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Treatment of Dementia-related Symptoms with Japanese Traditional Medicine (Kampo): A Review of Clinical Studies

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Abstract

Japanese traditional medicine (Kampo) was the main medical treatment in Japan from the 6th century until Western medicine was introduced from Europe several hundred years ago, and it had been developed to treat all kinds of human diseases. Recently, Kampo has received renewed attention because it provides a valid alternative for treating symptoms refractory to modern conventional medicine. Some Kampo formulas have accumulated clinical evidence for their effectiveness, especially in postoperative bowel dysfunction, functional dyspepsia, and dementia. This article reviews clinical studies showing evidence for the efficacy of Kampo formulas in treating dementia-related symptoms.

Keywords: Yokukansan; Orengedokuto; Chotosan; Asian medicine; Herbal medicine; Traditional Chinese medicine (TCM)

Introduction

In 2005, the US Food and Drug Administration (FDA) issued a warning about atypical antipsychotics being associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis; in 2008, a similar warning about typical antipsychotics followed. Both types of antipsychotics, by their natures, are not indicated for the treatment of dementia-related psychosis. Thus, the control of psychiatric symptoms in dementia patients would seem to become more difficult due to this limitation on using antipsychotics, but it does not have to be. This is because an alternative approach was validated at around the same time in Japan, based on the Japanese traditional medicine, Kampo.

Kampo has its origins in Traditional Chinese Medicine (TCM). It was introduced to Japan in the 6th century and, after combining with Japan's original folk remedies, developed separately from Western medicine for the next 1400 years. Kampo has fewer adverse effects than modern conventional medicine, and Kampo formulas, consisting mostly of natural herbs, as well as minerals and animal materials, are manufactured by licensed pharmaceutical companies and are prescribed by Western-trained medical doctors (usually as the spray-dried extract granules). These prescription Kampo formulas are much easier to take because of the spray-dried granules, and safer because of the standardization and quality control procedures than decoctions prepared by patients themselves. In addition, the composition and amount of each herb are fixed in each granule-type Kampo formula (Tables 1-3). Quality control procedures for the herbs used in Kampo have been also established, and the safety and reliability of Kampo have been validated through the strict monitoring of side effects under the control of the Japanese Ministry of Health, Labor and Welfare, in the same way as modern conventional medicines are validated [1-4]. Therefore, as far as medical doctors use these granule-type formulas, they can share exactly the same quality and effectiveness which are confirmed by modern scientific methods. The Japanese Ministry of Health, Labor, and Welfare has approved 294 Kampo formulas for clinical use, which means that these formulas are

Constituent Herbs	Weight (g)
Angelica root	3.0
Atractylodes Lancea rhizome	4.0
Bupleurum root	2.0
Hoelen	4.0
Glycyrrhiza root	1.5
Cnidium rhizome	3.0
Uncaria thorn	3.0

YKS's daily dose is 7.5 g of granules containing extracts from 7 herbs, the dry weight of each of which is noted above.

Table 1: Components of Yokukansan (YKS).

Constituent Herbs	Weight (g)
Coptis rhizome	2.0
Scutellaria root	3.0
Phellodendron bark	1.5
Gardenia fruit	2.0

OGT's daily dose is 7.5 g of granules containing extracts from 4 herbs, the dry weight of each of which is noted above.

Table 2: Components of Orengedokuto (OGT).

Constituent Herbs	Weight (g)
Gypsum	5.0
Citrus Unshiu peel	3.0
Ophiopogon tuber	3.0
Pinellia tuber	3.0
Hoelen	3.0
Ginseng root	2.0
Saposhnikovia root	2.0
Glycyrrhiza root	1.0
Giger rhizome	1.0
Uncaria thorn	3.0
Chrysanthemum flower	2.0

CTS's daily dose is 7.5 g of granules containing extracts from 11 herbs, the dry weight of each of which is noted above.

Table 3: Components of Chotosan (CTS).

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also approved for reimbursement under the National Health Insurance (NHI) program. Kampo is thus integrated into Japan's national health care system and all citizens have access to government-approved Kampo formulas in Japan.

Kampo medicine has a unique diagnostic scheme that is totally different from that of Western medicine. An appropriate Kampo formula is chosen based on both the patient's subjective symptoms and objective signs using Kampo-specific diagnostic examinations such as abdominal diagnosis, pulse diagnosis, and tongue diagnosis, irrespective of conventional Western diagnosis. A Kampo formula could be chosen if the patient's subjective symptoms were distinguishing enough and could be expected to exert its Kampo formula's efficacy without the need for considering more extensive abdominal, pulse, and/or tongue diagnosis. Recently, Kampo has received renewed attention because it provides a valid alternative for treating symptoms refractory to modern conventional medicine. However, the details regarding the therapeutic mechanisms of each Kampo formula remain unclear and further studies are needed to increase its usefulness. In addition, each Kampo formula is usually comprised of multiple herbs, all of which can contain large numbers of active constituents; there is a need to elucidate the clinical effects of each herb as well.

In this article, we review the evidence of Kampo's effectiveness in treating dementia-related symptoms.

Effective Kampo Formulas for Dementia-related Symptoms

Yokukansan

Yokukansan (YKS) is a Kampo formula consisting of seven herbs: *Angelica root, Atractylodes Lancea rhizome*, *Bupleurum root*, *Hoelen*, *Glycyrrhiza root*, *Cnidium rhizome* and *Uncaria thorn* (Table 1). Many randomized controlled trials (RCTs) have accumulated clinical evidence of YKS's effectiveness in behavioral and psychological symptoms of dementia (BPSD). The first controlled study of YKS, a randomized, observer-blind, multicenter, controlled trial, was performed in early 2005 and showed that 4 weeks of treatment with YKS significantly improved BPSD [5]. The same group also reported the efficacy of YKS in treating visual hallucinations and neuropsychiatric symptoms of dementia with Lewy bodies (DLB) in late 2005 [6]; YKS has been the second-line treatment for DLB in Japan since then. In fact, since 2010, YKS has been listed alongside modern conventional medicine in the Japanese Guidelines for the Management of Dementia by the Japanese Society of Neurology (http://www.neurology-jp.org/guidelinem/nintisyo.html). YKS has a different therapeutic mechanism from that of anti-psychotic agents and improves BPSD and activities of daily living (ADL) without impairing cognitive function or causing extrapyramidal symptoms, which is its greatest advantage in the treatment of elderly patients [5-10]. Interestingly, YKS used to be a TCM medicine for symptoms in children such as night cry and sleep terrors. Meanwhile, starting in 2005, 5 RCTs have provided support for YKS's efficacy in treating dementia-related symptoms [5,7-10] and YKS is now used widely for various symptoms in elderly patients as well as in children in Japan.

There are also reports showing YKS's effectiveness in treating neurodegenerative diseases. A prospective, single-arm, open-label study reported the efficacy of YKS in treating visual hallucinations in patients with Charles Bonnet syndrome [11]. A prospective, cross-over, open-label study in Huntington's disease patients showed a significant decrease in motor assessment scores following eight weeks of YKS treatment [12]. As mentioned in our review article on YKS [13], YKS ameliorates involuntary movements as well as psychiatric symptoms. Twelve-week treatment by YKS significantly improved both tardive dyskinesia and psychotic symptoms in schizophrenia patients with neuroleptic-induced tardive dyskinesia [14].

Orengedokuto

As YKS is widely used for dementia-related symptoms, augmentation therapy with other Kampo formulas, rather than antipsychotics, becomes necessary when YKS is only partially effective. Orengedokuto (OGT), consisting of four herbs-*Coptis rhizome, Scutellaria root, Phellodendron bark* and *Gardenia fruit* (Table 2) is the first choice to add onto YKS. *Coptis rhizome* and *Gardenia fruit*, which are two of the four components of OGT, often used to be added to the decoction medicine of YKS in the classic Japanese medical books to augment its efficacy. Therefore, OGT augmentation in cases that are partially responsive to YKS is reasonable when granule prescriptions but not the decoction medicines are available. In addition, OGT itself should be considered as an alternative treatment for irritability, impulsivity, and aggression. Lately, several reports on the effectiveness of OGT add-on therapy to YKS have been published, in both English and Japanese [15].

Chotosan

Another promising Kampo formula for dementia is Chotosan (CTS) consisting of eleven herbs: *Gypsum*, *Citrus Unshiu peel*, *Ophiopogon tuber*, *Pinellia tuber*, *Hoelen*, *Ginseng root*, *Saposhnikovia root*, *Glycyrrhiza root*, *Giger rhizome*, *Uncaria thorn* and *Chrysanthemum flower* (Table 3). Two double-blind controlled studies showed the effectiveness of CTS in the treatment of vascular dementia [16,17]. CTS administration for twelve weeks significantly improved neuropsychiatric symptoms compared to the placebo. The dementia score in the CTS group had a tendency to be improved compared to the placebo group though without statistical significance. There has been no additional clinical study on CTS's effect on dementia since then, but several basic studies suggest that *Uncaria thorn* is the main active component in CTS and has a neuroprotective effect [18-20]. This is interesting because *Uncaria thorn* is also one of the important components of YKS.

Other Kampo formulas

Basic studies suggest that other Kampo formulas such as Kamikihito, Juzentaihoto, Zokumeito and Kamiuntanto may have ameliorating effects on dementia. More research is required to further clarify the effectiveness of those Kampo formulas [21-24].

Adverse effects

The most frequently reported side effect is mild hypokalemia resulting from pseudoaldosteronism, presumably caused by *Glycyrrhiza root* (licorice)-containing Kampo formulas. While this is a very rare adverse effect to Kampo formulas, the potential for hepatotoxicity, dermatitis, and interstitial pneumonitis, which are caused by a drug-induced autoimmune response, is considered to exist with any Kampo formula. However, given the totality of evidence and the wide use of Kampo formulas in the Japanese healthcare system, Kampo products are considered very safe for clinical use, with less serious and less frequent adverse effects than the majority of pharmaceutical medications [13].

Summary and Conclusion

Kampo has recently had a stronger presence in treating dementia, especially DLB, as well as in treating a wide variety of other refractory diseases. Although there is no evidence yet that Kampo also improves cognitive function, many RCTs have shown Kampo's significant efficacy

in dementia-related symptoms. In particular, YKS improves BPSD and ADL without impairing cognitive function or causing extrapyramidal symptoms. It is no wonder Japanese physicians are turning to Kampo as a promising alternative in treating dementia-related symptoms. The therapeutic mechanisms of most Kampo formulas remain unclear; further studies are needed to enhance their usefulness for clinical practice.

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