Use of Yokukansan (TJ-54) in the treatment of neurological disorders: A review

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Abstract

Kampo herbal remedies are reported to have a wide range of indications and have attracted attention due to reports suggesting that these remedies are effective when used in disease treatment while maintaining a favourable quality of life. Yokukansan, also known as TJ-54, is composed of seven herbs; Angelica acutiloba, Atractylodes lancea, Bupleurum falcatum, Poria cocos, Glycyrrhiza uralensis, Cnidium officinale, and Uncaria rhynchophylla. Yokukansan is used to treat insomnia and irritability as well as screaming attacks, sleep tremors and hypnic myoclonia, and neurological disorders which include dementia and Alzheimer’s disease – the focus of this article. It is concluded that Yokukansan is a versatile herbal remedy with a variety of effects on various neurological states, without reported adverse effects. Traditional herbal medicines consist of a combination of constituents which account for the clinical effect seen. Likewise, the benefits of Yokukansan are probably attributable to the preparation as a whole, rather than to individual compounds.

Keywords: Alzheimer’s disease, dementia, herbal remedy, Kampo, TJ-54, Yokukansan

1. Introduction

Kampo medicines are traditional herbal medicines which have been used in China for more than 2000 years. Chinese herbal remedies were first introduced into Japan around the 5th century and have since been modified by the Japanese (Okamoto et al., 2004). These Kampo herbal remedies are reported to have a wide range of
indications and have attracted attention due to reports suggesting that the remedies are effective when used in disease treatment while maintaining a favourable quality of life (Mizukami et al., 2009). The Japanese Ministry of Health, Labor and Welfare has approved more than 120 Kampo prescriptions for use in clinical practice (Takeda et al., 2008).

It is known that the effects of Japanese traditional herbal medicines differ in each case according to the ‘Sho’ of each individual (Aizawa et al., 2002). The word ‘Sho’ can be roughly translated in English as symptoms, signs or evidence (Terasawa, 2004). ‘Sho’ encompasses psychic and somatic symptoms as well as the patient’s constitution and physical condition (Kanba et al., 1991). Ancient Kampo physicians abhorred invasions into a patient’s body and examinations such as biopsy or endoscopy were unimaginable. The only approaches left were; visual observation, listening to the sounds made by the patient’s body, smelling and touching the patient and listening to what they say (Terasawa, 2004). Although this seems to be a very qualitative approach to disease diagnosis, biochemical and pharmacological research has found evidence that the physician’s intuition has a firm scientific basis, even though some of the ‘Sho’ and herbal formulae in Kampo still await the discovery of their molecular basis (Terasawa, 2004).

Yokukansan, also called TJ-54, is a Kampo prescription known as Yi-gan-san in Chinese. It was developed in 1555 by Xue Kai as a remedy for agitation and restlessness in children (Iwasaki et al., 2005). It is composed of seven herbs; Angelica acutiloba L. (Umbelliferae), Atractylodes lancea DC. (Compositae), Bupleurum falcatum L. (Umbelliferae), Poria cocos Wolf. (Polyporaceae), Glycyrrhiza
uralensis (Leguminosae), Cnidium officinale Makino (Umbelliferae), and Uncaria rhynchophylla Schreb. (Rubiaceae) in a ratio of 3:4:2:4:1.5:3:3, respectively. The mixed dried extract of these herbs are sold in packages containing 2.5 g and is recommended to be taken three times daily before meals (Tateno et al., 2008). Yokukasan is used to treat insomnia and irritability as well as screaming attacks, sleep tremors and hypnic myoclonia (Ishii, 2000; Aizawa et al., 2002; Okamoto et al., 2004). Noting the increasing life expectancy of the Japanese population, geriatricians have begun to use traditional regimens to treat dementia symptoms in the elderly and Yokukansan is one of the Kampo medicines being used. This review focuses on the use of Yokukansan in treating neurological disorders which include dementia and Alzheimer’s disease.

Indications of yokukansan

(i) Dementia

Behavioural and psychological symptoms of dementia (BPSD) include aggression, agitation, screaming, wandering, hallucinations, and delusions which occur in 20-80% of such patients (Lawlor, 2004; Mizukami et al., 2009). The pathophysiology of BPSD is related to an imbalance between the different neurotransmitters; acetylcholine, serotonin, dopamine and noradrenaline (Lanari et al., 2006). Adverse reactions such as deterioration of cognitive function, extrapyrimidal symptoms and gait disturbance, limit the use of atypical antipsychotics in the treatment of these symptoms (Schneider et al., 2006). Therefore other treatments for dementia symptoms which can be used more safely are warranted. A possible solution is herbal medicines which have been used for millennia with apparent safety and
efficacy in China, Korea, Taiwan and Japan for the treatment of dementia in the elderly (Iwasaki et al., 2005).

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterised by the accumulation of amyloid β (Aβ)-plaques in the cerebral cortex leading to loss of neurons and memory dysfunction, accompanied by BPSD (Cha et al., 2001; Blennow et al., 2006). Tabuchi et al. (2009) investigated the effects of Yokukansan on learning and non-cognitive disturbances in Tg2576 mice expressing the human form of the APP6955WE gene (APP-Tg mice), which is considered to be an animal model of AD. Yokukansan (0.5% and 1.0%) was given to mice for 10 months, after which evaluation of learning and non-cognitive disturbances was performed using the Morris water-maze test, elevated plus-maze test and open-field test. Results showed Yokukansan to improve learning and non-cognitive defects as well as to decrease anxiety in the APP-Tg(+) mice.

Mizukami et al. (2009) reported the effectiveness and safety of Yokukansan for the treatment of dementia symptoms in 106 patients diagnosed with AD. BPSD and cognitive functions were evaluated using the Neuropsychiatric Inventory (NPI) and the Mini-Mental State Examination (MMSE), respectively. Patients who had received Yokukansan (7.5g t.i.d.) for 4 weeks showed significant (p<0.05) improvement in the NPI scores during the treatment period as well as in NPI subscales (delusions, hallucinations, agitation/aggression, depression, anxiety and irritability) which lasted for 1 month. Although the treatment did not show any effect on cognitive function, there were no serious adverse effects and it is suggested that Yokukansan is
effective and well tolerated in BPSD patients (Mizukami et al., 2009). In another clinical study fifteen AD patients were treated with 2.5g of Yokukansan three times a day, for 12 weeks (Monji et al., 2009). The NPI examinations revealed significant improvement (p<0.001) in the treatment group with no improvement in the control group. The authors concluded that Yokukansan improved BPSD and reduced the doses of antipsychotics required for treatment of BPSD in elderly patients. No adverse effects were noted. Furthermore, improvement of behavioural and psychological symptoms such as agitation, aggression and irritability were noted in 52 Alzheimer’s patients who received 2.5g of Yokukansan, 3 times a day for 4 weeks (Iwasaki et al., 2005).

(ii) Neurotransmitter systems

Glutamate is a major excitatory neurotransmitter which is involved in many brain functions including cognition, memory, learning, as well as other neuronal functions such as synapse induction and elimination (Takeda et al., 2008). Glutamate performs its signalling functions via glutamate receptors, however, excessive activation of these receptors is harmful to neurons just as high concentrations of extracellular glutamate are toxic to neurons (Danbolt, 2001; Takeda et al., 2008). Glutamate excitotoxicity, which is induced by excessive glutamate in the synaptic cleft, causes neuronal cell death and can be seen in many neurological diseases including stroke, epilepsy and Alzheimer’s (Choi and Rothman, 1990; Lipton and Rosenberg, 1994; Obrenovitch and Urenjak, 1997). This disturbance in the glutamatergic system may be associated with behavioural and psychological symptoms in patients with dementia (Steele et al., 1990).
The effect of Yokukansan on thiamine-deficient rats was investigated and results indicated that Yokukansan ameliorated degeneration of neuronal and astroglial cells in the rat brain stem, cerebral cortex and hippocampus, which are responsible for learning, memory and various psychological functions (Ikarashi et al., 2006). Takeda et al. (2008) showed that administration of Yokukansan (300 mg/kg body weight) to zinc-deficient (elevated glutamate) rats, significantly suppressed the increase in extracellular concentrations of glutamate and aspartate in the hippocampus of these rats after stimulation with 100mM KCl. This suggests that Yokukansan is involved in the modulation of excitatory neurotransmitter systems.

In an attempt to clarify the mechanism of Yokukansan against glutamate-mediated excitotoxicity, Kawakami et al. (2009) investigated the effects of Yokukansan on glutamate uptake function as well as its effect on glutamate-induced neuronal death, using cultured cells. Results showed Yokukansan to improve glutamate uptake and inhibited glutamate-induced neuronal death in a dose-dependent manner. This suggests that Yokukansan exerts a neuroprotective effect by amelioration of the dysfunction of astrocytes and also by direct protection of the neuronal cells (Kawakami et al., 2009).

Abnormalities of the serotonergic 5-hydroxytryptamine (5-HT) system have been associated with BPSD of Alzheimer’s patients (Garcia-Alloza et al., 2005). Egashira et al. (2008) investigated the effect of Yokukansan on the head-twitch response in
mice induced by 2,5-dimethoxy-4-iodoamphetamine (DOI), which is a 5-HT$_{2A/2C}$ agonist. Acute treatment with Yokukansan (100 and 300 mg/kg p.o) was shown to provide no improvement of the head-twitch response, but repeated treatment with 300 mg/kg p.o. of Yokukansan significantly inhibited the twitch response (p<0.05) and also decreased the expression of 5-HT$_{2A}$ receptors (p<0.01) in the pre-frontal cortex of the mice.

(iii) Sleep disorders

Studies have shown that dementia patients experience a decrease in the amount of slow wave sleep (Prinz et al., 1982) and rapid eye movement (REM) sleep (Satlin et al., 1991), resulting in sleep disturbances. The effects of Yokukansan (2.5g, before meals, three times a day for 4 weeks) on both BPSD and sleep structure in dementia patients showed significant improvements (p<0.05) in NPI scores, reduced delusions, hallucinations, agitation/aggression, anxiety and irritability as well as increases in total sleep time (Shinno et al., 2008). The authors suggested that the serotonergic and GABAergic effects of Yokukansan are responsible for the beneficial effects seen.

Patients suffering from somatoform disorder often complain of headache, tenseness, fatigue and tinnitus (Hiller et al., 1997). Tinnitus is characterised by continuous auditory perception of various sounds such as buzzing, ringing and tends to cause insomnia, irritability and depressive mood. A case of a 44 year old woman who had been suffering from tinnitus and insomnia for 3 years without successful treatment
was reported (Hideki et al., 2005). The patient was later diagnosed with somatoform disorder and sulpiride (150 mg per day) was chosen as treatment, however, the tinnitus and headache were still present after 3 weeks. When Yokukansan (dose not provided) was added to the sulpiride treatment, the tinnitus, headache and insomnia cleared within 2 weeks, suggesting the effectiveness of Yokukansan in the treatment of tinnitus in undifferentiated somatoform disorder complicated with headache and insomnia.

Yokukansan (7.5 g/day, 3 times daily for 3 days) significantly (p<0.05) extended the total sleep time of 20 adult male patients compared to the control group (Aizawa et al., 2002). The former therefore exhibits a profile similar to that of benzodiazepines, which are commonly known to improve sleep (Nishino et al., 1995; Aizawa et al., 2002).

(iv) Personality disorders

Yokukansan is reported to be valuable in the treatment of various emotional symptoms in borderline personality disorder (Miyaoka et al., 2007a), tardive dyskinesia and psychotic symptoms in schizophrenia (Miyaoka et al., 2007b). There is currently no definite treatment for borderline personality disorder (BPD), because despite the efficacy of some medications, side effects do seem to limit their use (Miyaoka et al., 2007a). A 12-week open-label study investigated the effect of Yokukansan (6.4±1.9 g daily) on 25 female BPD patients. Significant improvements (p<0.0001) in the various symptoms of BPD, including depression, aggression,
impulsivity and anxiety were noted, without significant side effects (Miyaoka et al., 2007a). Furthermore, a decrease in γ-aminobutyric acid (GABA) receptors as well as serotonin levels was reported in such patients (Hansenne et al., 2002; Friedel, 2004).

Tardive dyskinesia (TD) in schizophrenic patients consists of abnormal, involuntary, irregular movements of the muscles of the head, limbs, and trunk which are often irreversible (Chouinard et al., 1988). Serotonergic and dopaminergic neurotransmitter systems are implicated in tardive dyskinesia (Goldman, 1976; Seibyl et al., 1989). In an open-label study performed by Miyaoka et al. (2008), 22 patients with schizophrenia who had neuroleptic-induced tardive dyskinesia were given 7.5 g/day of Yokukansan for 12 weeks. A significant improvement in tardive dyskinesia and psychotic symptoms was reported (p<0.0001). The authors suggest that the effect of 5-HT2A antagonism by Yokukansan can restore and maintain “normal” dopamine function in patients with schizophrenia and may produce antipsychotic effects without including sedation or extrapyramidal symptoms.

Other effects associated with neurological states

Biochemical and histological investigations carried out by Tabuchi et al. (2009) suggested that the ameliorative effect of Yokukansan on cognitive and non-cognitive symptoms in Alzheimer's patients is independent of Aβ deposition. Aβ also has an effect on cholinergic and serotonergic neurons (Harkany et al., 1995; 2001) as well as glutamatergic neurons (Fitzjohn et al., 2001). This means that Aβ deposition
leads to impaired cognitive and non-cognitive functions via long-term potentiation of the dysregulated neuron systems (Jacobson et al., 2006). Yokukansan is said to inhibit excessive glutamate release in the hippocampus of zinc-deficient rats (Takeda et al., 2008), reduce expression of 5-HT receptors in the prefrontal cortex of rats (Egashira et al., 2008) and increase choline acetyltransferase activity and acetylcholine levels in experimental animals (Ito, 1997; Yabe et al., 2005). Recently, Yokukansan was demonstrated to inhibit Aβ-induced cytotoxicity in primary culture of rat cortical neurons (Tateno et al., 2008), indicating that Yokukansan exerts a protective effect on glutamate-induced cell death via an anti-cytotoxic mechanism.

Plant components of Yokukansan and their relevant biological activities/toxicities

Some of the compounds in Yokukansan have an affinity for dopamine and serotonin receptors, antagonising dopamine receptors and hence extrapyrimidal side effects are not present when using Yokukansan as opposed to most antipsychotic treatments (Iwasaki et al., 2005).

Angelica acutiloba has been reported to have ameliorative effects on cognitive impairment induced by scopolamine (Hatip-Al-Khatib et al., 2004), ischemia (Zhao et al., 2005) and hypoperfusion (Murakami et al., 2005). This plant also affects GABA and 5-HT receptors (Liao et al., 1995), further explaining the ameliorative effect of Yokukansan on BPD symptoms (Miyaoka et al., 2007a). A. acutiloba contains alkylphthalide derivatives and furanocoumarins, both of which have been shown to
possess acetylcholinesterase inhibitory activity (Mitsuhashi et al., 1960; Kang et al., 2001). This plant should not be taken with warfarin, heparin, aspirin, nonsteroidal anti-inflammatory drugs nor other antioxidants as it may affect blood clotting.

*Uncaria rhynchophylla* has a potent anti-aggregation effect on Aβ proteins, a deposition which is characteristic of Alzheimer's disease. The water extract of *U. rhynchophylla* contains oxindole and indole alkaloids which possess neuroprotective properties (Fujiwara et al., 2006; Tabuchi et al., 2009). This plant also contains the alkaloids hirsuteine and hirsutine which are known for their protective effects against glutamate-induced neuronal death (Shimada et al., 1999). Epicatechin, caffeic acid and quecetin, found in this plant, have been shown to protect against oxidative damage by H2O2 in NG108-15 cells (Mahakunakorn et al., 2004). The latter is an important function seeing that stimulation of N-methyl D-aspartate (NMDA) receptors by glutamate (especially excessive glutamate such as with dementia), causes an overload of intracellular Ca2+ which in turn activates neurons to produce excessive nitric oxide and other reactive oxygen species which cause neuronal death (Weikert et al., 1997). Furthermore, *U. rhynchophylla* can block NMDA-induced neuronal death by inhibiting the current in these neurons (Lee et al., 2003; Sun et al., 2003). The compounds, rhynchophylline and isorhynchophylline, have been reported to antagonise the NMDA receptor (Kang et al., 2002), possibly making these constituents of Yokukansan an important contributor to its neuroprotective effect. The alkaloid, hirsutine, possesses local anaesthetic properties, showing “curare-like” ability on neuromuscular transmission (Jones, 1994). The pentacyclic oxindole alkaloids seem to be responsible for anti-inflammatory activity (Aguilar et al., 2002). This species seems to be the most important of the seven plant species in the
treatment of neuropsychiatric conditions (Tateno et al., 2008). *Uncaria* may potentiate the action of antihypertensive drugs and should not be used by patients receiving immunosuppressive therapy or with autoimmune disorders due to its' potential immunostimulating effects.

*Poria cocos* is used in Korea and Japan to treat age-related brain disorders and to improve cognitive and memory function in old age (Adams et al., 2007). The plant contains several monosaccharides, triterpene derivatives and 15 amino acids (Chihara et al., 1970; Kanematsu and Natori, 1970; Lee et al., 2004). *Poria* has been reported to improve cerebral blood flow (Jingyi et al., 1997), promote hippocampal long-term potentiation *in vivo* (Smriga et al., 1995), improve memory and inhibit acetylcholinesterase activity (Liu et al., 1993). *Poria* has been reported to exert anti-inflammatory effects (Nukaya et al., 1996; Cuellar et al., 1997). No adverse reactions or toxicity has been reported for *Poria*.

*Atractylodes lancea* contains sesquiterpenoid glycosides (attractyloside), L-tryptophan and syringin (Yahara et al., 1989). Atractyloside is a known hepatotoxin (Wainright et al., 1977). *Cnidium officinale* and *Glycyrrhiza uralensis* have both been shown to contribute to the repairing of Aβ-induced memory loss in mice with Alzheimer’s disease (Tohda et al., 2003). *G. uralensis* contains the flavone, liquiritin, which has been shown to possess antidepressant-like effects in induced depression rat models (Zhao et al., 2008). Other compounds present in *Glycyrrhiza* are the glycoside, glycyrrhizin, glycyrrhizic acid and glycyrrhizinate (Isbrucker and Burdock, 2006). Glycyrrhetic acid has anti-inflammatory and antiarthritic activity and a number
of compounds present in this plant possess antioxidant activity (Isbrucker and Burdock, 2006). High doses of the plant used for extended periods of time may cause hyperkalemia, mineralocorticoid hypertension and paralysis of extremities (Sigurjonsdottir et al., 1995; Elinav and Chajek-Shaul, 2003; Schapera, 2003).

*Bupleurum falcatum* is listed as one of the seven historical Korean plants which are used for the general improvement of cognition and memory function in old age and a methanolic extract of this plant was shown to inhibit acetylcholinesterase by 24.7% (Oh et al., 2004). *Bupleurum* contains triterpene saponins known as saikosaponins as well as pectin-like polysaccharides (bupleurans) (Hocking, 1997). Anti-inflammatory activity has been reported to be increased by saikosides (Chevallier, 1996). Although the toxicity profile is low, *Bupleurum* has caused sedative effects in some patients (Bone, 1996).

In summary, a review of the literature led us to the conclusion that Yokukansan is a versatile herbal remedy with a variety of effects on various neurological states with no reported adverse effects. Traditional herbal medicines consist of a combination of constituents which account for the clinical effect seen. Likewise, the benefits of Yokukansan are probably attributable to the preparation as a whole, rather than to individual compounds.
References


