REVIEW

Yokukansan and its ingredients as possible treatment options for schizophrenia

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Abstract: Schizophrenia is a debilitating psychotic mental disorder that affects almost the entire range of human mental function. The devastating effect of the illness is usually long-lasting and requires lifelong treatment. Despite an evolved psychopharmacological understanding, the overall therapeutic effect of antipsychotics is still not satisfactory. The choice of proper medication presents a clinical dilemma between efficacy and safety. As a result, searching for comparable treatment options with safer profiles is very important. Yokukansan (TJ-54), also called yi-gan san in Chinese, is a traditional herbal medicine with evident therapeutic effect for neuropsychiatric disorders. There are several open-label clinical studies upholding the possibility of using yokukansan to treat schizophrenia or schizophrenia-like psychosis. Evidence from animal studies and neurobiology also sheds light on the antipsychotic implications of yokukansan and its ingredients. Nevertheless, correlations between the experimental environment and clinical settings may be complicated by a number of confounders. Clinical trials with more sophisticated designs are required to fill the gap between the experimental environment and clinical settings.

Keywords: herbal medicine, geissoschizine methyl ether, glycyrrhizin, antipsychotics, D2 receptor

Background

Schizophrenia is often a severe and debilitating psychotic disorder. It usually begins in late adolescence or early adulthood and affects approximately 1% of the population.[1] The devastating effect of the illness is usually long-lasting and requires lifelong treatment. Considering the substantial burden on patients, their families, and society, schizophrenia is becoming one of the most important public health problems.[1] The core symptoms and signs of the illness include hallucinations, delusions, abnormal behaviors, and disorganized speech. Deficits in the ability to experience pleasure, flattening of emotional expression, loss of drive, and impoverishment of mental activity are also noticed. Vocational and social disabilities usually result from the accompanied cognitive impairments in memory, attention, and executive function.[2] Almost the entire range of human mental function is affected by the disorder.

People with schizophrenia have difficulties in regulating information. They are unable to filter out the stimuli that most people can ignore[3] and lack the skills to assess their significance.[4] Together with the paranoid psychopathology, patients become hypervigilant and struggle to decide what experiences are real.[5] Violence in response to these symptoms may occur,[6] as can suicidal behaviors.[7] There are several pathological processes of the brain that express schizophrenia as a disease of the mind. The unfortunate convergence of these factors results in altered neurotransmitter mechanisms and loss of neuronal connectivity, both of which contribute to deficits in inhibitory function and the inability to sort information.[5]

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Antipsychotics

Antipsychotics are the primary treatments for schizophrenia. Since the first discovery of the neuroleptic effects of chlorpromazine in the 1950s, modulation of dopamine D2 receptors has played an important role in treating psychotic disorders.[8] Along with the similar modulation, newer-generation antipsychotics have been developed since the enhanced treatment effect of clozapine was reported in 1988.[9] The pharmacological picture has also evolved, from understanding of simple blockade of D2 receptors to combined dopamine–serotonin antagonism, to even more advanced functionally selective actions at dopamine receptors.[10–12] Nonetheless, the overall therapeutic effect is not satisfactory. Around one-fifth to one-third of patients with schizophrenia do not respond adequately to typical antipsychotics.[13] The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) showed that none of the examined medications could provide the majority of patients with a treatment they were able to tolerate for the full study period.[14,15] Although olanzapine was found to be slightly superior to the conventional and other novel agents in terms of the Positive and Negative Syndrome Scale (PANSS) ratings,[14] and clozapine was found to diminish the frequency of suicidal behavior, including serious suicidal acts,[15] both clozapine and olanzapine are more likely to cause severe weight gain and potentially fatal metabolic problems.[16,17] Patients with schizophrenia not only exhibit higher prevalence of metabolic syndrome, but are also at greater risk for developing cardiovascular mortality than the general population.[18,19] Choosing proper medication is always a clinical dilemma. As a result, searching for comparable treatment options with safer profiles is very important.

Yokukansan

Traditional herbal medicines have drawn a lot of attention in recent decades regarding the balance between effectiveness and side effects.[20–24] They have been utilized for a long time in the People's Republic of China and oriental countries, Japan, Taiwan, Korea and Vietnam. Herbal remedies were first introduced into Japan as Kampo medicine in the 5th century and have been modified over hundreds of years in Japan.[25] Yokukansan (TJ-54), also called yi-gan san in Chinese, is one of the Kampo prescriptions and has evident therapeutic effects for neuropsychiatric disorders. It contains a mixture of seven dried herbs, including *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[26] (Table 1).

Table 1 Components of yokukansan

Constituent herb	Ratio of constituent*
Angelica acutiloba L. (roots)	3
Atractylodes lancea DC. (roots)	4
Bupleurum falcatum L. (roots)	2
Poria cocos Wolf. (fungus)	4
Glycyrrhiza uralensis (roots)	1.5
Cnidium officinale Makino (roots)	3
Uncaria rhynchophylla Schreb. (hooks)	3

Note: *These are the ratios relative to each other.

The mixed extract is sold in packages with 2.5 g per unit and is usually taken three times daily before meals.[25] Yokukansan was developed in 1555 by Xue Kai as a treatment for agitation and restlessness in children,[20] and has been used in Japan for indications of insomnia, neurosis, irritability in children, and behavioral and psychological symptoms of dementia.[22,27–30] Because of accumulating reports of yokukansan in treating psychiatric disorders,[31] there is an emphasis on establishing its clinical implication in schizophrenia and schizophrenia-like psychotic symptoms (Table 2).

Following the observation that yokukansan may have beneficial effects on dyskinesia,[32] Miyaoka et al performed a 12-week, open-label study examining its efficacy, safety, and tolerability as an adjunctive treatment in 22 schizophrenic patients with tardive dyskinesia (TD).[33] They found statistical improvement not only of TD, but also of psychotic symptoms. Transient nausea and constipation were reported in only two cases. However, after yokukansan was stopped, the condition of TD deteriorated.[33] In order to evaluate its antipsychotic effects, the same group performed a 4-week, open-label control study to assess the usefulness of adding yokukansan in treating refractory patients with schizophrenia.[34] A significant decrease was observed in each subscale in PANSS ratings by the end of 4 weeks. Mild nausea or tiredness were noticed in three cases, but no serious adverse events were reported. This result suggests that an adjunction of yokukansan might be effective for treatment-resistant schizophrenia.[34] Furthermore, based on an experience of successful treatment of visual hallucination due to vision loss,[35] a 4-week, open-label study was initiated to investigate the monotherapeutic effect of yokukansan in treating Charles Bonnet Syndrome (CBS).[36] A significant decrease of visual hallucination was revealed by psychometrics, including the Neuropsychiatric Inventory (NPI), the hallucination subscale of the PANSS, and Clinical Global Impression (CGI). CBS is defined by the triad of ocular pathology causing visual deterioration, complex visual hallucinations, and preserved cognitive status. The hypothetical pathophysiology is the deafferentation theory, which means a loss of sensory input after damage to neurons

Table 2 Clinical trials using yokukansan for patients with schizophrenia and schizophrenia-like psychosis

Study, year	Sample size and study design	Average daily dosage (g/day) mean ± standard deviation	Assessment	Adverse events
Miyaoka,[33] 2008	13 males 9 females Mean age: 57.1 years 12-week open-label study Adjunctive therapy	7.5	AIMS (12.1±2.2–>1.6±1.3)** PANSS: Positive (22.2±4.2–>16.6±3.1)** Negative (26.5±6.3–>14.5±2.3)** General (42.9±6.7–>25.0±4.9)** CGI-S (4.86±0.9–>1.73±0.6)**	Nausea and constipation (2 cases)
Miyaoka,[34] 2009	Treatment group 16 males 18 females Mean age: 45.5 years Control group 10 males 15 females Mean age: 45.2 years 4-week open-label control study Adjunctive therapy	6.7±2.5	PANSS: Positive (27.7±6.1–>11.9±3.7)** Negative (30.4±5.8–>18.2±2.2)** General (65.1±5.4–>39.6±6.9)** DIEPSS (7.8±4.7–>6.9±4.1)	Nausea (2 cases) Tiredness (1 case)
Miyaoka,[35] 2009	A 2-week-treatment case report Monotherapy	7.5	Self-report	No adverse events reported
Miyaoka,[36] 2011	7 males 13 females Mean age: 66.3 years 4-week open-label study Monotherapy	5.8±2.6	NPI (20.4±2.4–>5.4±1.5)** HS-PANSS (6.4±2.4–>1.6±1.2)** CGI (4.5±1.8–>1.3±0.3)**	Nausea (3 cases)
Miyaoka,[38] 2013	20 males 20 females Mean age: 73.1 years 4-week open-label study Monotherapy	Baseline 5.02±1.06 Week 4 5.23±1.22	BPRS (36.7±4.65–>20.1±1.6)* CGI-S (5.03±0.89–>1.73±0.55)* PANSS (66.0±7.3–>34.3±2.2)* Simpson-Angus Scale (0.27±0.45–>0.15±0.36) Barnes Akathisia Rating Scale (0.20±0.41–>0.13±0.34) AIMS (0.23±0.42–>0.18±0.39)	Tremor (3 cases)

Notes: *$P<0.001$, **$P<0.0001$.
Abbreviations: AIMS, Abnormal Involuntary Movement Scale; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression; CGI-S, CGI-Severity; DIEPSS, Drug-Induced Extrapyramidal Symptom Scale; HS-PANSS, hallucination subscale of the PANSS; NPI, Neuropsychiatric Inventory; PANSS, Positive and Negative Symptom Scale.

leading to excessive response of the deafferented neurons.[37] In the central nervous system, this results in cortical hyper-excitability, a similar phenomenon observed in mechanisms of schizophrenia-like psychosis.[5] There is no established treatment for CBS. The positive result of these trials support Yokukansan as possible treatment for psychosis.

Recently, a more naturalistic 4-week, open-label study of yokukansan monotherapy for very-late-onset schizophrenia was conducted.[38] Considerable improvement of psychotic symptomatology was noticed in all 40 patients. The statistically significant reduction on psychopathology was shown in all measures, including the Brief Psychiatric Rating Scale (BPRS), CGI-Severity, and the PANSS. Scores on the Simpson-Angus Scale, Barnes Akathisia Rating Scale, and Abnormal Involuntary Movement Scale (AIMS) decreased slightly but not significantly. There was no impairment in overall cognitive function as measured by the Mini-Mental State Examination (MMSE). These

preliminary results demonstrate the possibility that yokukansan could be an effective and safe treatment option for schizophrenia.
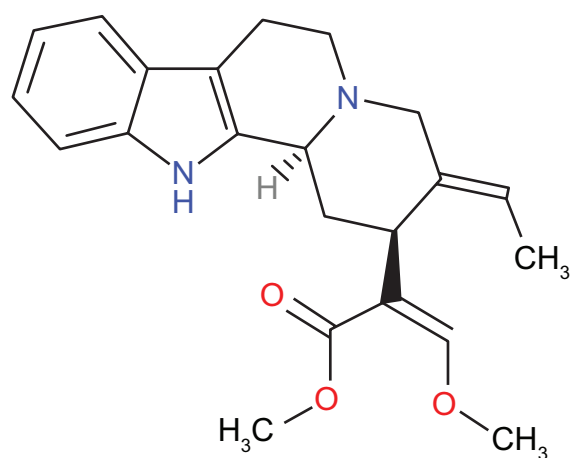
Evidence from animal studies and neurobiology also sheds light on the antipsychotic implications of yokukansan. Several neurotransmitter systems involved in the neuropsychiatric effects of yokukansan and its ingredients have important roles in schizophrenia. Yokukansan was reported to inhibit the increased release of glutamate in zinc-deficient rats, which was regarded as a neurological disease model with the perturbed glutamatergic neurotransmitter system, and a modulation function on excitatory neurotransmitters was suggested.[39] A further study revealed that yokukansan exerted a neuroprotective effect by ameliorating the dysfunction of glutamate transporters in astrocytes.[40] This was mediated by one of the constituents of yokukansan, *G. uralensis*, and its main metabolite, 18β-glycyrrhetinic acid, which can access the brain through the blood–brain barrier.[41,42] However,

excessive release of glutamate not only induces neuronal death, as described in neurodegenerative disorders,[43] but also enhances the frequency of excitatory postsynaptic potentials in cortical pyramidal cells, as observed in schizophrenia.[5,44] These processes might be reversed by yokukansan in some way.

Repeated administration of yokukansan was found to decrease expression of 5-hydroxytryptamine (5-HT)$_{2A}$ receptors in the prefrontal cortex and inhibit the head-twitch response induced by serotonin 5-HT$_{2A/2C}$ receptor agonist in mice.[45] These results suggest the involvement of the serotonin system in the psychopharmacological effects of yokukansan. Constituent analysis of yokukansan revealed that compounds with affinities for 5-HT$_{1A}$, 5-HT$_{2A}$, 5-HT$_{2C}$, and 5-HT$_7$ were only contained in *U. rhynchophylla*.[46] Further study demonstrated that geissoschizine methyl ether, a corynanthean-type alkaloid contained in *U. rhynchophylla*, had high blood–brain barrier permeability[47] and behaved as a partial agonist at the serotonin 5-HT$_{1A}$ receptor and as an antagonist at the serotonin 5-HT$_{2A}$, 5-HT$_{2C}$, and 5-HT$_7$ receptors.[48]

Geissoschizine methyl ether

Geissoschizine methyl ether is an indole alkaloid with a β-carboline structure, also called methyl (16Z,19E)-16-(methoxymethylidene)coryn-19-en-17-oate (Figure 1). The molecular formula is $C_{22}H_{26}N_2O_3$, and its molecular weight is 366.4534. β-carboline derivatives have been shown to have different affinities at different 5-HT receptors, depending on their ring substituents and ring saturation.[49] An in vivo experiment also showed that geissoschizine methyl ether could ameliorate isolation-induced increased aggressiveness and decreased sociality, a function thought to be related

Figure 1 Chemical structure of geissoschizine methyl ether.
Notes: Molecular formula: $C_{22}H_{26}N_2O_3$. Molecular weight: 366.4534 g/mol.

to 5-HT$_{1A}$ agonist.[50] Atypical antipsychotics often exhibit serotonergic properties, especially 5-HT$_{2A}$ and 5-HT$_{2C}$ receptor antagonism.[10] Activation of the 5-HT$_{1A}$ receptor has been suggested to decrease extrapyramidal symptoms and increase dopaminergic neurotransmission in the frontal cortex.[51] Although the clear role for the 5-HT$_7$ receptor is not fully understood, blockade of it could be useful in treatment of psychotic symptoms,[52] and some atypical antipsychotics, such as clozapine and risperidone, express high antagonistic affinity for this receptor.

Besides its serotonergic function, geissoschizine methyl ether has also been reported to be a partial agonist/antagonist at the cloned dopamine D$_{2Long}$ receptors with a low intrinsic activity and a partial activation response.[48] All these qualities are similar to the properties found in aripiprazole. Aripiprazole, a so-called third-generation antipsychotic, acts on D$_{2Long}$-mediated signaling pathways with multiple intrinsic activities. This functionally selective profile, combined with actions at other neurotransmitter systems, was suggested to be responsible for the development of novel antipsychotics.[11] Moreover, yokukansan has been proven to increase central acetylcholine release,[53] and this atypical antipsychotic-like property may be helpful in preserving cognitive ability in schizophrenia.[54]

Adverse events

Some reversible adverse events of yokukansan have been reported, including sedation,[22] vomiting/diarrhea, nausea, epigastric discomfort, leg edema, and hypokalemia.[28] Glycyrrhizin, contained in *G. uralensis*, is able to facilitate potassium excretion in the renal tubules, and this may result in hypokalemia.[28] There are no metabolic side effects documented. On the contrary, a large epidemiological study disclosed that the prevalence of diabetes was significantly increased for patients who received clozapine, olanzapine, and quetiapine.[55] Nonetheless, Izumi et al found that yokukansan was able to suppress lipid synthesis and reduce fat accumulation in adipocytes by modulating the transcription factors without affecting glucose uptake.[56] Considering the increased metabolic problems in patients with schizophrenia, choosing a drug without aggravation of lipid metabolism is essential in clinical practice.

Conclusion

This review of the literature highlights the possibility of yokukansan and its ingredients as new treatment options for schizophrenia. Nevertheless, correlations between the experimental environment and clinical settings may be complicated by a number of confounders. In order to bridge between basic

research and clinical applications, further studies with more sophisticated designs are necessary.

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Disclosure

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