A double-blind, placebo-controlled study of traditional Chinese medicine sarsasapogenin added to risperidone in patients with negative symptoms dominated schizophrenia

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Abstract: Objective To identify whether sarsasapogenin, a sapogenin from the Chinese medicinal herb *Anemarrhena Asphodeloides* Bunge, would augment the efficacy of risperidone and significantly improve cognitive functions in patients with negative symptoms dominated schizophrenia. **Methods** The trial was a double-blind, placebo-controlled, parallel-group design. The eligible patients were randomized into 2 treatment groups: sarsasapogenin group (sarsasapogenin plus risperidone for 8 weeks, $n = 41$) and placebo group (risperidone only for 8 weeks, $n = 39$). At the baseline, as well as at weeks 2, 4 and 8 of treatment, the therapeutic response was measured by using scales including Positive and Negative Symptoms Scale (PANSS), Wechsler Memory Scale (WMS), modified Chinese Wechsler Adult Intelligence Scale (mWAIS), Clinical Global Impression (CGI) and Brief Psychiatry Rating Scale (BPRS). The study period for each subject was 8 weeks and duration of overall trial was 2 years. **Results** Patients treated with sarsasapogenin plus risperidone demonstrated no statistically significant differences in changes in PANSS, WMS or mWAIS score at the end-point of the trial compared with patients treated with placebo plus risperidone. The incidence of treatment-emergent adverse events in patients treated with sarsasapogenin was not different from that observed in placebo group. **Conclusion** Sarsasapogenin did not augment the efficacy of risperidone in treating negative symptoms dominated schizophrenia. Sarsasapogenin at a dosage of 200 mg per day added to a flexible dosage of risperidone at 2–4 mg per day is safe and well tolerated by patients with negative symptoms dominated schizophrenia.

Keywords: schizophrenia; sarsasapogenin; risperidone; trial; double-blind

1 Introduction

Schizophrenia is a chronic and devastating mental disorder affecting approximately 1% of the population worldwide^[1,2]. The symptoms of schizophrenia are regu-

larly categorized as either positive or negative according to their appearance. Positive symptoms include hallucinations, delusions and disorganized behaviors that reflect distorted brain function, whereas negative symptoms such as anhedonia, alogia, and avolition are thought to represent a loss of brain function^[3–5]. Although the etiology of schizophrenia is still unclear, the clinical characteristics and biological features of these negative symptoms have suggested the presence of a neurodegenerative process in

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the brains of affected individuals^[6-8]. Significant cortical atrophy has been detected in schizophrenia patient brain by neuroimaging techniques, indicating a significant loss and disorientation of neurons in grey and white matter^[9,10]. Computerized tomography, magnetic resonance imaging, and cerebral blood flow studies have revealed that patients with negative symptoms dominated schizophrenia usually show reduced blood flow in the caudate nucleus and frontal lobe, reduced hippocampal size, slightly enlarged ventricles, along with other structural changes of the brain^[11-14]. These patients have a history of a prolonged prodromal period with poor social functioning before the onset of psychotic symptoms^[15,16]. The treatment of negative symptoms of schizophrenia remains a major clinical challenge as the negative symptoms respond less well to neuroleptics than do positive symptoms^[17,18].

Sarsasapogenin is an active ingredient derived from traditional Chinese medicinal herb *Anemarrhena Asphodeloides* Bunge^[19]. The chemical structure of sarsasapogenin is 5 β , 20 α , 22 α , 25s-spirostan-3 β -ol^[20]. It has been demonstrated that sarsasapogenin improves the cognitive function of animal models via a distinctive mechanism compared with that of acetylcholinesterase inhibitors (AChEIs) or muscarinic acetylcholine receptor (M receptor) agonist. Hu *et al.*^[21] found that oral administration of sarsasapogenin could significantly improve the learning ability and memory in aged rats and in neurodegenerative disease models as measured by Y-maze test and step-through test. Besides, marked increases in densities of both total M receptor and the M₁ subtype receptor were observed in the brain of animal models treated with sarsasapogenin compared with those without sarsasapogenin treatment, suggesting an alternative nootropic mechanism of sarsasapogenin. More recently, it is further demonstrated that sarsasapogenin can up-regulate M₁ receptor density in aged cells by promoting cyclic AMP responsive element-binding protein (CREB) production and phosphorylation^[22]. Sarsasapogenin is also demonstrated to exert several other effects including apoptotic^[23,24], anti-oxidant^[25] and antidepressant-like effects^[26]. Most of the mechanisms underlying these effects have not been well recognized. Never-

theless, lines of evidence suggest that sarsasapogenin may serve as a novel cognitive enhancer for neurodegenerative disorders as well as negative symptoms dominated schizophrenia, via an alternative mechanism as compared with those of AChEIs or M receptor agonist.

With the hypothesis that sarsasapogenin can ameliorate cognitive impairment of negative symptoms dominated schizophrenia, the present study aimed to determine whether sarsasapogenin could augment the effects of risperidone in patients with negative symptom dominated schizophrenia in an 8-week, double-blind, placebo-controlled, parallel-group designed clinical trial.

2 Materials and methods

2.1 Drugs Sarsasapogenin was produced by Shengzhen Tai Tai Pharmaceutical Industry, Co., LTD, and risperidone was purchased from Xian-Janssen Pharmaceutical LTD.

2.2 Subjects Adult patients (aged 18 years or over, of either sex) meeting the diagnostic criteria of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)^[27], with scores of negative symptom sub-scale higher than that of positive symptom sub-scale on the Positive and Negative Symptoms Scale (PANSS), were employed in the study^[28]. All patients had sufficient vision and hearing for compliance with test procedures, and received risperidone monotherapy at a constant dosage for at least one month prior to the trial. All the subjects were recruited and followed up in Shanghai Mental Health Center.

Patients with evidence of other psychiatric disorders or active renal, hepatic, endocrine, cardiovascular diseases were excluded from the trial. Patients with severe heart disease, severe hypertension, severe obstructive pulmonary disease, or hematological or oncological disorders were also excluded. In addition, all the patients were free of sarsasapogenin treatment within the 4 months prior to the trial. Patients taking other nootropics (except that the medication was discontinued for at least 4 weeks prior to the trial), hypnotics (except the short-acting benzodiazepines), drugs influencing cerebral blood flow, or stimulants were also excluded.

The study was conducted in accordance with the Dec-

laration of Helsinki. All participants and their legal representatives were well informed about the purpose of the investigation and informed consent was obtained from the patients or their legal representatives.

2.3 Study design A double-blind, placebo-controlled, parallel-group trial was conducted. Eligible subjects were assigned into sarsasapogenin+risperidone group and risperidone only group by a computerized completely random design. Patients received a flexible dosage (2–4 mg per day) of risperidone, and sarsasapogenin at the dosage of 200 mg per day (for the sarsasapogenin+risperidone group) or placebo of exactly the same size and color as sarsasapogenin (for the risperidone only group) for a total of 8 weeks. Each subject was assessed at baseline and at weeks 2, 4 and 8 of the treatment.

2.4 Efficacy measurements All assessments were performed by experienced clinical psychiatrists. The therapeutic response was measured by using scales as follows.

2.4.1 PANSS PANSS was a 30-item rating scale evaluating the presence/absence and severity of positive, negative and general psychopathology of schizophrenia. All 30 items were rated on a 7-point scale (1 = absent; 7 = extreme)^[28].

2.4.2 Wechsler Memory Scale (WMS) WMS was a comprehensive measurement of adult memory functioning and both auditory and visual memory. The scale was comprised of a number of subtests including information, orientation, mental control, logical memory, digits forwards, visual reproduction and associate learning^[29].

2.4.3 Modified Chinese version of the Wechsler Adult Intelligence Scale (mWAIS) mWAIS was a general adult Intelligence Quotient (IQ) test measuring verbal and performance IQ^[30].

2.4.4 Clinical Global Impression (CGI) scale CGI scale was a 3-item scale assessing treatment response in psychiatric patients. The items included severity of illness (1 = normal; 7 = extremely ill), global improvement (1 = very much improved; 7 = very much worse) and efficacy index (1 = none; 4 = outweighs therapeutic effect)^[31].

2.4.5 Brief Psychiatry Rating Scale (BPRS) BPRS was an 18-item observer-rating scale measuring the severity of

positive symptoms, general psychopathological status and affective symptoms. Each item was rated on a 7-point scale (1 = not present; 7 = extremely severe)^[32].

Primary efficacy was determined by the changes in scores of PANSS, WMS and mWAIS from baseline to the end of the trial. The endpoint rating score on CGI was used as the secondary efficacy measure.

2.5 Safety All adverse events were recorded based on the complaint of the patients as well as observations of clinicians and caregivers, in terms of duration, severity and relation with pharmacological treatment using Treatment Emergent Side effects Scale (TESS). Measurements of haemoglobin, haematocrit erythrocyte count, total and differential leukocyte and platelet counts were used to monitor hematological effects at the baseline and the endpoint of study. Similarly, clinical chemistry parameters were monitored to assess liver function (alkaline phosphates, aspartate transaminase, alanine transaminase and total bilirubin), renal function (blood urea nitrogen and creatine), metabolic function (total cholesterol, glucose, total protein and albumin) and electrolytes (sodium, potassium, chloride, calcium and phosphorus). Electrocardiography and routine urinalysis (specific gravity, dipstick chemistry, pH, protein, glucose, ketones) were also performed at the baseline and the endpoint. Vital signs for assessment included blood pressure, heart rate, body temperature, respiratory rate and body weight.

2.6 Statistical analysis Efficacy of treatment was assessed based on the combined results of each patient's last assessment during the double-blind therapy-defined study endpoint. All hypothesis tests were two-sided, and $P < 0.05$ was considered to be statistically significant. Continuous demographic variables (*e.g.* age, height and weight) were examined and compared between the 2 groups using the *t*-test, and categorical demographic variables were analyzed using the chi-square test or Fisher's exact test. Analysis of covariance (ANCOVA) method was conducted to adjust the influence of the confounding factors at baseline. The ordinal scaled data or data with multi-model distribution were subjected to the Wilcoxon-Mann-Whitney U test. Analysis of adverse events was conducted by tabulating

treatment-emergent signs and symptoms, which were defined as events that occurred during or after administration of the first dose of study medication, or became more severe during treatment.

3 Results

3.1 Patient deposition A total of 90 patients meeting the diagnostic criteria of schizophrenia according to DSM-IV were recruited in the study. The patients were then randomized into 2 treatment groups: the placebo group (risperidone only, $n = 44$) and the sarsasapogenin group (sarsasapogenin plus risperidone, $n = 46$). Of the recruited patients, 80 completed the study. The reasons for study discontinuation included the occurrence of adverse events ($n = 1$ for placebo group), uncompliance of patients ($n = 1$ for placebo group), withdrawal of consent ($n = 3$ for both placebo group and sarsasapogenin group), switch in medication ($n = 1$ for sarsasapogenin group) and physical disease ($n = 1$ for sarsasapogenin group). The final dataset

consisted of 80 patients (39 in the placebo group and 41 in the sarsasapogenin group), as shown in Fig. 1.

3.2 Baseline demographic and clinical characteristics

As shown in Table 1, there was no significant difference between placebo group and sarsasapogenin group in gender distribution, initiating factors, marital status, educational level, family history of psychotic illness, disease duration or age of disease onset, at the first admission to a psychiatric hospital. Significant differences were observed in mean age and the dosage of risperidone taken at baseline of the trial. The mean age of patients in placebo group at the onset of the trial was (55.21 ± 15.74) years, which was significantly higher than that of the patients in sarsasapogenin group $[(46.02 \pm 17.23)$ years, $P = 0.006$]. Besides, patients in sarsasapogenin group received a higher dosage of risperidone $[(3.33 \pm 0.99)$ mg/d] than did the patients in placebo group $[(2.69 \pm 0.98)$ mg/d] before trial ($P = 0.005$), although both were within the range of inclusion criteria.

The baseline measurements of PANSS, BPRS, mWAIS

Fig. 1 A diagram of patient disposition.

Table 1. Baseline demographic and clinical characteristics of the patients in both groups

	Placebo (<i>n</i> = 39)	Sarsasapogenin (<i>n</i> = 41)	χ^2 or <i>t</i>	<i>P</i>
Gender				
Male	19 (48.7%)	20 (48.8%)	0.58	0.99
Female	20 (51.3%)	21 (51.2%)		
Initiating factor				
Yes	14 (35.9%)	10 (24.4%)	1.48	0.32
No	25 (64.1%)	31 (75.6%)		
Family history of psychiatric disease				
Yes	11 (28.2%)	13 (31.7%)	0.11	0.81
No	28 (71.8%)	28 (68.3%)		
Age (years)	55.21±15.74	46.02±17.23	1.97	0.006*
Education (years)	10.31±3.1	10.59±3.54	0.34	0.72
Age of disease onset (years)	33.79±13.42	32.93±13.27	0.29	0.77
Age of first hospitalization (years)	39.00±14.87	35.98±14.05	0.93	0.35
Number of times of hospitalization	2.95±3.07	1.80±2.04	1.96	0.053
Dosage of risperidone (mg)	2.69±0.98	3.33±0.99	2.87	0.005*

**P* < 0.05

and WMS of patients were presented in Table 2. The comparison of disease severity between the 2 groups at baseline was shown in Table 3. Patients in both groups were negative symptoms dominated as shown by the PANSS. Patients in sarsasapogenin group demonstrated higher PANSS total score (*P* = 0.041) and negative score (*P* = 0.010) than did the patients in placebo group, indicating more severe negative symptoms in patients in sarsasapogenin group at baseline. In addition, there was no significant difference in PANSS positive score, BPRS, mWAIS, WMS scores or disease severity between the 2 groups.

3.3 Primary efficacy outcomes The changes in PANSS scores after treatment were presented in Table 4. Patients in both groups demonstrated improvement in negative and positive symptoms of schizophrenia over time as measured by PANSS at weeks 2, 4 and 8 of the treatment. Significantly greater decreases in PANSS total scores and negative scores were observed in patients of sarsasapogenin group at each interview, but the difference was not otherwise significant after being adjusted for the difference

in PANSS total score, negative score and dosage of risperidone taken between the 2 groups at baseline. The increases in the scores of mWAIS and WMS were similar between placebo group and sarsasapogenin group at each interview (Table 5).

3.4 Secondary efficacy outcomes The comparisons of disease severity and disease improvement between the 2 treatment groups were presented in Table 6 and Table 7. At the end of treatment, the disease severity was comparable between 2 groups as measured by CGI (*P* = 0.736, Table 6). Besides, there was no significant difference in disease improvement between placebo group and sarsasapogenin group (*P* = 0.394, Table 7).

3.5 Safety and tolerability The overall adverse events occurring during treatment in the 2 groups were presented in Table 8. Adverse events occurred in at least 5% of patients in either group, including abnormal liver function, drowsiness, weight gain, abnormal electrocardiogram, and tremor. The frequencies of most of these adverse events were comparable between the 2 treatment groups. Only

Table 2. Scores on PANSS, BPRS, mWAIS and WMS at baseline (mean $\pm$ SD)

	Placebo (<i>n</i> = 39)	Sarsasapogenin (<i>n</i> = 41)	<i>t</i> value	<i>P</i>
PANSS total score	63.92 $\pm$ 19.11	72.10 $\pm$ 15.96	-2.081	0.041*
PANSS positive score	11.74 $\pm$ 4.84	11.73 $\pm$ 4.57	0.011	0.991
PANSS negative score	22.28 $\pm$ 8.66	26.80 $\pm$ 6.49	-2.653	0.010*
BPRS score	32.97 $\pm$ 9.33	33.95 $\pm$ 7.47	-0.518	0.606
mWAIS Information	7.85 $\pm$ 3.68	7.90 $\pm$ 3.77	-0.067	0.946
mWAIS Similarities	6.72 $\pm$ 2.78	7.20 $\pm$ 2.53	-0.803	0.424
mWAIS Picture Completion	5.64 $\pm$ 3.05	6.12 $\pm$ 2.50	-0.773	0.442
mWAIS Block design	6.72 $\pm$ 3.58	8.37 $\pm$ 2.97	-2.246	0.028
mWAIS Verbal IQ	89.23 $\pm$ 13.69	89.00 $\pm$ 14.86	0.072	0.943
mWAIS Performance IQ	86.56 $\pm$ 13.30	88.34 $\pm$ 11.58	-0.638	0.525
mWAIS Total IQ	87.23 $\pm$ 13.29	87.68 $\pm$ 13.47	-0.151	0.88
WMS Experience	4.05 $\pm$ 1.05	4.10 $\pm$ 1.04	-0.20	0.844
WMS Orientation	4.03 $\pm$ 1.42	3.88 $\pm$ 1.33	0.48	0.633
WMS 1 $\rightarrow$ 100	5.74 $\pm$ 4.25	7.34 $\pm$ 3.31	-1.88	0.063
WMS 100 $\rightarrow$ 1	5.46 $\pm$ 4.66	5.56 $\pm$ 4.42	-0.10	0.922
WMS Accumulation	8.33 $\pm$ 3.89	8.15 $\pm$ 3.86	0.22	0.83
WMS Picture	4.26 $\pm$ 2.87	4.63 $\pm$ 3.05	-0.57	0.57
WMS Recognition	4.08 $\pm$ 3.39	4.95 $\pm$ 3.92	-1.07	0.29
WMS Reproductions	3.74 $\pm$ 3.55	4.15 $\pm$ 4.03	-0.47	0.637
WMS Paired Associates	3.9 $\pm$ 4.12	3.61 $\pm$ 3.85	0.32	0.748
WMS Tactile Sensation	4.44 $\pm$ 4.1	4.37 $\pm$ 3.81	0.08	0.937
WMS Apprehension	4.26 $\pm$ 2.77	4.07 $\pm$ 2.53	0.31	0.758
WMS Figural Memory	4.62 $\pm$ 3.61	6.20 $\pm$ 4.04	-1.84	0.07
Memory IQ	58 $\pm$ 21.82	56.12 $\pm$ 23.11	0.37	0.71

P* < 0.05Table 3. Comparison of disease severity between the 2 groups at baseline**

Disease severity	Placebo (<i>n</i> = 39)	Sarsasapogenin (<i>n</i> = 40)	<i>z</i>	<i>P</i>
Extremely mild	1	0	-1.770	0.077
Mild	4	5		
Moderate	19	13		
Minimally severe	15	15		
Severe	0	6		
Extremely severe	0	1		

one withdrawal in placebo group during the study was associated with adverse events, and there was no discontinuation in sarsasapogenin group resulting from adverse events. The levels of serum glucose and lipoproteins were stable in the 2 treatment groups during the trial, which suggested that sarsasapogenin had little influence on metabolism. In addition, there was no severe treatment-emergent events in either group during the treatment, indicating that sarsasapogenin added to risperidone was safe for patients with negative symptoms dominated schizophrenia.

Table 4. Changes in PANSS scores at weeks 2, 4 and 8 (mean $\pm$ SD)

	Placebo (<i>n</i> = 39)	Sarsasapogenin (<i>n</i> = 41)	<i>t</i>	<i>P</i>
Week 2				
Decrease in PANSS total score	4.23 $\pm$ 10.30	9.78 $\pm$ 11.91	-2.210	0.030*
Decrease in PANSS positive score	0.44 $\pm$ 2.78	1.50 $\pm$ 2.75	-1.715	0.090
Decrease in PANSS negative score	2.00 $\pm$ 4.16	3.88 $\pm$ 5.07	-1.806	0.075
Week 4				
Decrease in PANSS total score	8.31 $\pm$ 13.58	15.71 $\pm$ 13.06	-2.484	0.015*
Decrease in PANSS positive score	0.90 $\pm$ 4.52	2.61 $\pm$ 3.52	-1.895	0.062
Decrease in PANSS negative score	4.28 $\pm$ 5.17	6.80 $\pm$ 5.20	-2.176	0.033*
Week 8				
Decrease in PANSS total score	10.95 $\pm$ 16.13	19.98 $\pm$ 16.29	-2.489	0.015*
Decrease in PANSS positive score	1.13 $\pm$ 4.49	3.29 $\pm$ 4.08	-2.258	0.027*
Decrease in PANSS negative score	5.64 $\pm$ 6.71	9.34 $\pm$ 6.28	-2.546	0.013*

**P* < 0.05

4 Discussion

As far as we know, this is the first study to investigate the efficacy and safety of sarsasapogenin added to risperidone in the treatment of negative symptoms dominated schizophrenia.

A preclinical study has shown that sarsasapogenin can improve the learning ability and memory in aging or neurodegenerative disease rat models, and this effect is achieved by elevating the density of muscarinic acetylcholine receptor in the brain instead of inhibiting acetylcholinesterase or agonizing M receptor in these sites^[21]. Based on the possibility that schizophrenia dominated by negative symptoms and neurodegenerative diseases such as Alzheimer's disease share the mechanism of M receptor deficits, we hypothesize that sarsasapogenin may augment the efficacy of risperidone in ameliorating the negative symptoms of schizophrenia. In the present study, after administration of sarsasapogenin (200 mg per day) added to a flexible dose of risperidone for 8 weeks, patients in both placebo and sarsasapogenin groups demonstrated improvements in positive symptoms, negative symptoms, cognitive function and memory as measured by PANSS, mWAIS and WMS, but the improvements between the 2 treatment

groups were not statistically significant after being controlled for the baseline differences in clinical characteristics, indicating that sarsasapogenin dose not augment the efficacy of risperidone in treating schizophrenia dominated by negative symptoms. Although the clinical features of negative symptoms of schizophrenia appear to overlap some symptoms of neurodegenerative disorders, their underlying causes may be significantly different, which might contribute to the negative results of our investigation.

Furthermore, no severe adverse events were observed during the whole period of treatment and there was no significant difference in occurrence of adverse outcomes between the 2 treatment groups. This suggests that at the dosage of 200 mg per day, sarsasapogenin added to a flexible dosage (2–4 mg per day) of risperidone is safe and can be well tolerated for patients with negative symptom dominated schizophrenia.

Nevertheless, several limitations of this study must be taken into account when interpreting these results. Firstly, this study was conducted over a period of 8 weeks, which may be not long enough for the detection of therapeutic effects. Although patients in both groups demonstrated improvement in symptoms at each time point of interview, manifestation of the additional efficacy of sarsasapogenin

Table 5. Increase in mWAIS and WMS scores at weeks 2, 4 and 8 (mean $\pm$ SD)

	Placebo (<i>n</i> = 39)	Sarsasapogenin (<i>n</i> = 41)	<i>t</i>	<i>P</i>
Week 2				
Information	0.87 $\pm$ 1.30	1.05 $\pm$ 1.53	0.31	0.58
Similarities	0.74 $\pm$ 1.43	1.02 $\pm$ 1.51	0.73	0.396
Picture completion	1.18 $\pm$ 1.57	0.88 $\pm$ 1.29	0.89	0.35
Block design	1.13 $\pm$ 2.28	0.49 $\pm$ 1.68	2.06	0.155
Verbal IQ	3.79 $\pm$ 5.44	4.41 $\pm$ 6.87	0.20	0.657
Performance	5.79 $\pm$ 8.19	3.95 $\pm$ 7.05	1.17	0.283
Full IQ	4.87 $\pm$ 5.71	4.63 $\pm$ 6.21	0.03	0.859
Memory	12.10 $\pm$ 11.26	14.80 $\pm$ 12.07	1.07	0.304
Week 4				
Information	1.38 $\pm$ 1.53	1.44 $\pm$ 1.78	0.02	0.884
Similarities	1.44 $\pm$ 1.73	1.59 $\pm$ 1.92	0.13	0.716
Picture completion	1.85 $\pm$ 1.73	1.10 $\pm$ 1.50	4.31	0.041*
Block design	1.49 $\pm$ 2.38	0.95 $\pm$ 1.73	1.33	0.252
Verbal IQ	6.38 $\pm$ 6.25	7.39 $\pm$ 8.16	0.38	0.539
Performance	8.90 $\pm$ 9.06	6.07 $\pm$ 8.32	2.11	0.15
Full IQ	7.87 $\pm$ 6.20	7.32 $\pm$ 7.06	0.14	0.71
Memory	16.67 $\pm$ 14.70	22.15 $\pm$ 12.43	3.25	0.075
Week 8				
Information	1.62 $\pm$ 1.63	1.49 $\pm$ 1.87	0.11	0.747
Similarities	1.64 $\pm$ 1.63	1.80 $\pm$ 2.00	0.16	0.69
Picture completion	2.03 $\pm$ 1.46	1.56 $\pm$ 1.70	1.71	0.195
Block design	2.08 $\pm$ 2.52	1.10 $\pm$ 1.85	3.95	0.05
Verbal IQ	7.59 $\pm$ 6.48	7.76 $\pm$ 7.96	0.01	0.919
Performance	10.64 $\pm$ 9.52	7.61 $\pm$ 9.33	2.07	0.154
Full IQ	9.38 $\pm$ 6.36	8.44 $\pm$ 6.90	0.41	0.526
Memory	20.64 $\pm$ 16.67	23.46 $\pm$ 16.40	0.58	0.448

IQ: intelligence quotient. **P* < 0.05.**Table 6. Comparison of disease severity between the 2 groups at end-point**

Disease severity	Placebo (<i>n</i> = 39)	Sarsasapogennin (<i>n</i> = 40)	<i>z</i>	<i>P</i>
Extremely mild	6	6	-0.337	0.736
Mild	16	18		
Moderate	11	11		
Minimally severe	4	5		
Severe	2	0		

Table 7. Comparison of changes in CGI scores from baseline to end-point

Disease severity	Placebo (<i>n</i> = 39)	Sarsasapogennin (<i>n</i> = 41)	<i>z</i>	<i>P</i>
Marked improvement	6	8	-0.852	0.394
Moderate improvement	13	12		
Mild improvement	8	6		
No change	10	3		
Mild worsening	2	2		

Table 8. Adverse event occurrences in the 2 groups

Adverse events	Placebo (<i>n</i> = 44)	Sarsasapogenin (<i>n</i> = 46)
Abnormal ECG	1 (2.3%)	7 (15.2%)
Constipation	2 (4.5%)	1 (2.2%)
Abnormal liver function	6 (13.6%)	1 (2.2%)
Muscle rigidity	2 (4.5%)	1 (2.2%)
Akathisia	1 (2.3%)	2 (4.3%)
Blurred vision	1 (2.3%)	1 (2.2%)
Drowsiness	3 (6.8%)	2 (4.3%)
Tremor	1 (2.3%)	4 (8.7%)
Weight gain	3 (6.8%)	0 (0)
Headache	1 (2.3%)	0 (0)
Agitation	1 (2.3%)	0 (0)
Hypotension	1 (2.3%)	0 (0)
Dry in mouth	2 (4.5%)	0 (0)
Abnormality in urine	1 (2.3%)	0 (0)
Reversed movement	1 (2.3%)	0 (0)
Abnormal blood profile	0 (0)	1 (2.2%)
Tardive dyskinesia	0 (0)	1 (2.2%)
Depression	0 (0)	1 (2.2%)
Decreased activities	0 (0)	1 (2.2%)

ECG: electrocardiogram.

on negative symptoms of schizophrenia may need a longer period of time, which may contribute to a false-negative result of our investigation. Secondly, symptoms of schizophrenia are not always in a stable status. On the contrary, they, especially the positive symptoms, undergo a relapsing-and-remitting course. We presume that the measurement of effects of sarsasapogenin may be affected by the fluctuation in symptoms of the patients treated. Finally, in the present study, all the patients received sarsasapogenin administration at a common, fixed dosage, so we can not rule out the possibility that the blood concentration of sarsasapogenin did not reach the therapeutic level in most of the patients due to the pharmacokinetic variability among different individuals, which may influence the assessments of efficacy of sarsasapogenin. Considering the fact that no severe adverse event was observed in our study, we confer that patients with schizophrenia dominated by negative

symptoms may demonstrate greater improvement without apparent side effects when given a higher dosage of sarsasapogenin.

In conclusion, this study found that sarsasapogenin at a dosage of 200 mg per day did not significantly augment the effects of risperidone in treating cognitive deficits of patients with negative symptoms dominated schizophrenia. Sarsasapogenin treatment did not significantly affect the symptom severity either. The administration was not associated with or complicated by severe adverse events, indicating that the dosage given here is safe and well tolerated by patients with schizophrenia dominated by negative symptoms. A longer period of trial on the effect of sarsasapogenin at flexible doses in a larger size of subjects is required to fully elucidate the effects of sarsasapogenin on schizophrenic symptoms as well as on the cognitive improvements.

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利培酮合并知母皂甙元治疗阴性症状为主的精神分裂症的双盲随机对照研究

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摘要: **目的** 探讨知母皂甙元是否能增强利培酮的治疗作用, 以及两者联用是否能显著提高阴性症状为主的精神分裂症病人的认知功能。**方法** 本研究采用双盲、安慰剂对照的平行设计方案。研究对象随机分为知利培酮合并母皂甙组($n = 41$)和利培酮合并安慰剂组($n = 39$), 在治疗前及治疗第2、4、8周, 分别对患者进行阳性与阴性症状量表(Positive and Negative Symptoms Scale, PANSS)、韦氏记忆量表(Wechsler Memory Scale, WMS)、韦氏简式智力量表(modified Chinese Wechsler Adult Intelligence Scale, mWAIS)、简明精神量表(Brief Psychiatry Rating Scale, BPRS)和临床疗效总评量表(Clinical Global Impression, CGI)评定。每位患者共随访8周, 整个研究持续2年。**结果** 在治疗结束时, 两组在PANSS、WMS及mWAIS的减分上无统计学差异, 两组间不良事件发生率亦无明显差异。

结论 知母皂甙不会增强利培酮对阴性症状为主的精神分裂症的治疗作用。给予知母皂甙(200 mg/d)合并利培酮(2–4 mg/d)对治疗阴性症状为主的精神分裂症是安全及能够被耐受的。

关键词: 精神分裂症; 知母皂甙; 利培酮; 临床试验; 双盲随机