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Black sesame-fortified soymilk improves psychotic symptoms in first-episode schizophrenia patients

Kukiat Tudpor
Faculty of Public Health, Mahasarakham University, Thailand *and* Public Health and Environmental Policy in Southeast Asia Research Cluster (PHEP-SEA), Mahasarakham University, Thailand
*Corresponding author email: kukiat.t@msu.ac.th

Nitchara Toontom
Faculty of Public Health, Mahasarakham University, Thailand *and* Public Health and Environmental Policy in Southeast Asia Research Cluster (PHEP-SEA), Mahasarakham University, Thailand

Chiraporn Praditduang
Department of Nutrition, Khon Kaen Rajanagarindra Psychiatric Hospital, Khon Kaen, Thailand

***Abstract*---**Schizophrenia is a psychiatric disease with neural lesion. Black sesame, medicinal plant enriched with micronutrients has been reported to boost brain functions, but its effects on schizophrenia symptoms have not been elucidated. This prospective one-group pretest-posttest quasi-experimental design was aimed to investigate effects of the black sesame-fortified soymilk (a daily serving size of 180-mL soymilk contained 3.5 g of black sesame seeds and 2 g of black sesame oil) for 3 weeks on psychotic symptoms (brief psychiatric rating scale (BPRS) score) in 63 patients with first-episode schizophrenia. At baseline, 46 had normal (≤ 36) and 17 had high (> 36) BPRS scores. The mean BMI in all subjects was 22.5±0.4 Kg/m2. Twelve participants were underweighted, 30 were normal, and 21 were overweight. BPRS scores measured at baseline (pretest) were normal (n = 46) and high BPRS (n = 17). After 3 weeks of intervention of black sesame-fortified soymilk (posttest), number of the normal-BPRS patients significantly increased from 46 to 60 whereas number of the high-BPRS patients significantly reduced from 17 to 3 persons (McNemar test < 0.001, Cramer's V = 0.304). These results suggested that the 3-week black sesame-fortified soymilk was feasible to reduce the psychotic symptoms in schizophrenia patients. Further

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investigation in a large randomized controlled trial cohort study should be further performed.

***Keywords*---**schizophrenia, black sesame, brief psychiatric rating scale, micronutrients.

Introduction

Schizophrenia is one of major chronic mental health disorders worldwide. It is manifested by positive symptoms (suspiciousness, hallucinations, delusions, impaired cognitive ability, and disorganized speech or behavior) and negative symptoms (impairments in attention, loss of volition, social withdrawal, poverty of speech, and affective flattening) due to dysbalances of the dopamine (DA) system in the brain (Jablensky, 2010; Meisenzahl et al., 2007; Patel et al., 2014). The prevalence of the disease varies between sites with median of approximately 15/100,000 persons (McGrath et al., 2008). Pathogenesis of schizophrenia is initiated by various factors including genetic predisposition, ethnicity, medications, life style, drug and alcohol abuse, and malnutrition (Boskovic et al., 2011).

It has been reported that schizophrenia patients had poor patterns of food intakes (Amani, 2007). Epidemiological studies also demonstrated that prenatal nutritional deprivation was linked to increased risk of schizophrenia (McGrath et al., 2011). Many candidates of micronutrients were proposed to exert their biological roles in preventing schizophrenia including vitamin D, folate (folic acid), and iron. Vitamin D deficiency in neonates increases risk of schizophrenia development later in their adulthood (McGrath et al., 2010). Developmental vitamin D (DVD)-deficiency reduces nerve growth factor (NGF) and glial-derived neurotrophic factor (GDNF), resulting in neuron immaturities and impaired early brain connectivity (Cui et al., 2021). Moreover, DVD-deficiency in embryos has been found to slow down DA neuron development, predisposing psychotic disorders (Kesby et al., 2009). Beside DA, homocysteine (Hcy) was also associated with an overall 70% increased risk of schizophrenia (Muntjewerff et al., 2006). Folic acid and vitamins B supplementation has been determined as an effective way to reduce Hcy level (Moustafa et al., 2014). For iron, it is important for neurotransmission, electron transfers, and myelination (Hare et al., 2013). Iron dysregulation in early psychosis is associated with negative symptoms in first-episode schizophrenia patients (Kim et al., 2018).

As a phytochemical-rich ingredient in traditional medicine remedy, sesame has been widely used for energy boosting and anti-aging (Mahendra Kumar & Singh, 2015). Dietary supplement of sesame products has been reported to reduce oxidative stress, thereby improving neural functions, and reducing neurodegeneration (Mohamed et al., 2021). Various active ingredients in black sesame seeds were involved with neuroprotection such as vitamins (A, B1, B2, B12, D, E, and folate), electrolytes calcium (Ca^{2+} and iron), and phenolic compounds (lignans – sesamol, sesamin, and sesamolin) (Cheng et al., 2006; Panzella et al., 2018). Meanwhile, soy foods have been recognized to reduce risks of coronary heart disease, breast and prostate cancer, kidney diseases, and psychological disorders (Messina, 2016). However, effects of black sesame supplementation on psychotic symptoms in schizophrenia patients were still not known. This present study was aimed to evaluate effects of black sesame-fortified soymilk on psychotic symptoms as measured by BPRS (Kluge et al., 2007) in schizophrenia patients.

Materials and Methods

Study design

A one-group pretest-posttest quasi-experimental design has been registered to the Thai Clinical Trials Registry (TCTR20190301004) and approved by the Ethical Review Committee for Human Research, Faculty of Public Health, Mahasarakham University (PH075/2561). The study was conducted at Khon Kaen Rajanagarindra Psychiatric Hospital, Division of Mental Health, Department of Medical Services, Ministry of Public Health, Khon Kaen, Thailand. Written informed consent forms were obtained from all patients.

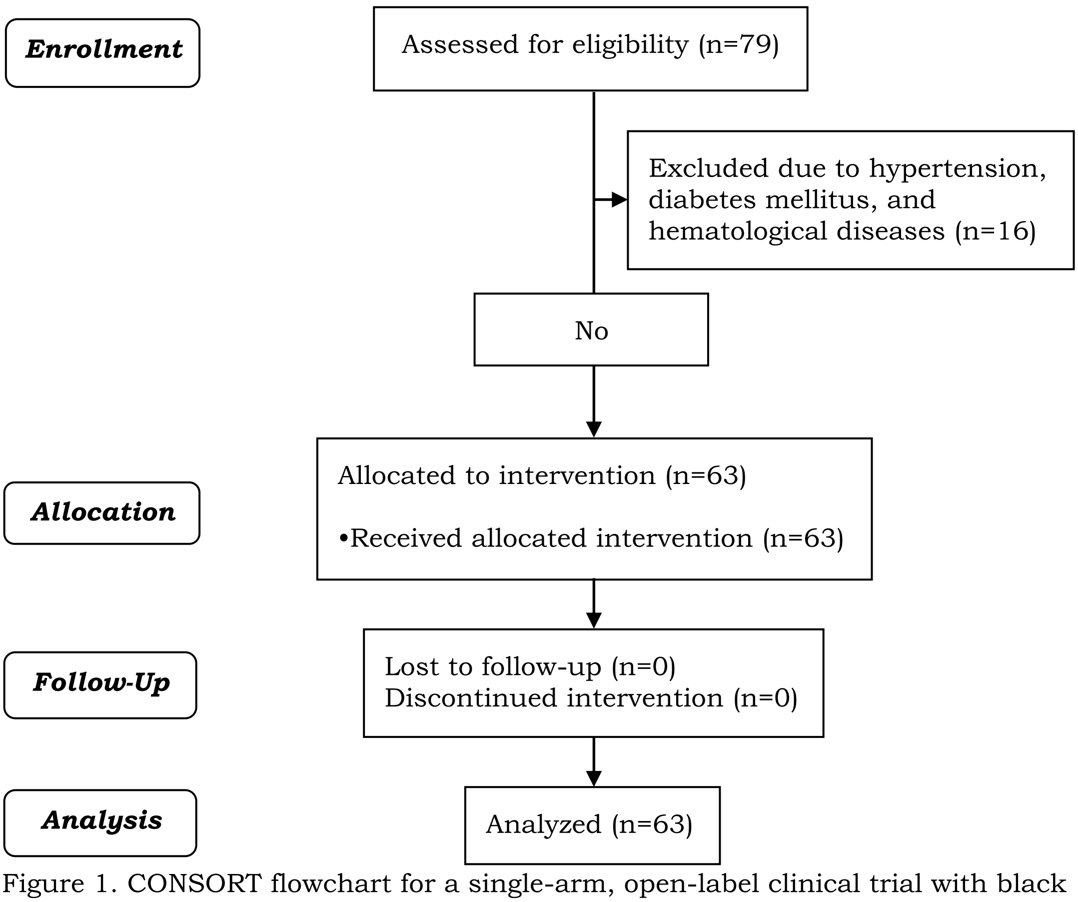

Figure 1. CONSORT flowchart for a single-arm, open-label clinical trial with black sesame-fortified soymilk in first-episode schizophrenia patients

Participants and baseline assessments

Seventy-nine schizophrenia patients were assessed for eligibility (Fig. 1). Inclusion criteria were 1) being the patients diagnosed with the first-episode schizophrenia by psychiatrists corresponding to criteria from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), 2) being hospitalized with age ≥ 18 years old, 3) being able to communicate and self-care, and 4) being informed consent. Exclusion criteria were 1) having gastrointestinal diseases and 2) having other physical complications such as cardiovascular and renal diseases, and diabetes mellitus. After recruitment, the participants were evaluated for BPRS, BMI, and other demographic data. Sixty-three patients were included in the study and all of them remained until the end of the project.

Intervention

The participants were enrolled to the 3-week dietary program designed by a registered dietitian. The carbohydrate: protein: fat ratio of the diet was 55:15:30. The consumed portion of the diet was used to calculate for energy and nutrient intakes on daily basis. A daily serving size of 180-mL soymilk contained 3.5 g of black sesame seeds and 2 g of black sesame oil. Nutritional values are shown in Table 1. Lignan concentration per serving were calculated based on data from literature (black sesame seeds: total lignan, 6.27 mg/g; sesamol, 0.01 mg/g; sesamin, 4.34 mg/g; and sesamolin, 1.92 mg/g; black sesame oil: total lignans, 8.86 mg/g; sesamol, 0.12 mg/g; sesamin, 5.83 mg/g; and sesamolin, 2.91 mg/g) (Shi et al., 2017).

Table 1
Percent Thai recommended daily intakes (% Thai RDI) per serving of original soymilk and black sesame-fortified soymilk for population over 6 years of age based on a 2,000-kCal diet (Rimpeekool et al., 2015)

Variable	Thai RDI	Original soymilk	% Thai RDI	Black sesame-fortified soymilk	% Thai RDI
Energy (kCal)	2,000	180	9	150	7.5
Macronutrients					
Carbohydrate (g)	300	20	6.7	16	5.3
Protein (g)	50	6	12	7	14
Fat (g)	65	8	12.3	6	9.2
Micronutrients					
Vitamin A (μg RE)	800	0	0	400	50
Vitamin B1 (μg)	1,500	0	0	450	30

Vitamin B2 (μg)	1,700	34	2	600	35.3
Vitamin B12 (ng)	2,000	0	0	500	25
Vitamin D (IU)	200	0	0	120	60
Vitamin E (mg α-TE)	10	0	0	3.5	35
Calcium (mg)	800	32	4	320	40
Niacin (mg NE)	20	0	0	8	40
Folate (μg)	200	0	0	100	50
Iron (mg)	15	0	0	3	20
Total lignan (mg)	N/A	Nil	N/A	39.67	N/A
Sesamol (mg)	N/A	Nil	N/A	0.28	N/A
Sesamin (mg)	N/A	Nil	N/A	26.85	N/A
Sesamolin (mg)	N/A	Nil	N/A	12.54	N/A

RE, retinol equivalent; IU, international unit; α-TE, alpha tocopherol equivalent; NE, niacin equivalent; N/A, not applicable.

Outcomes

The primary outcome was the BPRS score, which has been developed in the early 1960s by Overall and Gorham using factor analysis to assess the severity of schizophrenic states (Overall & Pfefferbaum, 1982). Before the interventions, the participants were screened for BPRS by a psychiatric nurse. Each of the 18 BPRS items were designed to represent a discrete symptom area. Each of the 18 items takes roughly 2-3 min to complete following the interview. Five of the items (tension, emotional withdrawal, mannerisms and posturing, motor retardation, and uncooperativeness) were based on observations of the patients. The remaining 13 items were based on the patient's verbal report. The items were rated on a 7-point Likert scale, from 1 = "not present" to 7 = "extremely severe", with scores ranging from 18 to 126 (achieved through summing the item scores). The BPRS score ≤ 36 was considered as normal level, while the score > 36 was in high level. Inter-rater reliability for overall scores ranged from 0.67 to 0.95 (Andersen et al., 1989). Other secondary outcomes were BMI, dietary intake, and daily energy. The BMI values were calculated by dividing weight (Kg) with height (m^2) and categorized into 3 subgroups according to BMI cutoffs for Asians and Asian Americans i.e., underweight (< 18.5 Kg/m^2), normal weight (18.5-22.9 Kg/m^2), and overweight (≥ 23 Kg/m^2) (Consultation, 2004). The daily dietary intake was calculated using weighed food record (WFR) procedure and INMUCAL-Nutrients V.3 (Institute of Nutrition, Mahidol University, Thailand) based on Thai food composition tables (Ishii et al., 2017; Ivanovitch et al., 2014). All entries were checked for accuracy by a nutritionist.

Sample size calculation

Having been allocated BPRS effect size of 0.38 (Pickar & Bartko, 2003), α-error level (one-sided) of 0.05, and power level (1-β error) of 0.9 with power analysis for the difference between two dependent means, the sample size was 61 as calculated by the G*power version 3.1.9.7.

Statistical analysis

The data are expressed as mean±SD and number (%). Normality of sample data was tested by Kolmogorov-Smirnov test. Categorical variables of pretest and posttest were compared by McNemar tests. The strength of association was determined by Cramer's V value. The level of statistical significance was $p < 0.05$. All data were analyzed by SPSS version 18.0.

Results

Baseline characteristics

Sixteen participants were excluded from the program due to initial findings of hypertension, diabetes mellitus, and hematological diseases. Sixty-three participants were allocated and completed the program. Among these, 46 had normal and 17 had high BPRS scores. The mean BMI in all subjects was 22.5±0.4 Kg/m^2. Twelve participants were underweighted, 30 were normal, and 21 were overweight. All other basic demographic data are shown in Table 2.

Table 2
Basic characteristics of schizophrenia patients at baseline (n =63)

Variable	Value
Age (years)	38.6±1.3
Gender (n)	
Male	50 (79.37)
Female	13 (20.63)
Height (cm)	164.3±0.8
Weight (Kg)	62.4±1.3
BPRS (n)	
Normal (≤ 36)	46 (73.02)
High (> 36)	17 (26.98)
BMI (n)	
Underweight (< 18.5 Kg/m^2)	12 (19.05)
Eutrophia (18.5-22.9 Kg/m^2)	30 (47.62)
Overweight (≥ 23 Kg/m^2)	21 (33.33)

Black sesame-fortified soymilk improved psychotic symptoms in schizophrenia patients

BPRS scores were measured at baseline (pretest) and after 3-week black sesame-fortified soymilk (posttest). Distribution of the scores is shown in Fig. 2. At baseline, 46 had normal and 17 had high BPRS. After 3-week intervention, number of the normal-BPRS patients significantly increased from 46 to 60 whereas number of the high-BPRS patients significantly reduced from 17 to 3 persons (McNemar test < 0.001, Cramer's V = 0.304, Table 3). These results suggested that the 3-week black sesame-fortified soymilk was effective to reduce the psychotic symptoms of schizophrenia patients.

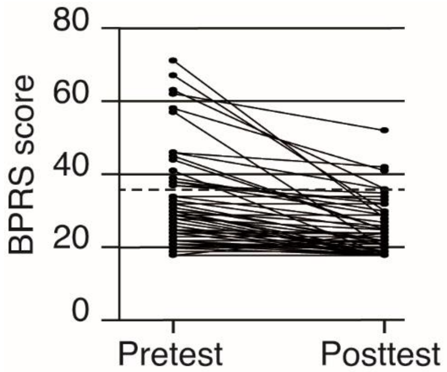

Figure 2. Distribution of BPRS scores at baseline (pretest) and post-intervention (posttest). Dashed line, BPRS cut-off point (BPRS score = 36).

Table 3
Analysis of BPRS scores of schizophrenia patients at baseline (pretest) and post-intervention (posttest)

Variable	BPRS score		
	Normal	High	Total
Pretest	46 (73.02%)	17 (26.98%)	63 (100%)
Posttest	60 (95.24%)	3 (4.76%)	63 (100%)
Total	106 (84.13%)	20 (15.87%)	126 (100%)
McNemar test < 0.001			
Cramer's V = 0.304			

Discussion

This present study showed that black sesame-fortified soymilk consumption for 3 weeks was able to improve psychotic symptoms in schizophrenia patients. The BPRS score has been used to assess the severity of psychiatric symptoms associated with schizophrenia such as, depression, anxiety, hallucinations, and unusual behavior (Wang et al., 2017). There were various possibilities mediating psychotic symptom improvements. Both macronutrients and micronutrients have been reported as pivotal factors determining psychotic symptoms in schizophrenia patients. Vitamins have been found to be associated with schizophrenia. Carotenoids are recognized as reliable indicators of antioxidant level in human body (Chow et al., 2010). Chow and co-workers reported that levels of carotenoids (provitamin A) are low in schizophrenia patients compared to healthy controls (Chow et al., 2010). Even though black sesame is enriched with vitamins B1, B2, and B12, only serum levels of vitamin B3 (nicotinamide) and vitamin B6 (pyridoxine) have been found to be associated with psychotic symptoms in schizophrenia patients (Cao et al., 2018). However, Roffman and co-workers also reported that 4-month supplement of vitamin B12 in combination with folic acid significantly improved negative symptom severity in patients with schizophrenia (Roffman et al., 2013). This signifies an importance of vitamins B in controlling the psychotic symptoms.

Besides, psychotic symptoms are also linked to levels of plasma electrolytes. Schizophrenia patients tend to isolate themselves and have limited outdoor exposure and sunlight (Gracious et al., 2012). Therefore, they are prone to deprive of vitamin D, a major stimulator of intestinal Ca^{2+} absorption and renal calcium reabsorption (Eklund et al., 2009). As a micronutrient, Ca^{2+} is required in tiny amount to maintain brain functions (Kawamoto et al., 2012). Under resting conditions, neurons in the brain maintain a steep gradient between low intracellular calcium ($[Ca^{2+}]i$) concentration of 0.1–0.5 µM and high extracellular Ca^{2+} levels (~1 mM). Ca^{2+} influx into the cell through the voltage-dependent Ca^{2+} channels (VDCCs), N-methyl-d-aspartate (NMDA) receptors, or transient receptor potential (TRP) channels on plasma membrane results in $[Ca^{2+}]i$ changes (Kawamoto et al., 2012). Ito and colleagues previously found that schizophrenic patients consumed more Ca^{2+} compared to healthy persons (Ito et al., 2015). However, they did not investigate an effect of dietary intake on psychotic symptoms. Ca^{2+} demand in schizophrenia patients was found to increased due to antipsychotic-induced hypocalcemia (Milovanovic et al., 2016). Moreover, McGrath and colleagues also reported that early long-term vitamin D supplementation reduced a risk of subsequent schizophrenia for infants (McGrath et al., 2004). Thus, it is suggested for patients to follow the RDI for vitamin D and Ca^{2+} consumption. Additionally, supplementation of vitamin E in combination with vitamin C and omega-3 fatty acids improved the BPRS and positive and negative syndrome scale (PANSS) scores in psychotic patients (Arvindakshan et al., 2003). In addition to Ca^{2+}, iron deficiency during pregnancy is associated with schizophrenia-related brain abnormalities in children (McGrath et al., 2011).

Lastly, lignans, low molecular weight polyphenols, were also found to regulate symptoms of schizophrenia. Lignans have been found to inhibit tryptophan-degrading activity of enzyme indoleamine 2,3-dioxygenase (IDO) (Kuehnl et al., 2013). Catabolism of tryptophan in kynurenine pathway produces neurotoxic compounds (3-hydroxykynurenine (3-OHKY) and quinolinic acid) and neuroinhibitory compound (kynurenic acid) (Condray et al., 2011). Plasma level of 3-OHKY is reversely correlated with psychotic symptoms in neuroleptic-naïve first-episode schizophrenia patients (Condray et al., 2011). Therefore, changes in tryptophan metabolism under control by lignans are potentially significant for schizophrenia pathogenesis (Condray et al., 2011).

Conclusion

In conclusion, our present study demonstrates that the black sesame-fortified soymilk was effective to reduce psychotic symptoms in schizophrenia patients. However, further study in a larger group of patients with randomized controlled trial should be further carried out.

Conflict of Interest

The authors have no conflicts of interest to declare.

Acknowledgments

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