The Latest Clinical Findings for Yokukansan Based on
Its Pharmacological Effects: Yokukansan Update

RIKA TSUKADA*, MASAKO ISEKI*

*Department of Anesthesiology and Pain Management, Juntendo University Faculty of Medicine, Tokyo, Japan

Yokukansan is a formulation containing 15% *Uncariae Uncis Cum Ramulus*, 10% *Bupleuri Radix*, 15% *Cnidii Rhizoma*, 15% *Angelicae Radix*, 20% *Atractylodis Lanceae Rhizoma*, 20% *Poria* and 7% *Glycyrrhizae Radix*. In addition to its well-established actions on serotonin and glutamate nerve systems, various other effects including suppression of nerve cell excitation, dose-dependent control of brain cell degeneration and protection of nerve sheaths have gradually been elucidated, among which its effectiveness on neuropathic pain has also been evidenced in basic research. In recent years, its wide spectrum of efficacy has given rise to increased use for neuropathic pain along with more conventional applications, such as for treating children's night cry and symptoms of dementia. Although yokukansan is an easy-to-use formulation, even for elderly patients, care must be taken for the complication of hypokalemia.

Key words: yokukansan, neuropathic pain

Introduction

Yokukansan (抑肝散) is a traditional Japanese medicine (kampo medicine- 漢方) that has long been widely used in Japan due to being "effective against sleeplessness, irritability and the tendency to easily become angry, which are caused by nervousness and lack of power in the abdomen, and was originally used against night crying, agitation and sleeplessness in children." Recently, however, yokukansan has been demonstrated to achieve significant improvements in the domains of psychiatry and pain relief, especially in patients with peripheral symptoms of dementia. Following recent progress in clinical trials and basic research, this formulation is now generally recognized to be a promising drug.

Composition

Yokukansan is a mixture of seven herbal medicines (Table-1), including 15% *Uncariae Uncis Cum Ramu-*

Table-1 The components of yokukansan

<i>Uncariae Uncis Cum Ramulus</i> (釣藤鈎)
<i>Bupleuri Radix</i> (柴胡)
<i>Cnidii Rhizoma</i> (川芎)
<i>Angelicae Radix</i> (当帰)
<i>Poria</i> (茯苓)
<i>Glycyrrhizae Radix</i> (甘草)
<i>Atractylodis Lanceae Rhizoma</i> (蒼朮)

lus (釣藤鈎), 10% *Bupleuri Radix* (柴胡), 15% *Cnidii Rhizoma* (川芎), 15% *Angelicae Radix* (当帰), 20% *Atractylodis Lanceae Rhizoma* (蒼朮), 20% *Poria* (茯苓) and 7% *Glycyrrhizae Radix* (甘草).

The principal agent of yokukansan is *Uncariae Uncis Cum Ramulus*, which reduces overexcitement of the liver function (肝気). *Bupleuri Radix* and *Cnidii Rhizoma* support this ingredient by harmonizing the flow of energy (qi - 氣). *Cnidii Rhizoma* smoothens the blood flow in conjunction with *Angelicae Radix*, helping to alleviate pain. *Poria* and *Atractylodis Lanceae Rhizoma* harmonize the digestive functions and improve the balance of water in the body. *Glycyrrhizae Radix* supports these functions and is

Corresponding author: Rika Tsukada

Department of Anesthesiology and Pain Management, Juntendo University Faculty of Medicine

2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan

TEL: +81-3-3813-3111 (ext. 5456) E-mail: usagipunch@tiara.ocn.ne.jp

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Figure-1 3D HPLC pattern of yokukansan

Table-2 Major components, medicinal properties and indications for each herbal ingredient

	Source	Major ingredients and their medicinal properties	Indication
Uncariae Uncis Cum Ramulus (釣藤鈎)	Thorns of <i>Uncaria rhynchophylla</i> Miquel, <i>Uncaria sinensis</i> Haviland or <i>Uncaria macrophylla</i> Wallich (Family: Rubiaceae)	• Rhynchophylline – dilation of blood vessels, sedation, laxation of the alimentary tract, slowing of the heart rate • Hirsutine – dilation of blood vessels, spasmolysis	Convulsion, high fever, spasm, headache or vertigo in children
Bupleuri Radix (柴胡)	Roots of <i>Bupleurum falcatum</i> L. (Family: Umbelliferae)	• Saikosaponin a: R = β-OH • Saikosaponin d: R = α-OH – anti-inflammatory activities, improvement of liver functions	Pain on pressure in the chest-abdominal or lower side regions, repeated fever and remission, depression, restlessness
Cnidii Rhizoma (川芎)	Roots of <i>Cnidium officinale</i> Makino, generally parboiled (Family: Umbelliferae)	• Ligustilide – spasmolysis • Cnidilide • Butylidenephthalide	Irregular menstruation, menstrual cramps, anemia, chill, pains, headache
Glycyrrhizae Radix (甘草)	Roots and runners of <i>Glycyrrhiza uralensis</i> Fischer or <i>Glycyrrhiza glabra</i> L. (Family: Leguminosae)	• Dipotassium glycyrrhizate –peptic ulcer agent, anti-inflammatory, antitussive, tocolysis, liver protection, anti-allergy	Abdominal pain, muscle pain, arthritis, peptic ulcer
Poria (茯苓)	Sclerotium of <i>Poria cocos</i> Wolf, generally most of the outer layer is removed (Family: Polyporaceae)	• Ergosterol – precursor to Vitamin D • Pachymic acid –anti-inflammation	Edema due to micturition disorder, diarrhea, lack of appetite due to gastric disorders, indigestion, palpitation, insomnia
Atractylodis Lanceae Rhizoma (蒼朮)	Roots of <i>Atractylodes lancea</i> De Candolle or <i>Atractylodes chinensis</i> Koidzumi (Family: Compositae)	• Hinesol, β-eudesmol –peptic ulcer agent, CNS depressant, anti-bacterial, vasopressin-angiotensin II receptor inhibition	Indigestion, diarrhea, diaphoresis, ague
Angelicae Radix (当帰)	Roots of <i>Angelica acutiloba</i> Kitagawa or <i>Angelica acutiloba</i> Kitagawa var. <i>Sugiyamae</i> Hikino, generally parboiled (Family: Umbelliferae)	• Ligustilide/Butylidenephthalide – spasmolysis • Ferulic acid – antioxidant, anti-agglutination	Women's diseases including irregular menstruation, menstrual cramps, abdominal pain, pain, chill and circulatory deficit

thought to act as a harmonizer of all ingredients in yokukansan.

Figure-1 and Table-2 list the main ingredients of yokukansan and their currently known medicinal properties. The ingredients of yokukansan synergize as well as countervail each other's effects, ensuring the efficacy of the entire formulation.

Traditional interpretation and clinical application of yokukansan

Yokukansan was first mentioned in a 20-volume series of pediatric medical books called "Hoei Satsuyou" published during the Ming (1368-1644) dynasty in China. In Japan, yokukansan was first mentioned in a publication from the "Momijiyama Bunko" library created and maintained by the Tokugawa shogunate¹⁾ and remains widely used today.

The "Hoei Satsuyou" mentioned above describes yokukansan as "... treat (ing) symptoms in children, such as convulsions due to kyonetsu (hollow fever) in the passage of the liver, fever and chills associated with clenched teeth or spasms, vomiting of slime, lack of appetite with abdominal bloating and/or being fractious at night.... This formulation should be administered to both the affected child and his/her mother." In summary, yokukansan is used to treat spasms or night cries in scrofulous children.

As the "yokukan" part of the name literally means to control the liver, yokukansan is a formulation for treating an overly increased liver function. Tables-3

and-4 summarize the functions of the liver and symptoms associated with their acceleration.

It should be noted that the term "liver (肝)" is used here as a concept unique to oriental medicine. Tables-3 and -4 present the functions of the liver in the oriental sense and list symptoms associated with their overactivation.

The "kyonetsu (hollow fever)" described in "Hoei Satsuyou" refers to fever believed to be caused by an insufficient blood flow in the liver, which differs from the "fever" that occurs in the general sense and requires pyretolysis. Yokukansan is positioned as a formulation for controlling clinical conditions in patients with aggravated kyonetsu causing neurological symptoms.

While yokukansan is originally a pediatric formulation, it is also widely prescribed to adults. For example, in the "Hoei Satsuyou," yokukansan is prescribed to both the affected child and mother.

In "Saneikan Ryochi Zatsuwa (餐英館療治雜話)," published in the late Edo period in Japan, MEGURO Dotaku (目黒道琢) states that, "Yokukansan is also effective against partial paralysis in adults. Indicated patients are those who feel Renkyu (攣急 - strong muscle tone) on the left side in addition to Renkyu and pulsation along the abdominal middle line starting from the epigastric fossa. The patient feels constriction in the abdomen even though there is no concentration of qi (氣 - vital energy) around the epigastric fossa and no firmness can be felt in the abdominal area. If the patient admits to having a tendency to become easily irritated, this formulation will certainly be effective. Yokukansan may also be indicated for insomnia. The diagnosis of insomnia should be based on Fukusho in conjunction with other symptoms. The formulation is particularly effective against insomnia in hot-tempered patients."

Fukusho (腹証 - abdominal conditions) is a diagnostic technique developed in the Edo era and is particular to Japanese Kanpo medicine. Feeling the abdomen of the patient in order to determine his/her Fukusho allows for a suitable prescription to be identified, as described in the above description of yokukansan.

On the other hand, OTSUKA Keisetsu (大塚敬節) indicated that Sho (証 - conditions/observance) for yokukansan include the flaccidness/dysphoria type of Sho in addition to the tension/excitation type described by Dotaku²⁾.

Table-3 Functions of the liver

• Controls Sosetsu (疏泄 - similar to metabolism) : Controls emotion, facilitates mental functions, facilitates digestion, maintains qi and blood
• Controls Zoketsu (藏血 - control of blood flow from liver) : Storage of blood, controls the volume of circulated blood
• Controls Kin (筋 - muscle) : Facilitates motor functions
• Kaikyo (開竅 - make senses clear) of eyes: Improves eyesight

Table-4 Symptoms of liver hyperactivity

• Hyperactivity of the mental function: depression and excitation
• Hyperactivity of the digestive function: indigestion, abdominal pain, sense of fullness in the abdomen, vomit, heart burn
• Hyperactivity of the head function: dizziness, ringing ear, headache, hot flush
• Hyperactivity of the circulatory function: muscle convulsion, paralysis, motor disorders, menstrual disorders

Pharmaceutical properties of yokukansan

In recent years, much progress has been made regarding the pharmaceutical properties of yokukansan, resulting in the knowledge described below (Table-5, Figure-2).

1. Mechanisms of action of yokukansan

It has been gradually elucidated that yokukansan has several mechanisms of action, including effects on the serotonin (5-hydroxytryptamine: 5-HT) and glutamate-mediated nervous systems, inhibition of excited nerve cells, dose-dependent suppression of the denaturation of brain cells in thiamine-deficient (TD) rats and protective actions in nerve sheaths.

2. Effects on the serotonin-mediated nervous system

A positive correlation has been suggested to exist between depression of the brain serotonin (5-HT) function and hallucinations or aggressive behaviors. Serotonin is a neurotransmitter that participates in the descending inhibitory system, which controls the transmission of pain signals from the brainstem to the spinal cord by suppressing the communication channels for these signals.

Known actions of yokukansan on the serotonin-mediated nervous system include a partial agonistic effect on 5-HT_{1A} receptors that suppresses excitement in the nervous system³⁾ and

downregulation of the 5-HT_{2A} receptors involved in excitement of the nervous system⁴⁾.

3. Effects on the glutamate-mediated nervous system

While glutamate controls high-order functions, such as memory, an excessive concentration of this compound in the extracellular fluid is believed to be responsible for cell death associated with certain neurological diseases.

It is estimated that yokukansan suppresses the death of nerve cells by inhibiting an elevation of the glutamate level in the extracellular fluid^{5) 6)}.

On the other hand, cells contain a cystine transport system involving glutamate/cystine antiporters (Xc-system) that move extracellular cystine into the cell and intracellular glutamate out of the cell. The cystine captured by this system is used to synthesize glutathione (GSH), which acts as a scavenger of radical oxygen or hydrogen peroxide

Table-5 Mechanisms of action of yokukansan

Serotonin-mediated nervous system

- 5-HT_{1A} partial agonistic activity
- 5-HT_{2A} down regulatory activity

Glutamate-mediated nervous system

- release inhibition
- Glutamate transporter activation
- Inhibition of the rise of extracellular glutamate level
- Effects through the glutamate receptors
- Suppression of oxidation stress, enhancement of GSH

(Adapted from: Katsuyoshi MINAKAI: Brain 21, 2009; 12: 400-403)

Figure-2 Mechanisms of action of yokukansan

Table-6 Symptoms of BPSD

Psychological symptoms	• Hallucination (including visual and auditory hallucinations) • Delusion (including delusions of theft, persecution and jealousy) • Delusions related to sleep disorders (including insomnia and REM sleep behavior disorder) • Mood disorders (including depression, mania, anxiety, excitement and apathy) • Personality disorders (including euphoria, disinhibition, tendency to become angry and lack of interest)
Behavioral disorders	• Aggressive behaviors (including violence and verbal abuse), fretfulness, screaming, rejection • Inappropriate/purposeless behaviors (including pseudo-work, unclean behavior, wandering and collection) • Eating disorders (including allotriophagy, overeating and refusal to eat)

generated by NMDA stimuli or other activities to protect cells from damage due to oxidative stress. In cells exposed to high levels of glutamate, however, overstimulation of NMDA receptors and inhibition of GSH production via the Xc-system induce apoptosis of cells triggered by oxidative stress^{7) 8)}.

Yokukansan is known to act as an antagonist of NMDA receptors by binding to these receptors^{9) 10)} and has been reported to suppress the death of P12 cells triggered by glutamate^{11) 12)}. These findings suggest that the ability of yokukansan to generate Xc-GSH directly protects cells.

These effects of yokukansan on the 5-HT and glutamate-mediated nervous systems may provide the basis for its ameliorating effects on the peripheral symptoms of dementia and ability to alleviate pain.

Clinical applications

In addition to its well-established position in traditional oriental medicine, yokukansan is now widely recognized as a therapeutic agent for neuropsychiatric conditions, including peripheral symptoms of dementia and neuropathic, chronic and/or idiopathic pain.

Improvements with yokukansan treatment have been reported for schizophrenia, borderline personality disorder, peripheral symptoms of Parkinson's disease¹³⁾⁻¹⁵⁾, REM sleep behavior disorder¹⁶⁾, restless legs syndrome¹⁷⁾, Charles Bonnet syndrome with hallucinations as the cardinal symptom¹⁸⁾, blepharospasm and delirium after heart or major blood vessel surgery in elderly patients.

Peripheral symptoms of dementia

In dementia patients, peripheral symptoms, including hallucinations, delusions, depression, delirium, excitement, aggressive behavior and wandering, are observed in addition to major symptoms, such as disturbances in memory or orientation. These peripheral psychoneurotic or behavioral symptoms are generally referred to as BPSD (behavioral and psychological symptoms of dementia) and are summarized in Table-6. BPSD is a major cause of admission to treatment facilities as it results in the deterioration of activities of daily living, which in turn increases the physical and psychological burdens of caregivers. As described above, yokukansan is thought to have ameliorating effects on these symptoms.

While BPSD is generally treated with psychotropic agents, these drugs may be associated with adverse events, including extrapyramidal symptoms, a tendency toward falls or a decrease in ADL's. With a treatment spectrum almost comparable to that of psychotropic agents with comparatively less side effects, yokukansan is now becoming a more important therapy.

Neuropathic pain

Neuropathic pain is believed to be caused by plastic transformation in the nerve circuit. While there remain many unsolved questions with respect to the mechanisms of nerve plasticity, it is generally accepted that NMDA glutamate receptors are involved.

Suzuki *et al.* used a rat chronic constriction injury model to demonstrate the anti-allodynic properties of yokukansan and identified the underlying mechanism as involving suppression of the extracel-

Figure-3 Pain levels before and after yokukansan administration²⁰⁾

Figure-4 Allodynia levels before and after yokukansan administration²⁰⁾

lular glutamate level via the activation of transporters¹⁹⁾.

Sakai *et al.* also demonstrated that pain and allodynia can be significantly decreased in the setting of postherpetic neuralgia by adding yokukansan to the patient's original drug regimen (Figure-3, 4)²⁰⁾.

Our experience with yokukansan

Various researchers have reported the effects of yokukansan in alleviating pain²¹⁾, including postoperative analgesia, migraine, fibromyalgia syndrome, chronic perineal pain and complex regional pain syndrome (CRPS). Our clinic also widely uses yokukansan in patients with neuropathic pain as well as mixed pain conditions, such as postherpetic neuralgia, diabetic neuropathy, sciatic neuralgia, numbness or pain associated with chemotherapy and postoperative pain. While therapeutic agents for neuropathic pain are associated with adverse

events primarily originating from the central nervous system, such as sleepiness or wobbliness, yokukansan is free of these drawbacks, making it safe to use in elderly subjects. Based on this safety profile, yokukansan is sometimes selected as the first-choice drug for high-risk elderly individuals. yokukansan may also be used when continuing or increasing the dose of therapeutic agents for neuropathic pain is difficult as a result of side effects. Our clinic has also experienced cases in which combining yokukansan with antidepressants, antiepileptic agents or opioids increases the therapeutic effects of treatment.

Since chronic pain is not limited to physical pain, but rather is an overall experience involving both emotional and cognitive aspects, such pain must be evaluated with a holistic view of the patient, including mood, cognition and behavior, in addition to the degree of the pain itself, which is heavily affected by these factors.

Our clinical experience suggests that anger, hostility, distrust or exasperation may aggravate pain in some patients. Sarno has proposed that low back pain may be the result of anger unconsciously accumulated by the patient²²⁾.

In addition, patient irritability may delay the formulation of positive rapport between the patient and his/her medical staff, interfering with the course of treatment, as when the patient refuses to cooperate with the clinical examination.

Yokukansan, which has been used to treat irritated or excited patients since ancient times, continues to be useful in clinical practice.

Reported side effects of yokukansan

Although various side effects of yokukansan have been reported, including hypokalemia, digestive symptoms, pseudoaldosteronism, fatigue, increased blood pressure, edema, weight gain, numbness or pain in the limbs, twitches or shaking of the muscles and a sense of physical weakness, yokukansan remains relatively safe, with a lower risk of side effects than other treatments, making it easier to apply in elderly patients.

Conclusion

This chapter described the characteristics of yoku-

kansan, which has long been used in Japan. While the traditional herbal (Kanpo – 漢方) medicine brought to Japan from China between the 8th and 16th centuries exhibited significant progress in the Edo period (1603–1868), its place as mainstream medicine was superseded by the Western science Rangaku (蘭学) during the Meiji Restoration (明治維新) when Japan opened the country to the outside world and has since become generally recognized as a form of alternative or supplementary medicine.

In recent years, however, the efficacy of traditional Kanpo medicine has been reexamined based on new knowledge of the structures and fundamental activities of major ingredients. For example, EBM analyses are actively carried out in both clinical and basic research studies. Although many elements of yokukansan are not fully understood, it may be a useful remedy for many ailments, including dementia and chronic pain, both of which have become major sociological issues in Japan in association with increasing longevity and aging of the society.

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