A Natural Product Combination for 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, new therapies with more dramatic impact are sought.

There has been abundant interest in natural products to treat Alzheimer's. A large number of preclinical studies have demonstrated that many crude natural products have therapeutic potential. Clinical trials have been conducted on a few of these natural products. A number of traditional medicines which are combinations of natural products have been used to treat AD. Dozens of natural products in various combinations are regularly employed around the world, particularly in China, Japan and Korea. Some clinical trials have been conducted that support the usefulness of these combinations. 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, acetylcholine (AChE) 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.

Recent research has produced strong 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.

Here we conduct a review of the available literature in an attempt to determine which natural products are the most promising candidates for AD therapy. Preferred candidates will have success in clinical trial, clean safety profiles and robust biochemical rationale. We propose a combination of the best candidates to be tested in a new 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 majority of drugs derive from natural products. 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. [2] Antibiotic and antifungal compounds have come from leads provided by nature. Antibiotic discovery has been dependent on metabolites produced by soil bacteria. Willow bark, the source of aspirin, was used from ancient times. [3] Ethnobotany still provides a rich resevoir of CNS-active pharmacological leads. [4, 5]

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. [6] Synergistic relationships have been shown between substances in traditional combinations of natural agents. Multiple active components working together may be the key to future AD treatments. [7, 8]

Psycotropic medicines derived from natural products are particularly promising. [9] Significant evidence exists that suggests that NPs may be effective psychotherapeutics. [10] A wealth of NPs are candidates for the treatment of Alzheimer's in particular. [11] In addition to biochemical target activities, traditional medicine can provide improvements in cognitive impairments, energy/fatigue, mood, and anxiety. [12] Many acetylcholinesterase(ACHE) inhibitors with potential clinical relevance have been discovered from natural products. [13]

1.1 Conventional Understanding of Alzheimer's Dementia

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, 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. [14]

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. [15]

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. [16]

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. [17]

1.1.2 Microcirculation

A idea related to AB toxicity is that disturbed microcirculation in the brain causes AD. [18] 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. [19]

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.

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. [20]

1.1.3 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. [21]

1.1.4 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. [22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33] In addition, evidence has emerged that AB is antimicrobial and may be produced as an innate immune response to infection. [34]

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. [35, 36, 37, 38]

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. [39] 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. [40]

The possibility of fungal pathogenisis has been almost completely overlooked. [41]

Recently, a series of studies from the same research group have provided evidence that AD may be caused by fungal infection in the CNS [42, 43, **?**]

1.1.5 Other theories of causation

Deficits in glucose metabolism including insulin resistance have been implicated as risk factors for AD. [20] Some have even proposed that these irregularities could play a role in the etiology of the disease. [21] Research has indicated that those who develop type 2 diabetes and those who develop AD share some genetic risk factors. [44]

One review found that AD may be related to sleep apnea. [45]

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. [46]

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. [47] However, Kampo may evolve based on new scientific evidence. [48]

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 purposed 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

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.

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. [49] 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. [50] Another review of noted improvements in the activities of daily living (ADL) score. [51] Repeated

Genus	YKS	DTD	FMJ	PN-1	SZL	WD	BDW	CMT	HCKT	KRBT	CTS
Poria	X	X	X		X	X	X	X			X
Atractylodis	X								X		
Ligusticum	X										
Angelica	X								X		
Bupleurum	X								X		
Glycyrrhiza	X								X	X	X
Astragalus				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
Bambusa		X				X					
Zingiberis		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			
Ostrea										X	
Polygonum						X					
Ziziphus						X			X	X	
Aconitum							X				

Table 1: Mixture to Genus Matrix

clinical trials have proven the efficacy of YKS in improving NPI and ADL scores in patients with AD. [52]

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. [53] In a 52 patient RCT of Yokukansan to treat dementia, BPSD and ADL scores were improved. [49] 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. [54]

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. [55]

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. [56]

2.3 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. [57]

2.4 Chotosan

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. [58]

2.5 Kamikohito (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.

An animal model revealed that KKT improved amyloid-β-induced tau phosphorylation and axonal atrophy even after axonal degeneration had progressed. [59, 60]

2.6 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. [61]

2.7 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. [62]

In a placebo-controlled clinical trial of Hochuekkito showed that the formulation improved the QOL and immunological status of elderly patients with weakness. [63]

2.8 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. [64]

2.9 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. [65]

2.10 Yishen Huazhuo decoction (YHD)

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

[66]

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. [67, **?**]

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. [68] 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. [5]

3.1 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. [69]

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. [70]

Curcumin, a phenolic compound derived from turmeric, has been investigated for various neurological disorders including major depression, tardive dyskinesia and diabetic neuropathy. [71] 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%. [72] An effort has been made make curcumin more soluble in water through the use of synthetic nanoparticles. [73]

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. [74, 75, 76, 77, 78, **?**]

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. [79] 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. [80]

Compounds other than curcumin may be important to prevent cognitive decline in the elderly and even to help cure AD.

Curcumin is contraindicated for biliary tract obstruction, gallstones, obstructive jaundice. No major side effects have been identified; although, at higher doses, GI upset and allergic dermatitis,

Summarize, reprint ... or ...

Side Effect

No apparent side effects have been reported thus far. GI upset, chest tightness, skin rashes, swollen skin are said to occur with high dose. A few cases of allergic contact dermatitis from curcumin have been reported.[41]

The chronic use of curcumin can cause liver toxicity. For this reason, turmeric products should probably be avoided by individuals with liver disease, heavy drinkers and those who take prescription medications that are metabolized by liver. Curcumin was found to be pharmacologically safe in human clinical trials with doses up to 10 g/day. A phase 1 human trial with 25 subjects using up to 8000 mg of curcumin per day for three months found no toxicity from curcumin.[42]

Interaction

Curcumin is said to interact with certain drugs such as blood thinning agents, NSAIDs, reserpin. Co-supplementation with 20 mg of piperine (extracted from black pepper) significantly increase the bioavailablity of curcumin by 20000

Contraindication

Curcumin is not recommended for persons with biliary tract obstruction because it stimulates bile secretion. It is also not recommended for people with gallstones, obstructive jaundice and acute biliary colic. Curcumin supplementation of 20-40 mg have been reported to increase gallbladder contractions in healthy people.[44,45]

[81]

3.2 Salvia

Salvia lavandulaefolia (Spanish sage) had strong in vitro antiinflammatory activity relevant to AD. [82] Salvia is a large genus with antifungal properties. [83, 84]

3.3 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 [85]

3.4 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.

3.4.1 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. [86]

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). [87]

Ganoderma lucidum contains small molecules which inhibit AChE. [88]

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. [89]

Learning and memory were improved with administration of *Ganoderma lucidum* in senescent mice, improving antioxidant status. [90]

3.4.2 Hericium

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. [43] Recently, fungal infection was directly visualized in the brains of 11 of 11 AD patients and 0 of 10 controls. [42] Misfolded amyloid proteins may originate from a transmissible infectious process (like prion disease). Some proteins behave as prions in yeast and other fungi. [91] Neuroinflammation is associated with innate immunity, intended to fight infection at the blood-brain barrier (BBB). [92] 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. [93] Conversely, amyloids are also believed to be expressed on fungal cell surfaces. [94] The relationship between amyloid, prion and fungi is complicated. [95]

4.2 Innate Immunity

The innate immune system, preserved from ancient genes, is involved in response to pathogenic fungi. [96] The innate immune system in organisms as diverse as humans and plants is remarkably similar. [97, 98] 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. [99] Inflammation in AD may be mediated by innate immunity, according to transgenic animal model. [100]

Innate immune response to fungal infection is contributed to by Toll-like receptors (TLRs). [101] Immune response to to some pathogenic fungi is dependent on TLRs. [102]

Pathogen associated molecular patterns (PAMPs) are associated with both fungal infection [103] and AD. [104]

4.3 Amyloid-β

An animal model found ZMT effective in reducing Amyloid-β toxictiy. [64]

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). [105]

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. [106]

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. [107]

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. [108]

4.6 Hormonal Therapy

Postmenopausal hormone therapy was not found to affect AD risk in a systematic review of epidemiological studies. [109]

5 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. [60]

6 Conclusion

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