupleuri radix, Glycyrrhizae radix, and Uncariae uncis cum ramulus. Yokukansan is called Yi-Gan San in TCM. [60] Clinical trials have demonstrated Yokukan-sans efficacy in treating patients with BPSD. Accordingly, Yokukansan has been listed by The Japanese Society of Neurology in the Japanese Guidelines for the Management of Dementia since 2010. A recent review found 13 clinical trials of varying quality included a total of 466 patients that found YKS to be a safe and effective way to raise Neuropsychiatric Inventory (NPI) scores. The Mini-Mental State Examination (MMSE) score of cognitive impairment and the Disability Assessment for Dementia (DAD) score of caregiver burden were unimproved, however. [61] Another review of noted improvements in the activities of daily living (ADL) score. [62] Repeated clinical trials have proven the efficacy of YKS in improving NPI and ADL scores in patients with AD. [63]

In a cross-over study of 106 patients to investigate the use of Yokukansan to treat the behavioural and psychological symptoms of dementia (BPSD), a significant improvement in Neuropsychiatric Inventory (NPI) was found. Significant improvements were observed in delusions, hallucinations, agitation/aggression, depression, anxiety, and irritability/lability. Effects were sustained for one month after treatment was ceased. Cognitive function was not significantly improved. [64] In a 52 patient RCT of Yokukansan to treat dementia, BPSD and ADL scores were improved. [60] In an open-label study of 26 patients who received 7.5 grams/day of Yokukansan for 4 weeks, success was seen in reducing hallucinations, agitation, anxiety, irritability and abnormal behavior. But, overall disability and congnitive function were not improved. The mixture was well tolerated. [65] In a non-blinded, randomized, parallel-group comparison study with 61 participants, YKS with donepezil was better than donepezil alone in measures BPSD. Proving YKS to be safe and effective. [66]

Yokukansan is considered very safe. In a case series of 3 patients between 10 and 13 years old, YKS considered effective in treating pediatric emotional and behavioral problems within 14-21 days. [67]

Genus	YKS	DTD	FMJ	PN-1	SZL	WD	BDW	CMT	HCKT	KRBT	CTS	KKT
Poria	X	X	X		X	X	X	X			X	X
Atractylodis	X								X			X
Ligusticum	X											
Angelica	X								X			X
Bupleurum	X								X			X
Glycyrrhiza	X								X	X	X	X
Astragalus				X					X			X
Uncariae	X										X	
Arisaema		X										
Pinellia		X				X		X				
Citrus		X	X			X			X		X	
Acorus		X	X		X	X		X				
Ginseng		X							X		X	X
Bambusa		X				X						
Zingiberis		X							X	X	X	X
Rehmannia			X				X					
Gastrodia						X						
Ophiopogon			X								X	
Anemarrhena			X									
Paeonia			X				X			X		
Dendrobium			X									
Akebia			X									
Cistanche				X								
Codonopsis					X							
Cinnamomum					X		X			X		
Polygala					X			X				X
Ostrea										X		
Polygonum						X						
Ziziphus						X			X	X		X
Aconitum							X					
Saussurea												X
Dimocarpus												X
Gardenia												X

Table 1: Mixture to Genus Matrix

2.2 Di-Tan Decoction (DTD)

DTD is a combination of ...

A double-blind, randomized, placebo-controlled, add-on trial testing the efficacy of DTD to treat cognitive impairment in AD patients. [68]

2.3 Shen-Zhi-Ling (SZL)

SZL is an oral liquid consisting of 10 kinds of traditional Chinese medicine: Codonopsis pilosula, Cassia Twig, Paeonia lactiflora, honey-fried Licorice root, Poria Cocos, Rhizoma Zingiberis, Radix Polygalae, Acorus tatarinowii, Ossa Draconis, and Concha Ostreae.

98 patients completed a double-blind clinical trail of SZL. SZL was found to be more effective than placebo, delaying BPSD and improving scores of evening activity and nocturnal activity. [69]

2.4 Keishi-ka-ryukotsu-borei-to (KRBT)

KRBT is a mixture of 7 natural products: cinnamon bark, peony root, jujube fruit, oyster shell, fossilized bone, glycyrrhiza, and ginger rhizome that was found to effectively BPSD in a case report. Gonadotrophin profiles were positively altered. [70]

2.5 Chotosan (CTS)

Chotosan is a mixture of 11 natural products, Uncariae Uncis cum Ramulus, Aurantii Nobilis pericarpium, Pinelliae tuber, Ophiopogonis tuber, Poria cocos, Ginseng radix, Saposhnikoviae radix, Chrysanthemi flos, Glycyrrhizae radix, Zingiberis rhizome, and Gypsum fibrosum. Along with YKS, Chotosan has shown promise in clinical and preclinical studies as a treatment for AD. Both mixtures contain Uncariae Uncis. [71]

2.6 Kamikihito (KKT)

KKT is composed of 14 crude drugs:

Ginseng Radix (P. ginseng C.A. Meyer), Polygalae Radix (P. tenuifolia Willd.), Astragali Radix (A. membranaceus Bunge), Zizyphi Fructus (Zizyphus jujube Mill. var. inermis Rehd.), Zizyphi Spinosi Semen (Z. jujube Mill. var. spinosa), Angelicae Radix (Angelica acutiloba Kitagawa), Glycyrrhizae Radix (Glycyrrhiza uralensis Fisch), Atractylodis Rhizoma (Atractylodes japonica Koidzumi ex Kitamura), Zingiberis Rhizoma (Zingiber officinale Roscoe), Poria (Poria cocos Wolf), Saussureae Radix (Saussurea lappa Clarke), Longanae Arillus (Dimocarpus longana), Bupleuri Radix (Bupleurum falcatum Linne), and Gardeniae Fructus (Gardenia jasminoides Ellis). Eleven of the fourteen NPs are listed in 1. Saussurea, Dimocarpus, and Gardenia are unique to KKT.

In a small, unblinded clinical trial, KKT improved cognitive impairment in patients with mild dementia. [72]

An animal model revealed that KKT improved amyloid-β-induced tau phosphorylation and axonal atrophy even after axonal degeneration had progressed. [73, 74]

2.7 Ninjin'yoeito (NYT)

23 patients who had a insufficient response to donepezil received donepezil alone or donepezil and NYT. A 2-year follow-up showed that patients receiving NYT had an improved cognitive outcome and alleviation of AD-related depression. [75]

2.8 Hochuekkito

Hochuekkito is a mix of 10 natural products, Astragali Radix, Atractylodis lanceae Rhizoma, Ginseng Radix, Angelicae Radix, Bupleuri Radix, Zizyphi Fructus, Aurantii Bobilis Pericarpium, Glycyrrhizae Radix, Cimicifugae Rhizoma, and Zingiberis Rhizoma. [76]

In a placebo-controlled clinical trial of Hochuekkito showed that the formulation improved the QOL and immunological status of elderly patients with weakness. [77]

2.9 Zokumei-to (ZMT)

In an animal model of AD using Amyloid-β, ZMT treatment significantly increased the level of expression of synaptophysin up to the control level. Memory impairment and synaptic loss was ameliorated in the mice even after impairment had progressed. [78]

2.10 Ba Wei Di Huang Wan (BWD)

BWD is a traditional Chinese formulation of 8 natural products, Rehmannia glutinosa, Cornus officinalis, Dioscoreabatatas root, Alisma orientale rhizome, Poria cocos, Paeonia suffruti-cosa, Cinnamomum cassia, and Aconitum carmichaeli.

In a placebo-controlled RCT of 33 patients with AD, cognitive function was significantly improved by BWD compared to placebo based on the Mini-Mental State Examination (MMSE). The activities of daily living (ADLs) score was also improved versus placebo. Scores returned to baseline after eight weeks. [79]

2.11 Kai-xin-san (KXS)

KXS is a traditional formulation thought to be beneficial in the treatment of AD. It contains Panax, Polygala, Acorus, and Poria in at least 3 published ratios. First described around 650 by Sun Simiao, it is one of the most popular mixtures for depression in TCM and increased neurotrophic factors in cultured astrocytes. [80] KXS modulated neurological parameters in an animal model of depression. [81] The Chinese report progress in using KXS against AD. [82] KXS was thought to improve learning and memory in an animal model of dementia. [83]

2.12 Yishen Huazhuo decoction (YHD)

YHD was found to be comparable or better than the conventional AChE drug donepezil

[84]

2.13 And more?

Xixin Decoction is a mixture of Ginseng Radix et Rhizoma, Pinelliae Rhizoma, Poria, Aconiti lateralis Radix praeparata, et al(?) that was effective in an animal model of AD. [85]

Juzen-taiho-to (JTT), also known as Shi quan da bu tang in Chinese medicine is a mixture of 10 familiar ingredients, Panax ginseng (Ginseng), Angelica sinensis (Dong quai), Paeonia lactiflora (Peony), Atractylodes macrocephala (Atractylodes), Poria cocos (Hoelen), Cinnamomum cassia (Cinnamon), Astragalus membranaceus (Astragulus), Liqusticum wallichii (Cnidium), Glycyrrhiza uralensis (Licorice), and Rehmannia glutinosa (Rehmannia). JTT has been investigated in an animal model for its potential to help against *Candida* infection. [86] In another model that tested components individually, Ginseng, Glycyrrhizae radix, Atractylodis and Cni-

dii were found to be the promising antifungal components individually. [87]

An herbal formula consisting of aqueous extracts of *Poria cocos*, *Atractylodes macrocephala* and *Angelica sinensis* worked on an animal model of AD, reducing AChE activity. *Angelica* was the most cholinergic of the 3 ingredients. [88]

3 Evidence for Individual Natural Products

Natural products are evaluated for their effects as refined molecules and as crude drugs. Molecules of interest in AD include, polyphenols, flavonoids, alkaloids, phenylpropanoids, triterpenoid saponins, and polysaccharides which are investigated against multiple pathological pathways. [89, 8]

In addition to the traditional formulations, individual constituents are studied for their potential to treat AD including Huperzine, Gingko, Curcuma, Salidroside, Periwinkle-vinca, Centella, Melissa, Polygala, Salvia, and Withania. [90] Investigation in the West has been limited to a few herbs, notably Gingko. Some herbs used in traditional European medicine such as *Salvia officinalis* and *Melissa officinalis* are under investigation for their potential as AD treatments. [6]

3.1 Acorus

β-asarone, a constituent of some *Acorus* products, is regulated in the United States and Europe for its profound adverse effects at high doses in test animals. [91]

Acorus calamus (Ac), found in N out of M of the reviewed Asian combinations, has a long history of medicinal and recreational use including use in India, China, Thailand and by Native Americans. [92] Ac is known as one of the most important medicines in the Ayurvedic system. [93] *Acorus gramineus* is a smaller Japanese plant that is also used in medicine.

A study of *Acorus gramineus* essential oil as an olfactory stimulant revealed that it was able to enhance learning and memory in an animal model of AD. [94] The *in vivo* activities of the *Acorus calamus* root on learning and memory has long been suspected and studied. An animal model of learning and memory disability showed that *Acorus* may be promising drug. [95] Essential oil from *Acorus calamus* displayed *in vitro* acetylcholinesterase inhibitory activity, supporting its use for neurological disorders and dementia in traditional ayurvedic medicine and in modern practice. [96] Ac essential oil had positive effects in an animal model of depression. [97] Active components of Ac improved learning and memory in an animal model of dementia. [98] β-asarone and eugenol were able to protect amyloid-β-injured nerve cells *in vitro*. [99] Ac, as part of SZL, induced no significant adverse effects and was tolerable by more than 92% of the participants in a RCT of 98 AD patients. [69]

Many studies support the notion that Ac products exhibit clinical-relevant antifungal activity. A survey of Thai plants found that Ac exhibited strong antimicrobial activity against spoilage yeasts and moderate, antioxidant and AChE-inhibiting activities. [100] An *in vitro* study showed that β-asarone, an active constituent of Ac, was highly potent against *Candida albicans*, disrupting ergosterol synthesis, and suggested that β-asarone could be used as a topical antifungal [101] or as an antifungal in agricultural application. [102]

It has been reported that some variations of *Acorus calamus*, namely the American dipoloid varieties, do not contain β-asarone. [92] We have not seen a study indicating whether crude extracts of these non-β-asarone producing varieties are antifungal. Other related substances have been found to be potent antifungals. [103]

Further *in vitro* evidence suggest that an active fraction of Ac, by inhibiting ergosterol synthesis,

could help us overcome strains which have become resistant to current antifungal drugs. [104, 105] Researchers have become fairly confident based on *in vitro* results that α and β asarones are responsible for the pronounced antifungal activity. [106] Against *Candida* biofilms, compared to Amphotericin B and ketoconazole, the gold-standard antifungals, *Acorus calamus* fractions were superior. The fungal biomass was completely killed at 2mg/ml concentrations of the Ac concetrates; but, the standard antifungal drugs were unable to perfuse the biofilm and had little effect. [107] Although, an earlier review with a different assay showed that, while Ac and clove were moderately effective fungistatics ($Ac < clove < eugenol < AmphotericinB$), Amphotericin B was a far stronger fungicidal agent compared to *calamus*. [108] However, recently, it was shown that asarones from Ac interacted synergistically with standard antifungals, requiring less of each to express fungicidal activity. [109] The *in vitro* antifungal effects of Ac were confirmed *in vivo*. *Acorus calamus* extract was superior to ketoconazole in an animal model. [110]

3.2 Berberine

Berberine has been demonstrated to be clinically effective in alleviating type 2 diabetes. It is hypothesized that the observed positive effects on obesity and insulin resistance could be related to alterations in the gut microbiome induced by oral adminstration. Berbering alleviated inflammation by reducing the exogenous antigen load produced by the microbiota of the gut. [111]

Berberine ameliorated β-amyloid pathology gliosis, and cognitive impairment in an animal model of Alzheimer's disease. A "profound reduction" in β-amyloid was observed. [112]

Berberine reduced AB levels in human neuroglioma cells. [113]

Berberine prevented metastasis and tumor growth in an animal model of breast cancer. [114]

Berberine activates AMPK and thus prevents tumor metastasis *in vivo*. [115] Interestingly, AMPK activation ameliorated AD-like pathology in an animal model of AD. [116]

Berberine inhibits colon cell proliferation. This inhibition may be explained by the observation that berberine down-regulates epidermal growth factor (EGF). [117] Surprisingly, EGF receptor activation has been linke to AD, as well. [118]

Berberine was neproprotective in an animal model of hypertension furthering the idea that berberine may have diverse beneficial effects in pathologies related to metabolic syndrome. [119] Metabolic syndrome is strongly correlated with AD. [120]

Berberine acts on the Wnt/β-catenin pathway [121] which may have significance in the treatment of AD. [122]

Berberine improves glucose metabolism via multiple pathways, activating AMPK, inhibiting gluconeogenesis, and inhibiting lipogenesis in the liver. [123] Impaired glucose metabolism is associated with AD. [124]

A 2012 review of randomized clinical trials of berberine to treat type 2 diabetes found 14 trials of 1068 patients. The results suggested that berberine may be able to reduce blood sugar as well as prescription hypoglycaemics while improving lipid profile measures. [125]

In an animal model, the positive antidiabetic effects of 1 month of berberine-containing TCM treatment were sustained for 1 year after treatment was ceased. [126]

A number of cytochrome protien (CYP) enzymes were inhibited by berberine ingestion in human subjects. CYP2D6, 2C9, and CYP3A4 activities were decreased. [127] This finding indicates that berberine has potential interactions with other drugs. Berberine interactions could help to improve the bioavailability of other drugs and create a synergistic combination. However, care must be taken to in-

sure that the coadministration with berberine does not result in overdose. Berberine itself had higher bioavailability when coadministered with other herbs than when administered alone or as a crude extract of *Coptidis chinensis*, validating the idea that TCM combinations have synergistic pharmacokinetics. [128]

Berberine has antiinflammatory properties. Proinflammatory cytokines were decreased in an animal model of colitis. [129]

Berberine clearly reduced oxidative stress related to renal ischemiareperfusion injury *in vitro*. [130] Similarly, berberine reduces expression of cyclooxygenase-2 (COX-2) and inflammatory prostaglandins. [131] COX inhibitors and other NSAIDs are considered neuroprotective and have potential in AD treatment. [132]

3.3 Curcuma

Turmeric, *Curcuma longa* root, has a long history of use as medicine. [**?**] Curry consumption in old age may benefit cognitive function according to an epidemiological study. [133]

A case series reported that turmeric was remarkably effective in treating 3 patients with AD. Interestingly, two of these patients were also taking Yokukansan under the supervision of the Japanese physicians. [134]

Curcumin, a phenolic compound derived from turmeric, has been investigated for various neurological disorders including major depression, tardive dyskinesia and diabetic neuropathy. [135] Curcumin has been effective in animal models of AD. [**?**] The effects are hypothesized to be antioxidant, antiinflammatory, acetylcholinesterase-inhibiting, and AB inflammation-inhibiting. [**?**] *In vivo* studies have show that the bioavailability of curcumin alone is poor. [**?**] However, it has been show that curcumin can pass the BBB. Also, some compounds may be able to increase the bioavailability of curcumin. In one study, piperine, an alkaloid from black pepper, was able to increase curcumin concentrations in the serum of human volunteers by 2000%. [136] An effort has been made make curcumin more soluble in water through the use of synthetic nanoparticles. [137]

The success of curcuminoids in preclinical models of AD has been impressive, suppressing presenilin, reducing the burden of AB and tau, modulating the immune system, increasing AB efflux, and enhancing spatial memory. [138, 139, 140, 141, 142, 143]

At least 4 clinical trials have been initiated to test the efficacy of curcumin in treating AD. No trial has been done on a crude extract of turmeric.(?)

However, preclinical reviewers have emphasized that non-curcumin constituents of turmeric may be important in the overall therapeutic action of turmeric. [144] Human safety trials have shown that curcumin is relatively safe up to 12 grams a day. However, a review of clinical trials evaluating curcumin in AD have failed to establish curcumin as an effective drug. [145]

Compounds other than curcumin may be important to prevent cognitive decline in the elderly and even to help cure AD. In addition to curcumin, turmeric contains small molecules that were able to protect cell cultures from AB. [146]

3.4 Salvia

Salvia lavandulaefolia (Spanish sage) had strong in vitro antiinflammatory activity relevant to AD. [147] Salvia is a large genus with antifungal properties. [148, 149]

3.5 Syzygium

Syzygium is not mentioned in the traditional combinations used to treat AD from Japan, China and Korea. However, it was found that *Syzygium*

aromaticum (clove) extract was more potent than *Acorus calamus* in some assays. [150]

3.6 Citrus

Different species for Citrus are used in traditional medicines which are employed against AD. Typically, the mesocarpum and epicarpum are studied for their neuroprotective, antiinflammatory and antioxidant flavonoids. [**?**]

Nobiletin-rich Citrus reticulata peels, a kampo medicine for Alzheimer's disease: A case series [151]

3.7 Panax

Ginseng was part of a mixture that helped mice with macrophage abnormalities survive *Candida* infection. [86]

3.8 Polygala

The roots of *Polygala tenuifolia (Pt)* are used in Asian medicine for diverse purposes, including neurological conditions such as epilepsy.

Polygala, as part of KKT, was effective in a small pilot trial. [72]

Pt is cholinergic and prevents brain damage caused by glutamate, AB, D-galactose, or scopolamine, improving cognitive function and promoting neurogenesis in animal models of AD. [152, 153, 154, 155, 156, 157] Cholinergic and neurotrophic effects were observed after oral administration of *Pt* extract. [158] *Pt* improved behavioral disorders in an animal model of brain damage. [159]

Saponins from *Pt* induced NGF *in vitro*. [160] *Pt* strongly inhibited AB-induced cell damage *in vitro*. [161] Tenuigenin, extracted from *Pt*, decreased secretion of AB in cultured cells. [162] *Pt* had anti-inflammatory effects in microglia. [163] A closely related species, *Polygala tricornis*, also has constituents which reduce neuroinflammation *in vitro*. [164] *Pt* produces norepinephrine reuptake inhibitors with antidepressant potential. [165]

3.9 Fungi

Many mushrooms and other fungi are used around the world for medical purposes. There is a robust scientific rationale suggesting that some fungal products may prove to be effective treatments for AD.

3.9.1 Ganoderma

Aqueous extract of *Ganoderma lucidum* was able to prevent the harmful effects of amyloid-β in an *in vitro* study, preserving the synaptic density protein, synaptophysin in a dose-dependent manner. [166]

Ganoderma lucidum was able to prevent neurotoxicity and hippocampal degeneration while improving cognitive dysfunction in an animal model of AD produced by toxic oxidative stress via streptozotocin (STZ). [167]

Ganoderma lucidum contains small molecules which inhibit AChE. [168]

An immune-modulating polysaccharide from *Ganoderma atrum* was able to attenuate neuronal apoptosis by preventing oxidative damage by modifying the redox system and helping to maintain calcium homeostasis in an animal model. [169]

Learning and memory were improved with administration of *Ganoderma lucidum* in senescent mice, improving antioxidant status. [170]

3.9.2 Hericium (He)

He contains compounds with antibiotic, anticarcinogenic, antidiabetic, antifatigue, antihypertensive, antihyperlipidemic, antisenescence, cardioprotective, hepatoprotective, nephroprotective, and neuroprotective properties. [171]

Oral *Hericium erinaceus* fruit body was clearly better than placebo improving cognitive impairment measured by the Revised Hasegawa Dementia Scale in a double-blind clinical trial on 30 patients with mild cognitive impairment. [172]

Amyloban(tm), a standardized extract of He, performed admirably in an open label case series of 10 patients with refractory schizophrenia. [173] Similarly, Amyloban(tm) restored cognitive function in three patients. [174]

Preparations of the fruiting body of He attenuated amyloid-β damage in PC-12 cells. [175]

He extracts inhibited AChE and displayed antioxidative activity. [176]

Daily oral administration of aqueous extract of He mushroom promoted peripheral nerve regeneration in an animal model. [177, 178]

Over 20 years ago, the erinacines, strong inducers of nerve growth factor (NGF) were discovered in the mycelium of He. [179] These reults were confirmed in astroglial cells, *in vitro*. [180, 181] At least 9 erinacines have been found with potent NGF-inducing activities. Erinacine H at 33.3 μg/ml provoked 5 times the normal NGF production of normal astroglial cells in culture. [182, 183] A small molecule, non-erinacine, phenolic compound derived from the mycelium of He was noted as an antimicrobial. [184] Ethanol extract of He mycelium was able to prevent PC-12 apoptosis via the ROS-caspase dependent pathway. [185]

Hericium ramosum mycelium had potent antioxidant activity and oral administration was able to induce NGF in the hippocampus *in vivo*. [186]

Erinacine A was found to be non-genotoxic and non-mutagenic in a standard battery of assays. [187] Erinacine A enriched He mycelium caused no side effects in an animal model with 28 days of 3g/kg dosing. [188]

3.9.3 Poria cocos *Pc*

Poria is the most common ingredient in the many Asian mixtures which are used for AD.

In animal models Poria has been shown to be essential in the action of the Chinese mixture Kaixinsan. [189] Water extract of *Pc* attenuated amyloid-β-induced oxidative stress and apoptosis *in vitro* [190] Poria is used in a Korean medicine, Jangwonhwan, which shows promising preclinical results. [191, 192] Poria enhanced learning and memory in an animal model of scopolamine-induced dysfunction [193] and may have AChE-inhibiting activity as it did in an animal model when administered with *Polygala*. [194]

Decoction of *Pc* improved learning and memory in mice subjected to scopolamine and alcohol. [193]

Poria mitigated chronic kidney disease in an animal model. [195]

4 Biochemical Targets

4.1 Fungal Infection

Evidence has been put forth that fungal infection is detectable in brain samples from Alzheimer's disease patients. [50] Recently, fungal infection was directly visualized in the brains of 11 of 11 AD patients and 0 of 10 controls. [49] Misfolded amyloid proteins may originate from a transmissible infectious process (like prion disease). Some proteins behave as

	A-β	AF	AO	AI	AChE	NGF	AMPK
Acorus		XX	X		X		
Berberine				X	X		X
Curcuma	X	X	XX	XX			
Hericium			X	X		XX	
Poria	X						

Table 2: Genus to Effects

prions in yeast and other fungi. [196] Neuroinflammation is associated with innate immunity, intended to fight infection at the blood-brain barrier (BBB). [197] Fungal infection could explain the connection between neuroinflammation, innate immunity and the toxic cell debris associated with AD. Amyloid-β is toxic to yeast cells as well as nerve cells. A yeast model of amyloid toxicity has been proposed because of yeast's susceptibility to the protein. [198] Conversely, amyloids are also believed to be expressed on fungal cell surfaces. [199] The relationship between amyloid, prion and fungi is complicated. [200]

An early screening of 16 herbs for antifungal activity found that cloves, cinnamon, mustard, allspice, garlic, and oregano were promising. A possible synergism between Potassium sorbate and cloves was identified. [201] The main constituent of clove oil is eugenol which is also present in nutmeg, cinnamon, basil and bay leaf. [**?**] Another screening of 52 herbs for their antifungal activity against phytopathogenic fungi showed that two herbs from the Apiaceae family, cumin and black zira, followed by cardamom from the Zingiberaceae family were active against *Fusarium*, *Verticillium*, *Botrytis* and *Alternaria*. In our matrix of Asian mixtures we have at least 3 Apiaceae, Ligusticum, Angelica, and Bupleurum. Ginger represents the Zingiberaceae.

Many screenings of antifungal activity focus on phytopathogenic fungi. However, all of the species that are suspected to play a role in AD are known human pathogens, not phytopathogens, *Candida Cladosporium Malasezzia Neosartorya Phoma Sacharomyces* and *Sclerotinia*. Because different fungi are susceptible to different antifungal agents, and different fungi are resistant to those same agents, we must narrow our search for antifungal evidence to these species.

4.2 Innate Immunity

The innate immune system, preserved from ancient genes, is involved in response to pathogenic fungi. [202] The innate immune system in organisms as diverse as humans and plants is remarkably similar. [203, 204] The signalling cascades involved in innate immune functions are providing insights into infectious disease, autoimmunity and allergy. The innate immune response to many infectious agents is associated with inflammation. [205] Inflammation in AD may be mediated by innate immunity, according to transgenic animal model. [206]

Innate immune response to fungal infection is contributed to by Toll-like receptors (TLRs). [207] Immune response to to some pathogenic fungi is dependent on TLRs. [208, 209]

Pathogen associated molecular patterns (PAMPs) are associated with both fungal infection [210] and AD. [211]

4.3 Amyloid-β

An animal model found ZMT effective in reducing Amyloid-β toxictiy. [78]

4.4 Inflammation

Long-term use of Non-Steroidal Antiinflammatory Drugs (NSAIDs) have been associated with a dramatic decrease in the risk of AD in a large cohort. The risk ratio was 0.20 (95 percent confidence interval, 0.05 to 0.83). [212]

Other epidemiological evidence suggests that individuals with diets right in antiinflammatory Curmcumin are at lower risk of developing AD. [**?**]

Inflammation may be the key to initiating the toxic cascade that characterized Alzheimer's rather than the result of midfolded proteins such as amyloid and tau. [213]

Because greater neuroinflammation is observed in human disease than current animal models, new animal models are sought with increased neuroinflammation. One such model is involving increased interleukin-6. [214]

4.5 Cholinergic Drugs

Cholinergic drugs were able to slow the progression of AD after 2 years of follow-up. Although, cognitive deterioration was not stopped. [215]

4.6 Hormonal Therapy

Postmenopausal hormone therapy was not found to affect AD risk in a systematic review of epidemiological studies. [216]

5 Safety

Most of the promising natural products used for AD are generally recognized as safe (GRAS) food supplements. Some specific products have been tested in human safety trials.

Turmeric is considered safe in normal doses. Curcumin is considered safe up to several grams a day in normal subjects. However, several contraindications have been identified. There is also the possibility of allergic reaction. Interactions have also been noted. Some interactions may be valuable, if carefully applied. For instance, co-administration with piperine resulted in a 20000% increase in the bioavailability of curcumin. [217]

6 Challenges

A major concern raised about crude natural products is the challenge of standardization.

A formulation called kamikihito (KKT) in Japan and kami-guibi-tang (KGT) in Korea were comparable in enhancing memory in an animal model, although chromatography revealed differences in the formulations. [74]

Though there are many studies indicating that a combination of natural products should be effective AD treatment, we do not see many studies that failed to find evidence that a natural combination should be effective. Thus, we do not know to what extent our review falls victim to publication bias.

7 Conclusion

Write your conclusion here.

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