TRADITIONAL AND INTEGRATIVE MEDICINE

Trad Integr Med, Volume 7, Issue 3, Summer 2022

Original Research

Evaluation of the Effect of Alkaloid Berberine on the Positive and Negative Symptoms of the Patients with Schizophrenia: A Double-Blind Randomized Placebo-Controlled Clinical Trial

Ebrahim Moghimi Sarani[1], Fatemeh Ghorbannezhad[1]*, Mohammad Hassan Meshkibaf[2], Marjan Shakibaee[2], Seyed Hamdollah Mosavat[3]*

[1]*Department of Psychiatric, Shiraz University of Medical Sciences, Shiraz, Iran*
[2]*Department of Clinical Biochemistry, Fasa University of Medical Sciences, Fasa, Iran*
[3]*Research Center for Psychiatry and Behavioral Sciences, Shiraz University of Medical Sciences, Shiraz, Iran*

Received: 2 Dec 2021 **Revised:** 15 Apr 2022 **Accepted:** 7 May 2022

Abstract

Schizophrenia is a severe psychiatric condition that affects approximately 1% of the global population. Over the last decade, the efficacy of berberine as a complementary therapy in psychiatric diseases without significant side effects has been demonstrated. Therefore, this study assessed the effect of alkaloid berberine on the positive and negative symptoms in patients with schizophrenia. From December 2020 to March 2021, a total of 86 patients with schizophrenia who were referred to Shiraz Ebne Sina Hospital in South of Iran were divided into two groups; 42 patients with schizophrenia in the placebo group received risperidone at a dosage of 4-6 mg per day, and 44 patients in the treatment group, in addition to risperidone, received berberine at a dosage of 500 mg per day. This treatment regimen was followed for 30 days. The Positive and Negative Syndrome Scale (PANSS) was used to assess the patients' symptoms. According to data analysis, The PANSS score in both groups showed a statistically significant decrease after 30 days ($p < 0.05$); however, this decreasing trend was not statistically significant between the groups ($p > 0.05$). The current study showed that complementary use of alkaloid berberine capsule with a dose of 500 mg per day did not show better outcomes compared with the placebo in patients with schizophrenia.

Keywords: Alkaloid berberine; Positive and negative syndrome scale (PANSS); Schizophrenia

Introduction

Schizophrenia is known as a chronic and complicated mental health disorder. This disorder usually develops in late adolescence or the beginning of adulthood [1,2]. Males and females tend to have the same incidence of the disorder; while males display symptoms when they are younger than females [3,4]. Men are more likely than women to develop their first episode of schizophrenia in their early twenties; while women are more likely to have their first episode in their late twenties or early thirties [3,5]. Schizophrenia is a condition that affects a limited proportion of the population. A recently systematic review demonstrated a median population period prevalence of 3.3 per 1000 [1]. Heterogeneous positive and negative symptom constellations characterize this disorder. The distinction between these symptoms originated in neurology and was later accepted in psychiatry [6]. This distinction is related to clinical observations and allows the disorder to be described in terms of symptom domains. While positive symptom indicates an excess or distortion of normal function (e.g., hallucinations,

Citation: Moghimi Sarani E, Ghorbannezhad F, Meshkibaf MH, Shakibaee M, Mosavat SH. **Evaluation of the Effect of Alkaloid Berberine on the Positive and Negative Symptoms of the Patients with Schizophrenia: A Double-Blind Randomized Placebo-Controlled Clinical Trial**. Trad Integr Med 2022;7(3):287-293.

*Corresponding Authors: Fatemeh Ghorbannezhad
Department of psychiatric, Shiraz University of Medical Sciences, Shiraz, Iran
Email: fatemehghorbannejad90@yahoo.com
Seyed Hamdollah Mosavat
Research Center for Psychiatry and Behavioral Sciences, Shiraz University of Medical Sciences, Shiraz, Iran
Email: hamdi_88114@yahoo.com

delusions, and disorganized behavior), negative ones reveal a diminution or absence of normal behaviors related to motivation and interest (e.g., avolition, anhedonia), or expression (e.g., blunted affect, alogia) [6-8].

Studies have shown that first-generation antipsychotic medications of neuroleptic medications (such as haloperidol and chlorpromazine) have been more effective in treating positive symptoms of schizophrenia. Still, these medications cannot fully help propel the treatment of negative symptoms of schizophrenia [9]. Davis et al. (2003) found that neuroleptic medications, such as olanzapine and risperidone, had more appropriate therapeutic effectiveness on negative symptoms of schizophrenia [10]. According to Carman et al.'s study, risperidone effectively treats significantly negative symptoms in schizophrenic patients [11]. The investigation has revealed that even after receiving adequate doses of these medications, just about 30% of patients still have severe and persistent symptoms; more than 60% of these patients have some residual symptoms despite adequate treatment [12-14].

According to John Rathbone et al.'s study, medicinal plants, in combination with antipsychotic medicines, could be beneficial for the treatment of schizophrenia [15,16]. Numerous studies have described the effects of herbal remedies on the symptoms of schizophrenia [17]. Curcumin extract reduces some of the side effects related to the use of narcoleptics to schizophrenic patients such as orofacial dyskinesia [18]. Another study shows that *Bacopa monnieri* (L.) Wettst. may have a significant ability for the improvement of the cognitive symptoms of schizophrenia [19]. *Ginkgo biloba* L. extract has anti-inflammatory and antioxidant effects. Ginkgo increases the cerebral blood flow, so it could be a promising treatment for schizophrenia in combination with clozapine, as they significantly decrease the negative symptoms of patients with schizophrenia [20].

Traditionally, alkaloids with intense activity have always been used as herbal medicine. Through new research methods, active compounds in the extracts can now be detected and designed for new applications. Berberine is one of them, which is currently receiving great interest due to its up-and-coming pharmacological and biological properties [21,22]. Berberine could readily be crossed by the blood-brain barrier (BBB) and may be delivered into the neurons in a concentration-dependent and time-based way [14,23]. Preclinical research has shown its usefulness in many CNS-related disorders such as neuropsychiatric and neurodegenerative ones [14,23]. Berberine has neuroprotective effects against different animal models of CNS-related disorders such as depression, anxiety, forebrain ischemia, and Alzheimer's disease [24].

This plant metabolite has been recognized to reverse N-methyl-d-aspartate (NMDA)-induced excitotoxicity when assessed in the gerbil hippocampal neurons. In another study, it has been confirmed that berberine blocks morphine-induced locomotor sensitization in mice, and decreases NMDA receptor bindings and D1 dopamine in the cortex. Moreover, berberine has been revealed to decrease postsynaptic neuronal activation in the central dopaminergic systems and leads to inhibitory effects of nicotine-induced behavioral sensitization in rats. Furthermore, berberine influenced D1 dopamine receptor agonistic properties and D2 dopamine receptor antagonistic activity, which may be important in improving both the negative and positive symptoms of schizophrenia. [22,24,25]. Also, recent research has confirmed the positive effects of berberine on various diseases, such as infections, gastrointestinal disorders, cancer, and neurological and metabolic disorders.

On the other hand, given the wide variety of medications used to manage schizophrenia, there is debate about ideal medications for completing the patients' rehabilitation. Since the most common antipsychotic medications focus on dopamine, which is associated with positive symptoms, there is an urgent need for patients with negative symptoms [26]. Many critical clinical trials are currently evaluating berberine, which facilitates the further study of its mechanisms of action and possible applications. Therefore, this study aimed to evaluate the effect of alkaloid berberine on the positive and negative symptoms in schizophrenia patients.

Materials and Methods

Participants

In this interventional research, we enrolled 61 patients with schizophrenia who referred to Shiraz Ebne Sina Hospital in South of Iran. This research has been registered in the Iranian Clinical Trials Registry (IRCT20190726044339N1). It was also reviewed, approved, and monitored by the ethics committee of Shiraz University of Medical Sciences (License number: IR.SUMS.MED.REC.1399.371).

Sample size

The sample size was calculated using EPI Info software. The two-way comparative form in the dependent group was used to assess the sample size. In this analysis, the first and second form errors were calculated as 0.05 and 0.2, respectively. σ and d were also considered 0.38 and 0.2, respectively. By taking into account two-sided significance level of 0.05 and power of 80%, 10% possibility of failure to follow up and patients' drop out, the sample size was calculated 42 patients in each group (Equation 1).

Equation 1. $$n=\left(\frac{t_{n-1,\alpha/2}+t_{n-1,\beta}}{d}\right)^2\sigma^2$$

Inclusion criteria
The inclusion criteria in this study consisted of (a) all participants matched for age, sex, treatment, and duration of the disease; (b) the initial diagnosis of schizophrenia confirmed by a psychiatrist through the Positive and Negative Syndrome Scale (PANSS); (c) lack of any underlying disease in the participants in the placebo and treatment groups; and (d) lack of any other mental disorder such as depression, Parkinson's and Alzheimer's disease, etc. in the participants in the placebo and treatment groups.

Exclusion criteria
Exclusion criteria included: (a) digestive severe problem along with other unstable diseases; (b) history of alcohol and drug abuse in the past year; (c) patients undergoing Electroconvulsive therapy (ECT); (d) patients who were pregnant or breastfeeding; and (e) patients whose medication had changed during the study.

Study design and procedures
In this study, the patients were divided into two groups. Risperidone (Sobhan Pharmaceutical company, Iran) at a dosage of 4-6 mg per day was given to those in the placebo group (PG) (n = 42). Patients in the treatment group (TG) (n = 44) were prescribed a supplement of berberine (Amazing Nutrition Co., USA) at a dosage of 500 mg per day in addition to risperidone at a dose of 4-6 mg per day. This treatment regimen was followed for 30 days. Patients were given medications after breakfast, between 8 and 9 a.m., under the supervision of ward nurses. The PANSS Questionnaire was used to assess them after a 30-day treatment cycle.

Randomization, blinding, and allocation concealment
Prospective sequential sampling was done on all patients with inclusion criteria who referred to Shiraz Ebne Sina Hospital in Shiraz, Iran. Eighty-six patients were randomized in two parallel groups (drug and placebo group). A blocked randomization list was generated by a biostatistician using Number Cruncher Statistical System (NCSS) software (using block randomization with size 4 per block).

The drug and placebo capsules were coded by the pharmacist (who kept the sealed code of capsules until the end of the project). Patients, intervention deliverer, researcher, and epidemiologist were not aware of the group allocation. Placebo capsules were similar to berberine capsules in the same color, shape, and weight.

Cognitive function evaluation
The PANSS survey assessed the symptoms of schizophrenia at weeks 0, 2, and 4. The PANSS is a psychological scale used to assess the severity of symptoms of schizophrenia patients. It is commonly used to evaluate the efficacy of antipsychotic treatment [27]. The PANSS scale has 30 items divided into three subscales. It contains five positive symptoms questions, five negative symptoms questions, and five questions about global psychopathological symptoms. The questions are scored using a 5-point Likert scale with a range of 1-5. It is scored from 1 (not present) to 5 (extremely severe). The lowest score was 30 and the highest 150. A score of 30 to 60 indicates that the severity of schizophrenia symptoms is low. A score of 60 to 90 indicates that the severity of schizophrenia symptoms is mild. Also, a score of more than 90 indicates that the symptoms of schizophrenia are severe. The validity and reliability of the Persian version of the PANSS have been confirmed previously (r = 0.99) [28,29].

Ethical consideration
In the current study, the research protocol was approved by the Ethics Committee of the Shiraz University of Medical Sciences (Ethics committee reference number: IR.SUMS.MED.REC.1399.371). Moreover, the trial was registered by the Iranian Registry of Clinical Trials with the code of IRCT20190726044339N1. Ethical principles were followed in this study in compliance with the Declaration of Helsinki. The patients or their legal guardians gave informed consent in compliance with protocols of the institutional review board, and they were ensured that they could withdraw from the study at any time they decided.

Statistical analysis
Data analysis was performed using SPSS version 16.0 package. The Pearson Chi-Square test evaluated the relationships of demographic and clinical characteristics in both groups. Multivariate analyses of the general linear model were used to evaluate the contribution of the duration of the medication regimen to psychotic symptoms. The significance level was determined as a P value lower than 0.05.

Results
From December 2020 to March 2021, the patients were evaluated for eligibility. Eighty-six of them had the inclusion criteria. Forty-four patients were assigned to the berberine group and 42 to the placebo group. Figure 1 is a flowchart demonstrating the patients' screening, enrollment, allocation, follow-up, and analysis.

Clinical and demographic characteristics
The data of 61 participants with schizophrenia (52 males and 9 females) were analyzed. The means ±standard deviations of the patient's age in the treatment group

were 29.68 ± 5.67 and in the placebo group 32.67 ± 6.81; the difference was not statistically significant (P = 0.8) (Table 1). In the control group, 71.4% were male and 28.6% female, and in the treatment group, 68% were male and 32% female. The mean onset of the disease was more than five years (Table 1), and also a statistical difference was observed between the genders in the placebo and treatment groups (P = 0.013).

Psychological evaluation

Table 2 demonstrates that the general linear model (summing type III) was used between the placebo and treatment groups. Data analysis revealed a decrease in PANSS score in the treatment group compared to the placebo group during 0 to 4 weeks; however, this decreasing trend was not statistically significant (p > 0.05).

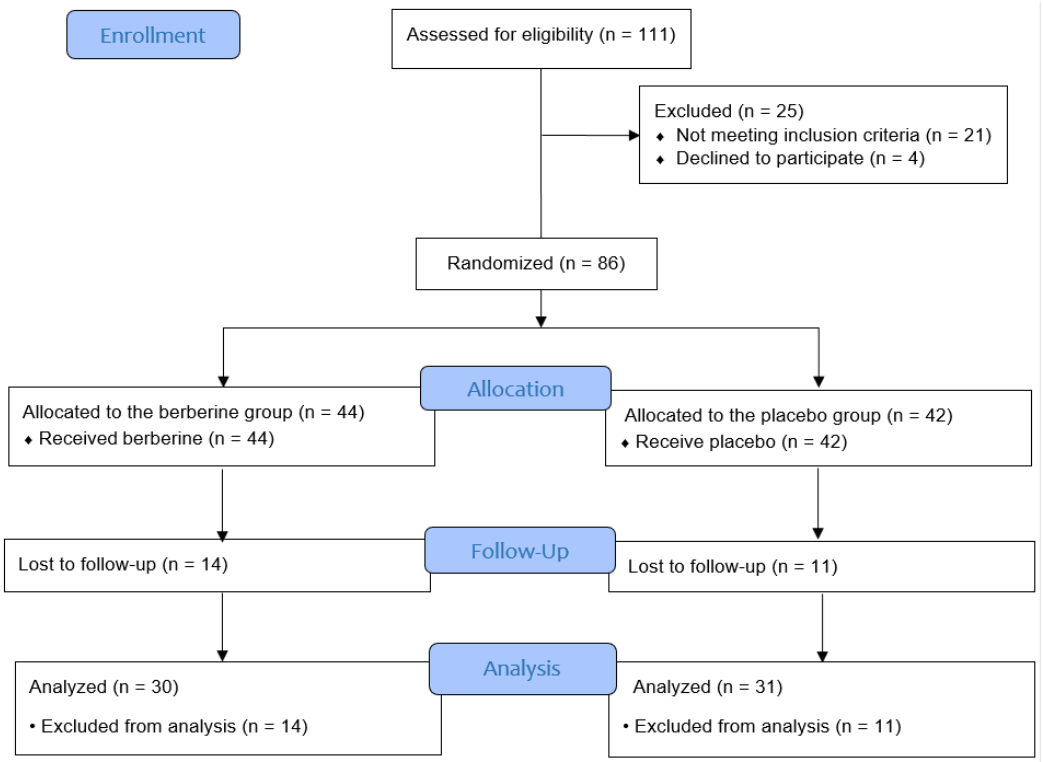

Figure 1. Flow diagram of the patients' enrolment, groups' allocation, follow up, and final analysis

Table 1. Chi-square score of categorical variables among patients with schizophrenia at Ebne Sina Hospital, 2019-2020.

Variable	Category	Group		X^2	df	P value
		placebo	Treatment			
Sex	Male	29	23	6.122	4	0.013
	Female	1	8			
Age (year)	Less than 20-40	18	22	0.812	1	0.367
	More than 40	12	9			
Educational status	Less than diploma	16	12	2.681	2	0.262
	diploma	13	19			
Marital status	Single	21	22	0.241	2	0.887
	Married	5	6			
	Divorce	4	3			
Substance	None	18	23	1.927	2	0.382
	Opioid	8	4			
	Stimulate	4	4			
Onset of disease (year)	Less than 5	13	17	2.700	1	0.170
	More than 5	7	23			

Discussion

Since the early 1950s, antipsychotic medications have been the cornerstone of schizophrenia treatment. While these therapies are beneficial for some, many still have significant symptoms or unpleasant consequences [16]. Second-generation antipsychotic medications have been substituted for the first generation to treat schizophrenia and related disorders due to their comparative effectiveness and lower side effects [30]. Antipsychotic medications are a crucial part of the treatment of schizophrenia. However, research has shown that even after receiving adequate doses of these medications approximately 30% of patients still have severe and persistent symptoms; more than 60% of these patients have some residual symptoms despite adequate treatment [12-14]. Positive and negative symptoms have long been considered as the characteristic of schizophrenia. Recent clinical studies have shown that cognitive dysfunction is the third major diagnostic category and is increasingly considered as the main defect of this disorder [13].

Table 2. Mean outcome measures scores between the two groups of the study before and after the study

Outcome Measure	Time	Berberine Group*	Placebo Group*	Mean Difference (95%CI)	P value	P value
Positive Symptoms	Baseline	28.32±4.67	29.36±5.50	1.044(-1.56,3.65)	0.427	0.730
	2th Week	20.51±5.33	21.46±7.46	0.950(-2.36,4.26)	0.569	
	4th Week	16.29±4.82	16.56±5.80	0.276(-2.45,3.00)	0.840	
Negative Symptoms	Baseline	20.74±4.84	19.10±4.56	1.20(-4.05,0.77)	0.179	0.140
	2th Week	14.29±3.95	14.13±4.18	-0.1.59(-2.24,1.92)	0.881	
	4th Week	9.74±3.66	10.69±3.79	0.891(-1.020,2.80)	0.355	
General Symptoms	Baseline	14.87±3.39	13.30±3.45	-1.57(-3.32,0.183)	0.078	0. 692
	2th Week	7.25±2.95	6.73±1.77	-0.524(-1.77,0.730)	0.406	
	4th Week	5.80±2.21	5.06±1.11	-739(-1.64,0.162)	0.106	

*Mean ± Standard Deviation

Herbal remedies are extensively utilized instead for psychiatry purposes in industrialized and developing nations, maybe due to the evident limitations of synthetic pharmaceuticals [16]. Plant extracts containing alkaloids have always been used in herbal medicine. Active compounds in the extracts can now be identified and designed for new applications using new research methods. Berberine is one of them because of its intriguing biological and pharmacological properties [21, 24]. Numerous studies have shown the anti-inflammatory and antioxidant properties of berberine [31,32].

The current study found that, after 30 days, berberine could reduce the positive and negative symptoms by the PANSS score in the treatment group as compared to the placebo group; however, this reducing trend based on PANSS score during 0, 2, and 4 weeks was not statistically significant (P > 0.05). One of the reasons that the result of our study was not satisfactory may be that the dose of berberine was not enough. In a recent published study, Li et al. found that berberine 900 mg/day for 8 weeks' treatment could improve metabolic disturbances in schizophrenia patients [33]. However, in different studies, different doses of berberine have been studied. For example, in one study, a dose of 500 to 1500 was used [34].

According to various studies, the effects of berberine on the nervous system and related diseases are still unknown. Patients with schizophrenia are prone to hyperlipidemia and diabetes due to the use of antipsychotic drugs because metabolic syndrome is the prevalent side effects of antipsychotic drugs [35]. Thus, treatment of high blood sugar and hyperlipidemia is a priority in these patients. Hence, drugs that could control the patient's sugar and lipid in patients with schizophrenia can be used as adjunctive therapy in the treatment of schizophrenia. Fortunately, berberine has been shown in some studies to be effective in the control of hyperlipidemia and hyperglycemia in schizophrenia [21,33]. However, despite its neuroprotective effect, some studies indicated that berberine accelerated the neurodegeneration process [36].

A lot of research on oxidative stress in patients with schizophrenia has shown conflicting results. As to the answer to that question, it is unclear if increased oxidants cause psychiatric disorders or whether psychiatric disorders cause oxidant increases [37]. Gunes et al. (2017) reported that in schizophrenia patients, oxida-

tive metabolism could be linked to negative symptoms [37]. Due to the antioxidant properties of berberine, it might be able to improve the positive and negative symptoms of schizophrenia patients in the present study. On the other hand, the activity of "biologically active peptides" and "peptide hormones" is regulated by the prolyl oligopeptidase family enzymes. These enzymes are involved in various diseases such as schizophrenia, memory loss, depression, diabetes, etc. Prolyl oligopeptidase activity is known to decrease depression and increase psychotic disorders like mania and schizophrenia. According to the available literature, antipsychotic medications do not affect this enzyme. Tarrago et al. in 2007 reported that berberine was a concentration-dependent inhibitor of prolyl oligopeptidase. This study indicated that berberine was supposed to effectively treat schizophrenia because of its prolyl oligopeptidase-inhibitory property [13]. Since berberine interacts with this enzyme in a dose-dependent manner, it is possible that berberine reduces the positive and negative symptoms in an appropriate dose. Many researchers in various countries have been involved in berberine clinical studies in recent years, and research on schizophrenic patients in phases 2, 3, and 4 is currently in progress [21].

Berberine also affects the D2 dopamine receptor (DRD2) antagonistic and DRD1 (D1 dopamine receptor) agonistic activity [25,38]. Berberine has been shown to inhibit norepinephrine release, resulting in the activation of 2-adrenoceptors, which can then affect dopamine by blocking the D1 and D2 receptors [25,38]. Therefore, it could help both positive and negative symptoms of schizophrenia [25]. Kulkarni et al. demonstrated that acute berberine administration increased the dopamine levels in mice (31%). The result shows that berberine has an antidepressant effect, possibly modulating brain biogenic amines such as dopamine [38]. According to Yan Wang et al. (2021), oral berberine increases the brain dopamine levels to alleviate Parkinson's disease by controlling the gut microbiota [39]. However, the exact mechanism of action is unknown [34].

Limitations

Our study had some limitations; it had a single-center design and a small sample size. Although this study was performed as a first pilot study on the efficacy of berberine on schizophrenia, it required the least trial size. Thus, it is suggested that future studies should be performed with larger sample size. Short duration of the study and lack of drug dose adjustment or numerous dose evaluation in this study were the other limitations, which could be considered in future studies.

Conclusion

As a conclusion, the current study showed that complementary use of alkaloid berberine capsule with a dose of 500 mg per day did not show better outcomes compared with the placebo in patients with schizophrenia. Therefore, further clinical studies are recommended to include dose titration and longer duration and analyze the alkaloid berberine efficacy and relative risk.

References

[1] Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. PLoS Med 2005;2:e141.

[2] Patel KR, Cherian J, Gohil K, Atkinson D. Schizophrenia: overview and treatment options. Pharmacy and Therapeutics. 2014;39(9):638-645.

[3] Häfner H. From onset and prodromal stage to a life-long course of schizophrenia and its symptom dimensions: how sex, age, and other risk factors influence incidence and course of illness. Psychiatry J 2019:9804836..

[4] Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, et al. Pharmacotherapy: A Pathophysiologic Approach. McGraw-Hill Medical. New York 2014.

[5] Hill SK, Reilly JL, Keefe RS, Gold JM, Bishop JR, et al. Neuropsychological impairments in schizophrenia and psychotic bipolar disorder: findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. Am J Psychiatry 2013;170:1275-1284.

[6] Correll CU, Schooler NR. Negative symptoms in schizophrenia: a review and clinical guide for recognition, assessment, and treatment. Neuropsychiatr Dis Treat 2020;16:519-534.

[7] Seidman LJ, Mirsky AF. Evolving notions of schizophrenia as a developmental neurocognitive disorder. J Int Neuropsychol Soc 2017;23:881-892.

[8] Galderisi S, Mucci A, Buchanan RW, Arango C. Negative symptoms of schizophrenia: new developments and unanswered research questions. Lancet Psychiatry 2018;5:664-677.

[9] Tollefson GD, Beasley Jr CM, Tran PV, Street JS, Krueger JA, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Psychiatry 1997;154:457-465.

[10] Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry 2003;60:553-564.

[11] Bj S, Va S. Comprehensive textbook of psychiatry. Lippincott Williams and Wilkins. Philadelphia 2005.

[12] Bobes J, Cañas F, Rejas J, Mackell J. Economic consequences of the adverse reactions related with antipsychotics: an economic model comparing tolerability of ziprasidone, olanzapine, risperidone, and haloperidol in Spain. Prog Neuropsychopharmacol Biol Psychiatry 2004;28:1287-1297.

[13] Tarrago T, Kichik N, Seguí J, Giralt E. The natural product berberine is a human prolyl oligopeptidase inhibitor. ChemMedChem 2007;2:354-359.

[14] Stroup TS, Alves WM, Hamer RM, Lieberman JA. Clinical trials for antipsychotic drugs: design conventions, dilemmas and innovations. Nat Rev Drug Discov 2006;5:133-146.

[15] Sarris J, Kavanagh DJ, Byrne G. Adjuvant use of nutritional

and herbal medicines with antidepressants, mood stabilizers and benzodiazepines. J Psychiatr Res 2010;44:32-41.

[16] Rathbone J, Zhang L, Zhang M, Xia J, Liu X, et al. Chinese herbal medicine for schizophrenia: cochrane systematic reiew of randomised trials. Br J Psychiatry 2007;190:379-384.

[17] Kumari R, Kaundal M, Ahmad Z, Ashwalayan V. Herbal and dietary supplements in treatment of schizophrenia: An approach to improve therapeutics. Int J Pharm Sci Rev Res 2011;10:217-224.

[18] Anna M. Evaluation of Anticonvulsant Activity of Chloroform Root Extract of Aconitum Heterophyllum. KMCH College of Pharmacy. Coimbatore 2017.

[19] Piyabhan P, Wetchateng T. Bacopa monnieri (Brahmi) enhanced cognitive function and prevented cognitive impairment by increasing VGLUT2 immunodensity in prefrontal cortex of sub-chronic phencyclidine rat model of schizophrenia. J Med Assoc Thai 2015;98:S7-S15.

[20] Lodha S, Upadhyay S. Review on the role of herbs in schizophrenia. Pharmacogn Commun 2021;11:78-80.

[21] Och A, Podgórski R, Nowak R. Biological activity of berberine-a summary update. Toxins 2020;12:713.

[22] Kumar A, Chopra K, Mukherjee M, Pottabathini R, Dhull DK. Current knowledge and pharmacological profile of berberine: an update. Eur J Pharmacol 2015;761:288-297.

[23] Wang X, Wang R, Xing D, Su H, Ma C, et al. Kinetic difference of berberine between hippocampus and plasma in rat after intravenous administration of Coptidis rhizoma extract. Life Sci 2005;77:3058-3067.

[24] Kulkarni S, Dhir A. Berberine: a plant alkaloid with therapeutic potential for central nervous system disorders. Phytother Res 2010;24:317-324.

[25] Chu H, Jin G, Friedman E, Zhen X. Recent development in studies of tetrahydroprotoberberines: mechanism in antinociception and drug addiction. Cell Mol Neurobiol 2008;28:491-499.

[26] Kim Y-K, Choi J, Park S-C. A novel bio-psychosocial-behavioral treatment model in schizophrenia. Int J Mol Sci 2017;18:734.

[27] Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophre Bull 1987;13:261-276.

[28] Omranifard V, Karahmadi M, Jannesari Z, Maracy M. Efficacy of modified compliance therapy for schizophrenia patients. J Res Med Sci 2012;17:S258-S263.

[29] Bigdeli I, Farzin A, Talepasand S. Prospective memory impairments in schizophrenic patients. Iran J Psychiatry Behav Sci 2014;8:57-63.

[30] Boyda HN, Procyshyn RM, Tse L, Yuen JW, Honer WG, et al. A comparison of the metabolic side-effects of the second-generation antipsychotic drugs risperidone and paliperidone in animal models. PloS One 2021;16:e0246211.

[31] Li Z, Geng Y-N, Jiang J-D, Kong W-J. Antioxidant and anti-inflammatory activities of berberine in the treatment of diabetes mellitus. Evid-Based Complement Altern Med 2014;2014: 289264.

[32] El khalki L, Tilaoui M, Jaafari A, Ait Mouse H, Zyad A. Studies on the dual cytotoxicity and antioxidant properties of Berberis vulgaris extracts and its main constituent berberine. Adv Pharmacol Sci 2018;2018:3018498.

[33] Li M, Liu Y, Qiu Y, Zhang J, Zhang Y, et al. The effect of berberine adjunctive treatment on glycolipid metabolism in patients with schizophrenia: A randomized, double-blind, placebo-controlled clinical trial. Psychiatry Res 2021;300:113899.

[34] Fan J, Zhang K, Jin Y, Li B, Gao S, et al. Pharmacological effects of berberine on mood disorders. J Cell Mol Med 2019;23:21-28.

[35] Ananth J, Parameswaran S, Gunatilake S. Side effects of atypical antipsychotic drugs. Curr Pharm Des 2004;10:2219-2229.

[36] Kysenius K, Brunello CA, Huttunen HJ. Mitochondria and NMDA receptor-dependent toxicity of berberine sensitizes neurons to glutamate and rotenone injury. PloS One 2014;9:e107129.

[37] Gunes M, Altindag A, Bulut M, Demir S, Ibiloglu AO, et al. Oxidative metabolism may be associated with negative symptoms in schizophrenia. Psychiatr Clin Psychopharmacol 2017;27:54-61.

[38] Kawano M, Takagi R, Kaneko A, Matsushita S. Berberine is a dopamine D1-and D2-like receptor antagonist and ameliorates experimentally induced colitis by suppressing innate and adaptive immune responses. J Neuroimmunol 2015;289:43-55.

[39] Wang Y, Tong Q, Ma S-R, Zhao Z-X, Pan L-B, et al. Oral berberine improves brain dopa/dopamine levels to ameliorate Parkinson's disease by regulating gut microbiota. Signal Transduct Target Ther 2021;6:1-20.