# 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-$\beta$ 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.

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# 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]

NPs may play a role in inhibiting microglial neurotoxicity. [14]

In addition to curcumin, turmeric contains additional small molecules that were able to protect cell cultures from AB. [15]

# 2 Clinical 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 Traditions

### 2.1.1 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-coverd 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 prescrip-

tion of different formulations while different conventional diagnoses could result in the prescription of the same formulation. [16] The testing specfic individual formulations on a specific conventional diagnosis is the most useful for applying Kampo formulations in clinical practice in countries like the United States where expert Kampo practioners are very 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. Kampo may evolve based on new scientific evidence. [17]

#### 2.1.2 TCM

#### 2.1.3 Mixtures Used in Other Countries

### 2.2 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. [18] 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. [19] Another review of noted improvements in the activities of daily living (ADL) score. [20] Repeated clinical trials have proven the efficacy of YKS in improving NPI and ADL scores in patients with AD. [21]

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. [22] In a 52 patient RCT of Yokukansan to treat dementia, BPSD and ADL scores were improved. [18] 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. [23]

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. [24]

### 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. [25]

### 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. [26]

| 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

### 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-$\beta$-induced tau phosphorylation and axonal atrophy even after axonal degeneration had progressed. [27, 28]

### 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. [29]

### 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. [30]

In a placebo-controlled clinical trial of Hochuekkito showed that the formulation improved the QOL and immunological status of elderly patients with weakness. [31]

### 2.8 Zokumei-to (ZMT)

In an animal model of AD using Amyloid-$\beta$, 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. [32]

### 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. [33]

## 3 Clinical Evidence for Individual Natural Products

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. [34] 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 Salvia

Salvia lavandulaefolia (Spanish sage) had strong in vitro antiinflammatory activity relevant to AD. [35] Salvia is a large genus with antifungal properties. [36, 37]

### 3.2 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 [38]

## 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. [39] Recently, fungal infection was directly visualized in the brains of 11 of 11 AD patients and 0 of 10 controls. [40] Misfolded amyloid proteins may originate from a transmissible infectious process (like prion disease). Some proteins behave as prions in yeast and other fungi. [41] Neuroinflammation is associated with innate immunity, intended to fight infection at the blood-brain barrier (BBB). [42] Fungal infection could explain the connection between neuroinflammation, innate immunity and the toxic cell debris associated with AD. Amyloid-$\beta$ 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. [43] Conversely, amyloids are also believed to be expressed on fungal cell surfaces. [44] The relationship between amyloid, prion and fungi is complicated. [45]

### 4.2 Innate Immunity

The innate immune system, preserved from ancient genes, is involved in response to pathogenic fungi. [46] The innate immune system in organisms as diverse as humans and plants is remarkably similar. [47, 48] 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. [49] Inflammation in AD may be mediated by innate immunity, according to transgenic animal model. [50]

Innate immune response to fungal infection is contributed to by Toll-like receptors (TLRs). [51] Immune response to to some pathogenic fungi is dependent on TLRs. [52]

Pathogen associated molecular patterns (PAMPs) are associated with both fungal infection [53] and AD. [54]

Resveratrol is a promising neuroprotective substance. [55]

### 4.3 Amyloid-$\beta$

An animal model found ZMT effective in reducing Amyloid-$\beta$ toxictiy. [32]

### 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). [56]

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. [57]

### 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. [58]

## 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. [28]

## 6 Conclusion

Write your conclusion here.

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