A Randomized, Placebo-controlled, Double-blind Study on the Effects of SZL on Patients With Mild to Moderate Depressive Disorder With Comparison to Fluoxetine

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Abstract

Objective: Kaixinsan (KXS) decoction, as an ancient's herbal formula, has been demonstrated to be active in various animal models resembling human depression with multi-target effects. This very first study evaluated the efficacy and tolerability of Shen Zhi Ling (SZL) tablets (KXS preparation), compared with fluoxetine (FLX, positive comparator), in patients with mild to moderate depressive disorder.

Methods: In this randomized double-blind parallel-group study, 156 patients with mild to moderate depression without taken any antidepressants in the past 6 months or 4 straight weeks were randomized to receive either 3.2g/d SZL plus 20mg/d FLX placebo (SZL group) or 20mg/d FLX plus 3.2g/d SZL placebo (FLX group), for 8 weeks. Their clinical presentations and some metabolic indexes were assessed during the 8 weeks visiting period.

Results: Patients in SZL group showed a statistically significant improvement after 8 weeks of treatment in HAMD-17 score (18.79 ± 2.09 to 4.43 ± 4.71 , $p < 0.001$) and self-rating depression scale (SDS) score (58.49 ± 8.89 to 39.84 ± 12.09 , $p < 0.001$), but not in N-back total respond time (1145.55 ± 608.26 to 1128.47 ± 387.49 , $p > 0.05$). In addition, no significant difference at 8 weeks of treatment was found between SZL and FLX groups in SDS score (39.84 ± 12.09 vs. 36.63 ± 12.44) and N-back respond time (1128.47 ± 387.49 vs. 1089.43 ± 352.08) as well as reduction of HAMD-17 score (14.79 ± 4.88 vs. 15.24 ± 4.29) ($p > 0.05$ for all). However, the serum APOB, APOC3 and ALB levels and HDL-C/LDL-C ratio decreased significantly in patients after SZL treatment, while only APOB/APOA1 ratio decreased significantly in FLX group. Other metabolic indexes did not alter significantly after treated with SZL or FLX.

Conclusion: The efficacy and safety profile of SZL are comparable to that of fluoxetine in patients with mild to moderate depression. The beneficial effect of SZL is probably associated with improvement of lipid metabolic balance.

1. Introduction

Depression as one of the diseases that significantly degrade person's quality of life and produce functional impairments was the fifth global leading cause of years lived with disability from 1990 to 2016 ^[1]. The main underlying neurobiological mechanisms include altered neurotransmission, chronic stresses-induced abnormality of hypothalamus-pituitary-adrenal (HPA) axis, inflammation, decreased neuroplasticity and network dysfunction ^[2]. Recently studies have suggested a possible relationship between abnormal metabolism and depression. Actually, nonspecific disease mechanisms contribute to the metabolic syndrome–psychiatric disease comorbidity in large part. Individuals with metabolic syndrome have a higher risk to develop depressive disorders than those without. Using metabolic abnormalities to predict the onset and state of depression has been confirmed to be reliable ^[3]. On the contrary, disorders in lipid metabolism and increased atherogenicity may prime patients with mood disorders to developed metabolic disorders ^[4]. Depressed patients with significantly high level of serum oxidized-LDL-C antibodies resulted from elevated lipid peroxidation in youth with mood disorders have increased risk of early CVD ^[5].

The precise link of lipid profile to depression has not been well established. Thus, longitudinal studies in other settings are needed to strengthen the evidence for a causal relationship. Currently, there are three related

hypotheses in this regard. First, cortisol and glucocorticoid receptor (GR) as the main elements of the HPA-axis can increase the risk of hyperlipidemia and play important roles in depression [6, 7]. Similar hypothesis that elevated basal cortisol concentrations and lower circadian cortisol variability induce dyslipidemia in patients with depressive or anxiety disorders has also been proposed [8]. Secondly, changes in the lipid composition of cell membrane can modulate the microenvironment and consequently the function of its proteins, e.g. neurotransmission in brain, an organ with the highest lipid concentration in the body. The effect of ω -3 polyunsaturated fatty acids (ω -3-PUFA) in affective disorders attributes to their action on neurotransmission [9]. At last, adipose tissue produced cytokines like IL-6 and TNF α , which activate nuclear factor-kappa B (NF- κ B) pathways involving in inflammation, can modulate lipid metabolism, hyperglycemia and depression [5, 9].

Currently, the pharmacotherapy of depression includes antidepressants such as selective serotonin reuptake inhibitors (SSRIs). However, the above agents are associated with multiple adverse effects, such as insomnia, sexual dysfunction, weight gain, diarrhea, constipation, headache, and nausea, and thereby have poor tolerability in depressed patients [10, 11]. In addition, as one of SSRIs, fluoxetine (FLX) exerts a side effect on lipid index and balance [12, 13]. Traditional Chinese medicine is one of the commonly used complementary and alternative medicine therapies for depression [14]. It is especially popular in treatment for some comorbidity of depression and metabolic syndrome.

Shen Zhi Ling (SZL) tablet, a proprietary Chinese medicine formulated from a Kaixinsan (KXS) decoction, is composed of Renshen (Panax Ginseng), Fuling (Poria Cocos), Yuanzhi (Polygala Tenuifolia), and Shichangpu (Acorus Tatarinowii) at a ratio of 3:3:2:2 [15, 16, 17]. Its treatment has been demonstrated to be active in various animal experimental models resembling some features of human depression [18, 19] and a small size clinical study [20]. Researchers have found that KXS has multi-effect targets and could promote synaptogenesis via inducing synaptic protein expressions and increasing nerve growth factor binding in rat brain and improve the feedback control of HPA axis response by restoring corticosterone level in basal and stress conditions [18, 21]. In addition, proteomic and metabolomics analysis has indicated that SZL regulates several signal pathways and targets involved in lipid metabolism disorders, reduces the levels of serum TC, TG, free fatty acid (FFA) and apolipoprotein C3 (APOC3), and elevates the level of HDL-C in depression animal models [22, 23].

Based on the above, we, for the first time, conducted a randomized, double-blind, parallel-group case study to 1) evaluate the efficacy and tolerability of SZL in patients with mild to moderate depressive disorder, 2) compare its effects with positive comparator fluoxetine (FLX) and 3) investigate its additional advantages on lipid metabolic index in patients.

2. Methods And Design

2.1. Study design

The present trial is a randomized, controlled, intervention, double-blind study with 2 parallel groups including a total of 156 individuals. The study protocol was approved by Ethics Committee of Xijing Hospital of The Fourth Military Medical University of the Chinese people's Liberation Army (Xi'an China, Ethical approval No. YS20150507-4), and written informed consent was obtained from all patients. The eligible patients suffering

from mild to moderate depression were equally randomized into the following two groups, SZL Group (SZL plus FLX placebo) vs. FLX group (FLX plus SZL placebo). In observation period of 8 weeks, the therapeutic efficacy was evaluated by HAMD^[24], SDS^[25], and N-back task score. Besides, the serum lipid indexes were also evaluated at baseline and 8 weeks.

2.2. Participants recruitment

From December 2015 to April 2018, 180 patients were treated in the Department of Psychosomatic Xijing Hospital of the Fourth Military Medical University and the 261 Hospital of the Chinese people's Liberation Army (PLA Mental Health Center). Patients were required to provide their medical history, receive a physical examination and laboratory safety tests. The inclusion and exclusion criteria are shown in Table 1. All study-related information was stored securely with limited access. Laboratory specimens were identified by a coded identification to maintain participant confidentiality ^[26].

Table 1
Inclusion and exclusion criteria

Inclusion criteria
1 18–75 years of age, male or female, voluntarily participated in the trial and signed the informed consent form;
2 The patients who were diagnosed with mild to moderate depression with a HAMD score of 17–24 met the Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV) criteria for diagnosis of depression;
3 In accordance with the diagnostic criteria of TCM syndrome of deficiency of heart and spleen;
4 Conform to clinical laboratory tests within the normal range (e.g., blood pressure, heart rate, blood and urine tests, hepatic and renal function tests, and electrocardiograms).
Exclusion criteria
1 History of suicide or any other serious mental illness;
2 Take any antidepressants or lipid-lowering drugs for 4 consecutive weeks or in the past 6 months;
3 Pregnant or lactating women or those planning pregnancy;
4 Active psychotherapy is not allowed before and during the trial; Serious cardiovascular, cerebrovascular, hepatic, renal, or thyroid diseases; Hypersensitivity to fluoxetine or herbal compounds;
5 History of addiction or substance abuse;
6 Those who have participated in clinical trials of other drugs within 30 days.

2.3 Randomization

Randomization was computer-generated with a 1:1 allocation ratio and a block size range of 4. The drug numbers were obtained in the order from small to large according to the order of joining the group in treatment. In the process of the above experiments, researchers, data managers, statisticians and monitors were all in a blind state. There is no difference in shape, size, texture, color and smell between fluoxetine and placebo tablets, SZL and its placebo as well.

2.4. Interventions and group assessment

Participants were randomized into SZL and FLX groups on a 1:1 ratio. Based on previous dose response results from preclinical studies and TCM clinical trials ^[27, 28] ^[29], the dosage of fluoxetine and SZL tablets had been proved as a relatively safe and efficient standard. Patients in SZL groups received 3.2 g/d SZL (0.8 g, BID, No. 141001, provided by Beijing YueKangKaiYue pharmaceutical co. LTD) and 20 mg/d FLX placebo. Patients in FLX groups were given 3.2 g/d SZL placebo and 20 mg/d FLX (10 mg, BID, No. 201410102, provided by ChangZhouSiYao pharmaceutical co. LTD). Both the groups' safety was evaluated by changes in vital signs and adverse events reported by the patient or observed by the psychiatrist during 8 weeks periods.

2.5. Clinical Evaluation

All the researchers were trained in the use of diagnostic procedures and rating scales in a standardized manner by the same expert before the study. Most researchers have previously experience in diagnosis of mental illness and have participated in clinical trials of depression disorders.

Primary outcomes

The severity of depressive symptoms was measured by trained psychiatrists using the 17-item HAMD [19] at baseline (week 0), week 4, and week 8. Besides, the curative effect of each treatment stage was analyzed and evaluated in accordance with HAMD. The changes of the HAMD-17 score between baseline and the final examination at week 8 were specified as primary outcome measures of treatment efficacy.

Secondary outcomes

Further standardized scales assessed as secondary efficacy outcome measures included the self-rating depression scale (SDS) as a subjective feelings reflection of the subjects which was mainly applicable to adults with depressive symptoms, and the N-back evaluation, as a cognitive function assessment for the performances of working memory by paradigm a visual letter task with up to six load factors ^[30], at the right time line.

2.5. Laboratory Measurements

Blood samples were collected from each subject at baseline and week 8. Serum albumin (ALB), fasting plasma glucose (FPG), uric acid (UA), triglyceride (TG), total cholesterol (TC), total bilirubin (TBIL), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), lipoprotein A1 (ApoA1), lipoprotein B (ApoB), and lipoprotein E (ApoE) were assayed using a fully automated biochemistry analyzer (Roche Cobas 6000, Germany) at the laboratory of Chinese PLA General Hospital. ApoC3 was measured by Western Blotting, performed as previously described ^[22].

2.6. Statistical Analysis

Statistical analysis was performed using SAS software version 9.4 (SAS Institute Inc). Generally, differences of continuous variables between groups were assessed by Student's t-test, and differences of continuous variables within a group were compared by paired t-test. Differences of discrete variables were analyzed by Wilcoxon test or chi-squared test. Primary efficacy analysis was carried out with the full analysis set (FAS) comprising all patients randomized with at least one post-baseline efficacy rating (intention-to-treat principle) and per-protocol analysis (PP) was also conducted. The missing data was estimated by the last observed

carried forward (LOCF) with at least one post-treatment evaluation^[31]. Data are reported as mean ± standard deviation. $p < 0.05$ was considered statistically significant for all analysis.

3. Results

3.1. Baseline data: SZL vs FLX

A total of 156 patients were included and assessed for eligibility. Among them, 144 (SZL 73 vs. FLX 71) were randomized and treated, 129 patients were enrolled in the complete analysis set during treatment and 121 patients in the per-protocol analysis. Figure 1 shows the participants’ assessment flowchart and Table 2 summarizes the basic demographic and clinical features of patients in the two groups. The results showed no significant difference at baseline between SZL and FLX groups in age (47.14 ± 14.29 vs. 46.03 ± 11.92 years old, $p > 0.05$), HAMD score (18.79 ± 2.09 vs. 18.53 ± 1.95 , $p > 0.05$) and other indexes.

Table 2 Demographic and efficacy outcome measures at baseline (full analysis sets; absolute frequency and % or mean ± SD, two sided P-values)			
	SZL(n = 63)	FLX (n = 66)	p
Sex male/female	24 ± 38.10 /39 ± 61.90	22 ± 33.33 /44 ± 66.67	0.57 ^p
Age(years)	47.14 ± 14.29	46.03 ± 11.92	0.73 ^z
Height (m)	164.28 ± 8.35	164.63 ± 8.58	0.82 [*]
Weight(kg)	66.82 ± 11.16	69.33 ± 17.01	0.46 ^z
HAMD-17 total score	18.79 ± 2.09	18.53 ± 1.95	0.34 ^z
SDS assessment score	58.49 ± 8.89	59.83 ± 9.79	0.43 [*]
N-Back total respond time	1145.55 ± 608.26	1213.70 ± 531.17	0.59 ^z
HAMD-17: Hamilton Depression Rating Scale-17, SDS: self-rating depression scale; [*] : t-test, ^z : wilcoxon-test, ^p :chi-squared test.			

3.2. Changes of HAM-D scores and SDS scores after SZL or FLX treatment

In both SZL and FLX groups, a general improvement was seen continuously in the clinical features throughout the entire duration of treatment, as reflected as obvious reduction in the HAMD scores at both 4 and 8 weeks in comparison with baseline obtained with either paired t-test (4 weeks) or Wilcoxon-test (8 weeks) (Fig. 2A).

HAM-D17 score of SZL group reduced significantly from 18.79 ± 2.09 at the baseline to 8.27 ± 4.54 and 4.43 ± 4.71 at 4 weeks and 8 weeks of treatment, respectively ($p < 0.001$ for both, Fig. 2A & Table 3). Similarly, HAM-D17 score of FLX group also reduced significantly from 18.53 ± 1.95 at the baseline to 7.29 ± 5.02 and $3.30 \pm$

4.24 at 4 weeks and 8 weeks of treatment, respectively ($p < 0.001$ for both, Fig. 2A & Table 3). The reductions in HAM-D17 scores at 8 weeks in both groups were comparable (14.79 ± 4.88 vs. 15.24 ± 4.29 , $p > 0.05$) (Table 3).

Table 3
Efficacy outcome measures at week 8 (FAS; mean $\pm$ SD, and two-sided p-values)

category	index	SZL(n = 63)	FLX(n = 66)	p
Depression	HAM-D17 total score	4.43 ± 4.71	3.30 ± 4.24	0.12^z
	HAM-D17 score reduction (PPS)	14.79 ± 4.88	15.24 ± 4.29	0.64^z
	SDS assessment score	39.84 ± 12.09	36.63 ± 12.44	0.08^z
	SDS score reduction	18.82 ± 14.23	23.05 ± 13.00	0.10^*
Cognition	N-Back total respond time	1128.47 ± 387.49	1089.43 ± 352.08	0.74^z
	N-Back accuracy rate	69.44 ± 18.18	70.46 ± 20.60	0.55^z
HAM-D-17: Hamilton Depression Rating Scale-17, SDS: self-rating depression scale; *: t-test, ^z : wilcoxon-test.				

Table 4
Comparison Efficacy of SZL and FLX on metabolic status between baseline and week8 (full analysis sets;
mean $\pm$ SD, two sided p-values

variables	SZL group (n = 28)			Fluoxetine group (n = 38)			Difference in outcome measures between SZL and FLX groups	
	Baseline	week8	p	Baseline	week8	p	β (95% CI)	p
FPG(mmol/L)	6.25 $\pm$ 2.45	5.92 $\pm$ 1.08	0.43	5.84 $\pm$ 1.39	5.88 $\pm$ 1.22	0.64	-0.37 $\pm$ 0.42[-1.21,0.47]	0.38
ALB(g/L)	49.18 $\pm$ 3.62	47.56 $\pm$ 3.88	0.03*	46.85 $\pm$ 4.78	46.63 $\pm$ 4.32	0.56	-1.39 $\pm$ 1.01[-3.41,0.62]	0.17
TBIL(umol/L)	10.81 $\pm$ 5.57	10.35 $\pm$ 5.03	0.67	10.15 $\pm$ 4.83	9.71 $\pm$ 4.00	0.86	-0.02 $\pm$ 1.07[-2.15,2.11]	0.99
UA(umol/L)	304.36 $\pm$ 74.16	299.94 $\pm$ 63.11	0.67	298.50 $\pm$ 82.14	304.33 $\pm$ 84.94	0.74	-10.24 $\pm$ 14.74[-39.69,19.21]	0.49
TC(mmol/L)	4.77 $\pm$ 1.05	4.56 $\pm$ 0.97	0.08	4.36 $\pm$ 0.95	4.26 $\pm$ 0.95	0.84	-0.11 $\pm$ 0.16[-0.42,0.20]	0.48
TG(mmol/L)	1.72 $\pm$ 1.07	1.76 $\pm$ 0.80	0.84	1.60 $\pm$ 0.88	1.67 $\pm$ 1.12	0.76	-0.04 $\pm$ 0.20[-0.44,0.36]	0.85
LDL-C(mmol/L)	2.74 $\pm$ 0.90	2.52 $\pm$ 0.76	0.12	2.45 $\pm$ 0.83	2.39 $\pm$ 0.86	0.86	-0.16 $\pm$ 0.14[-0.45,0.12]	0.26
HDL-C(mmol/L)	1.25 $\pm$ 0.38	1.24 $\pm$ 0.37	0.72	1.13 $\pm$ 0.27	1.14 $\pm$ 0.30	0.89	-0.03 $\pm$ 0.06[-0.15,0.08]	0.58
APOAI(g/L)	1.64 $\pm$ 0.31	1.61 $\pm$ 0.30	0.43	1.48 $\pm$ 0.26	1.50 $\pm$ 0.25	0.63	-0.05 $\pm$ 0.05[-0.15,0.05]	0.34
APOB(g/L)	0.84 $\pm$ 0.21	0.80 $\pm$ 0.18	0.02*	0.79 $\pm$ 0.21	0.76 $\pm$ 0.21	0.58	-0.02 $\pm$ 0.03[-0.07,0.03]	0.39
APOE(mg/dL)	26.81 $\pm$ 108.75	6.08 $\pm$ 2.57	0.32	6.47 $\pm$ 5.66	7.50 $\pm$ 11.15	0.12	-21.76 $\pm$ 17.68[-57.07,13.56]	0.22
HDL-C/LDL-C	2.31 $\pm$ 0.79	2.15 $\pm$ 0.76	0.04*	2.29 $\pm$ 0.96	2.19 $\pm$ 0.84	0.11	0.01 $\pm$ 0.03[-0.04,0.06]	0.71
APOB/APOAI	0.53 $\pm$ 0.14	0.51 $\pm$ 0.12	0.11	0.55 $\pm$ 0.17	0.52 $\pm$ 0.15	0.02*	0.01 $\pm$ 0.02[-0.03,0.05]	0.66
FPG: fasting plasma glucose, ALB: Serum albumin, UA: uric acid, TG: triglyceride, TC: total cholesterol, TBIL: total bilirubin, LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, ApoA1: lipoprotein AI, ApoB: lipoprotein B, ApoE: lipoprotein E.*: t-test,*p < 0.05, ** p < 0.01.								

SDS score of SZL group significantly decreased from 58.49 $\pm$ 8.89 at the baseline to 48.27 $\pm$ 11.76 and 39.84 $\pm$ 12.09 at 4 weeks and 8 weeks of treatment, respectively. Similarly, SDS score of FLX group also decreased from 59.83 $\pm$ 9.79 at the baseline to 45.94 $\pm$ 12.32 and 36.63 $\pm$ 12.4 at 4 weeks and 8 weeks of treatment, respectively. There were no significant differences in SDS scores at both 4 and 8 weeks (p > 0.05) and in SDS score reduction at 8 weeks of treatment (18.82 $\pm$ 14.23 for SZL vs. 23.05 $\pm$ 13.00 for FLX, p > 0.05) between SZL and FLX groups (Table 3 & Fig. 2B).

Working memory is a memory system that temporarily processes and stores information with limited energy. N-back task can manipulate the working memory load by controlling the interval value of current value “N”, so as to investigate the processing mechanism of working memory under different memory loads. Our results of N-back task showed that neither SZL nor FLX improved total respond time and accurate rate after 8 weeks treatment, and no significant differences in N-Back total respond time (1128.47 ± 387.49 for SZL vs. 1089.43 ± 352.08 for FLX, $p > 0.05$) and N-Back accuracy rate (69.44 ± 18.18 for SZL vs. 70.46 ± 20.60 for FLX, $p > 0.05$) at 8 weeks of treatment between SZL and FLX groups (Figs. 2C&2D).

3.3. Lipid analysis

Lipid levels were analyzed after 8 weeks of treatment in both groups.

ALB and APOB levels decreased significantly from 49.18 ± 3.62 and 0.84 ± 0.21 at the baseline to 47.56 ± 3.88 and 0.80 ± 0.18 at 8 weeks of treatment in SZL group, respectively ($p < 0.05$ for both), but didn't change significantly in FLX group ($p > 0.05$). Additionally, HDL-C/LDL-C ratio decreased significantly from 2.31 ± 0.79 at the baseline to 2.15 ± 0.76 at 8 weeks of treatment in SZL group ($p < 0.05$), but only slightly from 2.29 ± 0.96 at the baseline to 2.19 ± 0.84 at 8 weeks of treatment in FLX group ($p > 0.05$). By contrast, APOB/APOA1 ratio decreased only slightly from 0.53 ± 0.14 at baseline to 0.51 ± 0.12 at 8 weeks of treatment in SZL group ($p > 0.05$), but significantly from 0.55 ± 0.17 at the baseline to 0.52 ± 0.15 at 8 weeks of treatment in FLX group ($p < 0.05$). Other indexes (FPG, TBIL, UA, TC, TG, HDL-C, LDL-C, APOA1, APOE) showed no significant differences in both groups during the treatment.

Western blot analysis revealed that serum APOC3 level decreased significantly after 8 weeks of treatment in SZL group ($p < 0.05$), but not in FLX group ($p > 0.05$). In addition, there was no statistical difference in APOC3 between the two groups at the end of the treatment (Fig. 3).

3.4. Safety analysis

Among the 156 enrolled subjects, 144 subjects including 73 in SZL group and 71 in FLX group who had complete documented data including at least one follow-up were eligible for safety evaluation. Out of the 73 patients in SZL group, adverse events occurred in 6 patients and adverse drug reactions occurred in 3 patients. Out of the 71 patients in FLX group, adverse events occurred in 12 patients and adverse drug reactions occurred in 10 patients. There were no severe adverse events taking place in both groups (Table 5).

Table 5
Patients with adverse events.

Adverse events		SZL(n = 73)	FLX(n = 71)
adverse drug reactions		3	10
severe adverse events		0	0
adverse events		6	12
adverse event symptoms	gastrointestinal reaction	2	5
	granulopenia	0	1
	xerostomia	2	2
	hyperlipemia	1	1
	dizziness	1	1
	fatigue	0	1
	headache	0	1
Safety set(SS), a data set for safety analysis, including all randomly enrolled, drugged, and documented at least one safety follow-up. SS contained 144 cases, 73 cases in trial group, 71 cases in control group.			

4. Discussion

The results obtained in this randomized, placebo-controlled, double-blind study provide insights into the use of SZL to treat patients with depression. First, the results indicated that SZL is an effective and safe drug for patients with mild to moderate depression. Second, SZL exhibits an antidepressant effect comparable to FLX at 8 weeks of treatment and is well tolerated by patients with mild to moderate depressive disorder. In addition, SZL treatment significantly reduces the levels of serum ALB, APOB and APOC3 as well as HDL-C/LDL-C ratio, suggesting that it might help balance the disorder of lipid metabolism caused by depression.

Previous studies have shown that natural plants or traditional Chinese medicine (TCM) alone or in combination with routine treatments are very effective in treatment of depression as they can significantly reduce HAMD scores. Xiaoyao pills combined with fluoxetine significantly decreased HAMD scores from 8.43 ± 2.01 to 3.50 ± 1.53 in 6 weeks^[32]. Shuganjiyu capsule was more effective than Citalopram and reduced HAMD scores from 22.7 ± 2.8 to 6.5 ± 4.3 in 6 weeks^[33]. Bushenshuganhuaajifang also significant decreased HAMD scores from 26.97 ± 8.46 to 16.94 ± 7.05 in 8 weeks^[34]. However, most TCM studies were small size studies without placebo control. KXS is a famous ancient herb and has been widely used to treat mental illness since Tang Dynasty in China. Many pharmacological and mechanism studies in recent two decades have approved its anti-depressive effect in animals and patients and demonstrated its multi-target regulation on traditional neurotransmitters, HPA axis and CREB-BDNF pathway^[16, 35, 36]. As an easy taking preparation of KXS, SZL is prepared using new crude prescription according to the characteristics of modern clinical medicines and improved traditional preparation technology. To our best knowledge, this study is the very first randomized, placebo-controlled, double-blind, parallel-group study on SZL. Consistent with previous studies on KXS, 8 weeks

of SZL treatment significantly decreased HAMD scores from 18.79 ± 2.09 to 4.43 ± 4.71 with minor adverse reaction, and demonstrated efficacy and safety comparable to FLX and other TCM in patients.

With our understanding on anti-depressive mechanisms deepening, it is well accepted that depression or anti-depressive treatment is related to metabolic abnormalities. FLX has side effects to increase serum TG, TC and LDL-C levels in depression mice model^[12], accumulate lipids in primary mouse hepatocytes via enhancing acetyl-CoA carboxylase 1 (ACC1) and fatty acid synthase (FAS) expression^[13] and alter human metabolism^[13, 37]. Clomipramine intervenes glycolysis and glycolysis in mice model^[38]. Paroxetine is a kind of SSRIs that mediate SERT deficiency can lead to adiposity and abnormal glucose metabolism^[39, 40]. Different from the above study on FLX, our results showed that FLX treatment significantly decreased APOB/APOA1 ratio while did not alter lipid indexes TG, TC, HDL-C, LDL-C, FPG, ALB, TBIL, UA, APOA1, APOB and APOE.

TCM with the advantages of multi-components, multi-targets and fewer adverse reactions might have desirable therapeutic effects on complicated depression with metabolic diseases. TCM can not only improve depression, but also regulate serum lipids and glucose levels, anti-lipid peroxidation and anti-atherosclerosis, in addition to enhancing cognition^[41–45]. Our previous studies using iTRAQ and RNA sequencing methods found that KXS (SZL) regulates not only the brain neural pathway and target, but also many genes and proteins related to lipid metabolism and cardiovascular system, such as thymosin Beta-4 (a biomarker of heart protection and heart failure), ADIPOQ (a target of blood lipid, diabetes and vascular endothelial damage), and apolipoproteins (APOA1, APOC1, APOC3, etc)^[22, 23]. Partly consistent with previous reports, our current study showed that SZL reduced the level of APOB and APOC3, as well as the ratios of HDL-C/LDL-C and APOB/APOA1. High APOB level is corresponding to high CES-D score in type 1 diabetes patients with mild to moderate or severe depressive symptoms^[46]. In addition, high serum ApoB level is also negatively correlated with delayed memory decline owing to its relation to the dysfunctions of lipid peroxidation, malondialdehyde (MDA) and immune system^[47]. The ratios of HDL-C/LDL-C and APOB/APOA1 are significantly correlated with depression and cardiovascular diseases^[48–50]. Abundant serum albumin which is related to cardiovascular disease^[51] is significantly decreased in depressive patients^[52]. APOC3 is correlated with risk of adverse events (AD)^[53] and associated with depression^[54]. These together indicate that SZL could improve the abnormalities of lipid metabolism in patients with depression to some extent and suggest that KXS exerts its antidepressant effects by regulating the signaling pathways involved in lipid metabolism disorders.

Limitations

Although our study provided an available assessment of SZL in the treatment of depression, it still had some defects. In spite of the advantage of placebo control used in the experiment, the number of cases included in the trial was limited. In addition, lipid-related evaluation was insufficient and the correlation between lipid level and response rate was absent. Due to ethical reasons, subjects with different degrees of mild to moderate depression were included, which could lead to a certain degree of deviation. Therefore, it is unclear whether patients with severe or other types of depression can also benefit from SZL treatment. Moreover, the period to observe metabolic indexes was short. Therefore, whether it may have a prognostic value in predicting SZL treatment responses needs to be investigated in a larger patient population.

Conclusions

To sum up, we found that SZL has efficacy and safety profile comparable to FLX in treatment of patients with mild to moderate depression. But in contrast to FLX, which did not significantly improve the levels of TC, TG, HDL-C, LDL-C, APOA1, APOB, APOE, TBIL, ALB, UA, FPG and APOC3 after 8 weeks of treatment, SZL treatment markedly down-regulated the levels of ALB, APOB and APOC3 as well as the ratio of HDL-C/LDL-C. It is possible that SZL would be more beneficial to depressed patients with metabolic disorder (e.g. heart disease). Further clinical studies are needed examine whether SZL treatment in combination with other antidepressant drugs may help improve their treatment efficacy.

Declarations

Ethical Approval and Consent to participate

The study protocol was approved by Ethics Committee of Xijing Hospital of The Fourth Military Medical University of the Chinese people's Liberation Army (Xi'an China, Ethical approval No. YS20150507-4), and in accordance with Helsinki declaration, written informed consent was obtained from all patients.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

Yuan Hu and Yichen Wang conducted statistical analysis and prepared the manuscript. Yichen Wang, Chao Chen, Wenshan Yang and Weiyu Zhu recruited subjects and collected samples. Yuan Hu and Ping Liu edited the manuscript and provided the funding. All authors have performed the experiments and approved the final manuscript.

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Figures

Figure 1

Summary of the enrollment and follow-up data collection analysis for the trial. Data missing or incomplete occurred at the onset and process of the trial due to all kinds of reasons.

Figure 2

Medication for depression with SZL has the same effect as FLX. A. a clear downward trend of HAM-D17 total score appeared in both groups (SZL vs. FLX); B. Effect of SZL and FLX on SDS standard score in 4 or 8 weeks (Mean $\pm$ SD); C. Effect of SZL and FLX on N-Back total respond time in 4 or 8 weeks (Mean $\pm$ SD); D. Effect of SZL and FLX on N-Back accuracy rate in 4 or 8 weeks (Mean $\pm$ SD). # $P < 0.05$, ## $P < 0.01$, ### $P < 0.001$ wilcoxon-test, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ paired t-test, 4 or 8 week vs. baseline within group; SZL—Shen Zhi Ling FLX—Fluoxetine.

Figure 3

Effect of SZL and FLX on expression of APOC3 at 8 weeks. * p < 0.05 , ** p < 0.01 Wilcoxon-test.