Original Research Article

Herbal adjuvant therapy with a combination of Green Tea, Persian Borage, and Purslane to reduce antipsychotic-induced weight gain in Schizophrenia: A randomized controlled trial

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Abstract

Objective: Second-generation antipsychotics can lead to metabolic problems. This study investigated whether an herbal compound with green tea, Persian borage, and purslane extracts could help in antipsychotic-induced weight management in schizophrenia patients.

Materials and Methods: This triple-blind, placebo-controlled study at Hijazi Psychiatry Hospital in Mashhad, Iran, involved 73 schizophrenia patients. Participants received either an herbal compound or a placebo, alongside their antipsychotic medication. The primary outcome was changes in body mass index (BMI), with secondary outcomes including waist-to-hip ratio (WHR), fasting blood sugar (FBS), HbA1c, lipid profile, blood pressure, appetite, quality of life, and psychotic symptom severity.

Results: The herbal compound significantly reduced BMI (p<0.001), WHR (p<0.001), HbA1c (p=0.042), low-density lipoprotein (LDL) concentration (p=0.009), and systolic blood pressure (p=0.015) compared to the placebo. No significant differences were observed in FBS or lipid profile (except LDL) between the two groups. The intervention group had significantly lower appetite levels than the placebo group at weeks four and eight (p=0.001). There was no significant difference between the two groups in the Positive and Negative Syndrome Scale (PANSS) score at any time. Participants reported no serious adverse effects.

Conclusion: Adding herbal compound to antipsychotics significantly lowered BMI, WHR, HbA1c, LDL levels, systolic blood pressure, and appetite in schizophrenia patients.

Introduction

Schizophrenia is a psychiatric disease affecting 1% of the population, and its is characterized by positive symptoms (e.g. hallucinations, delusions), negative symptoms (e.g. lack of pleasure or difficulty with speech), and cognitive impairments (Rahman and Lauriello 2016). It is classified among the top ten contributors to the global disease burden by the World Health Organization (Salleh 2018).

Schizophrenia treatment primarily involves antipsychotic medications, classified as typical and atypical. Atypical antipsychotics or second-generation antipsychotics (SGAs) are preferred due to fewer extrapyramidal effects. Nonetheless, their use is associated with higher metabolic and cardiovascular risks including obesity and reduced life expectancy (Patel et al. 2014). Given the potential side effects and the requirement for long-term use of these medications, patient adherence to treatment may decline (Tschoner et al. 2007). Thus, it is crucial to identify strategies to mitigate these issues.

Current research demonstrates that medicinal plants serve an essential function in disease management and symptom relief (Javidi et al. 2024; Salehsari et al. 2024). Incorporation of medicinal herbs alongside antipsychotic medications may effectively diminish side effects and enhance the well-being of schizophrenia patients. Utilization of medicinal plants is beneficial owing to their affordability, accessibility, and capacity to tackle various metabolic and psychological complications simultaneously (Naghibi et al. 2023; Shi et al. 2021).

Research indicates that neurochemical alterations, hormonal variations, and sedation-related behaviors lead to heightened appetite and notable weight gain in SGA users (Smith et al. 2012; Stip et al. 2012; Werneke et al. 2013). To enhance pharmacological effectiveness and regulate appetite and weight fluctuations associated with SGAs in schizophrenia, our multidisciplinary research team utilized a synergistic plant-based approach to formulate a novel herbal composition. This new compound consists of herbal extracts of green tea, Persian borage, and purslane for weight control in schizophrenia patients.

Green tea, from Camellia sinensis L., comprises several phytochemicals such as catechins and theanine, which possess antioxidant and anti-inflammatory characteristics (Rani et al. 2014). It may help to prevent weight gain and obesity by reducing intestinal fat absorption, enhancing fat oxidation, increasing energy expenditure (Hursel et al. 2011; Macêdo et al. 2023; Rani et al. 2014; Suzuki et al. 2016; Yang et al. 2016), and improving metabolic parameters, insulin sensitivity, and glucose level (Liu et al. 2013; Wan et al. 2024; Xu et al. 2020). It promotes cardiovascular health through improved blood pressure and endothelial function (Onakpoya et al. 2014; Potenza et al. 2007; Yıldırım Ayaz et al. 2023). Green tea may also suppress appetite via increased dopamine and serotonin levels (Sirotkin and Kolesárová 2021; Zheng et al. 2004). Furthermore, L-theanine in green tea enhances cognitive function and promotes tranquility by regulating neurotransmitters (Hidese et al. 2019; Lardner 2014; Mancini et al. 2017). Green tea shows potential as an adjunctive treatment for schizophrenia and those receiving SGAs (Loftis et al. 2013; Razavi et al. 2017; Ritsner et al. 2011).

Persian borage (Echium amoenum L.), an Iranian medicinal herb, contains various compounds like flavonoids and essential oils that give it anti-inflammatory, antioxidant, anxiolytic, and antidepressant properties (Bekhradnia and Ebrahimzadeh 2016; Miraj and Kiani 2016). Green tea is used in traditional medicine for respiratory, inflammatory, and psychological issues (Azizi et al. 2018; Jafari et al. 2018; Ramezani et al. 2020). Persian borage can prevent inflammatory disorders, regulate dopamine and serotonin levels (Rabbani et al. 2004; Saiiah bargard et al. 2005), lower

glucose and lipid levels (Mahmoudi et al. 2015), reduce oxidative stress in the nervous system (Kh and Siddiqui 2024; Sultana et al. 2022), lower blood pressure through its alkaloids and flavonoids and show cardioprotective effects (Roy et al. 2022; Zarshenas et al. 2016). It also has anti-obesity effects by inhibiting pancreatic lipase activity, increasing energy expenditure, promoting fat oxidation, and improving lipid profiles (Abed et al. 2012; Kang et al. 2018; Mahboob et al. 2023).

Purslane (Portulaca oleracea L.), a nutritious vegetable, has omega-3s, vitamins, and minerals, with health benefits like heart disease prevention, and is approved for obesity or diabetes management (Iranshahy et al. 2017; Li et al. 2024; Srivastava et al. 2023). Its antioxidants and anti-inflammatory properties combat oxidative stress and inflammation (Milkarizi et al. 2024), improve insulin sensitivity (Jafari et al. 2023; Jung et al. 2021), regulate appetite (Cho et al. 2019; Golzar et al. 2023), and improve blood lipids (Azizah et al. 2022; Hadi et al. 2019; Sabzghabaee et al. 2014). Purslane lowers blood glucose by boosting insulin, aiding glucose transport, reducing inflammation, offering polysaccharides and fiber, and protecting against oxidation, making it a valuable addition to combat obesity and diabetes (Ebrahimian et al. 2022; Jung et al. 2021). A recent study suggests that omega-3 supplements can help to improve symptoms of schizophrenia (Hsu and Ouyang 2021).

Therefore, purslane may be beneficial for SGA-related metabolic changes in schizophrenia patients.

This study examined the effects of an herbal compound made from green tea, Persian borage, and purslane on weight gain and obesity in schizophrenia patients treated with second-generation antipsychotics at Hijazi Psychiatry Hospital in Mashhad, Iran.

Materials and Methods

Study design

The present triple-blind study tested a new herbal compound's effects on weight gain and obesity in schizophrenia patients. All patients, researchers, and data analysts were blinded to the study conditions. It was registered in the Iranian Clinical Trials Registry (IRCT 20210707051813 N1), and conducted from 2021-2023 in Mashhad psychiatric center, Iran.

Preparation of medication

Three plants - Camellia sinensis L., Echium amoenum L., and Portulaca oleracea L. - were collected with approval from Mashhad Faculty of Agriculture and Plant Sciences. The herbarium at the Ferdowsi University of Mashhad validated the botanical specimens. Voucher specimen numbers are E-1335 FUMH for C. sinensis L., E-1334 FUMH for E. amoenum L., and E-1248 FUMH for P. oleracea L. After drying, the plants were macerated in 70% ethyl alcohol for 48 hr, then filtered and extracted into dry extracts. Oral herbalcapsules were formulated with 350 mg C. sinensis L. leaves extract, 225 mg E. amoenum L. flowers extract, and 125 mg P. oleracea L.

Aerial parts extract. The appropriate dosages for each extract were determined from relevant books, reliable sites, and recent articles (Chen et al. 2016; Drugs.com 2022a; Drugs.com 2022b; Duke et al. 2002; Ghahremanitamadon et al. 2014; Girard and Vohra 2011; Huang et al. 2018; Jafari et al. 2023; Jamilian et al. 2014; Lin et al. 2020; Loftis et al. 2013; Nouri et al. 2019; Razavi et al. 2017; Ritsner et al. 2011; Sabzghabaee et al. 2014; Sayyah et al. 2006; Zahedi et al. 2004; Zamansoltani et al. 2008). Based on these references, safe daily dosages for various purposes of extracts are established: green tea extract at 300-1500 mg/dayPersian borage extract at 200-4000 mg/day, and purslane extract at 300-800 mg/day. Considering the risks of liver and kidney damage for SGA consumers, the research team, consisting of a psychiatrist, pharmacist, and herbal

medicine specialists, revised the dosages to 700 mg/day for green tea, 500 mg/day for Persian borage, and 250 mg/day for purslane.

Avicel was employed in identical quantity as the herbal capsules to create placebo capsules.

Standardization of herbal extract capsules

The phenolic compounds in herbal capsules were measured by diluting the product, mixing it with reagents, and assessing the mixture after 2 hr using a spectrometer. The herbal capsule contained 330 mg of gallic acid equivalent per gram of total phenols.

Participants

The current study focused on schizophrenia patients aged 18-65 with a BMI of 25-40 kg/m^2 at Hijazi Psychiatry Hospital of Mashhad, Iran, who were admitted during the period from 2021 to 2023. They were on SGAs (including one or more of risperidone, olanzapine, clozapine, or quetiapine) without dosage changes for at least three months and were in the remission phase.

The ineligibility criteria were being patients with serious systemic illness, substance addiction (except nicotine), pregnancy or lactation, liver test elevations (twice the upper limits of normal and more), allergies to herbal medications, or those taking aripiprazole. Dropouts might result from allergic reactions, gastrointestinal intolerance, worsening symptoms, increased blood pressure, or unwillingness to continue participation.

Intervention

This placebo-controlled trial studied eligible patients randomly assigned to intervention or placebo groups. The intervention group received herbal extract capsules capsules twice daily for eight weeks as a supplement to their antipsychotic regimen. Herbal extract dosages were safe, chosen based on similar studies. Liver function, and urea, and creatinine levels were monitored for potential adverse effects. The control group received identical capsules containing Avicel. Patients were assessed at baseline and weeks four and eight.

Randomization and allocation

The present study used a triple-blind approach, using letters A and B to blind participants, researchers, and data analysts. It employed permuted block randomization, with a software-generated unique code concealing the identity of subjects during the randomization process. Sixteen blocks were created to randomize a sample size of 64.

Outcome measurements

The primary outcome was BMI (kg/m^2). Secondary outcomes included the assessment of waist-to-hip ratio (WHR) and blood biochemistry analyses. These analyses encompassed fasting blood sugar (FBS), HbA1c, lipid profile, blood urea nitrogen (BUN), creatinine, alanine transaminase (ALT), and aspartate transaminase (AST). Measurements were conducted at baseline and repeated at the end of week eight.

Appetite levels, the severity of psychotic symptoms, and blood pressure (using the Visual Analog Scale (VAS), the PANSS, and a device mercury manometer, respectively) were evaluated at baseline and weeks four and eight, while the quality of life was assessed with the WHOQOL-Bref questionnaire at baseline and week eight.

The WHOQOL-BREF is a 26-item questionnaire that assesses physical and psychological health, social relationships, and environmental health (Wong et al. 2018). It is a reliable test for evaluating the quality of life in schizophrenia patients (Dong et al. 2019; Mas-Expósito et al. 2011) and has been validated in Iran (Masoomi et al. 2018).

PANSS is a widely used tool to assess schizophrenia symptoms, comprising three subscales: Positive, Negative, and General

Psychopathology, each rated on a scale of 1 to 7. The total score is the sum of all three subscales. Lower scores indicate milder symptoms, while higher scores suggest more severe symptoms (Smith 2023). The Persian version of this questionnaire is reliable and valid, with a Cronbach's alpha coefficient of 0.83 and 0.77 from two studies, and its validity was confirmed by factor analysis (Abolghasemi 2007; Ghamari Givi et al. 2010).

The visual analog scale is a validated measure of appetite in which subjects rate their appetite levels on a scale of 0 to 10. It was developed by Flint et al. at the Fredrik Berg School of Nutrition in Denmark (Flint et al. 2000). The VAS instrument has been employed in different domains in research on schizophrenia patients (Carrasco-Picazo et al. 2023; Medeiros-Ferreira et al. 2013).

Sample size calculation

The sample size was determined utilizing a formula for comparing BMI in two groups with a power of 80 % and an alpha error of 5 %, resulting in 64 samples enrolled after accounting for a 10% dropout rate based on a study by Nasri and Taghian (Nasri and Taghian 2020).

Statistical analysis

Statistical analysis was conducted utilizing SPSS version 26 software to analyze quantitative and qualitative variables in the study. Descriptive statistics such as mean, standard deviation, frequency, and percentage were employed. The normality of the data was checked through the Kolmogorov–Smirnov test, while baseline characteristics were assessed using chi-square and t-tests for categorical and continuous variables, respectively. Within-group differences were compared using paired t-tests or Wilcoxon tests, and between-group analyses were done with independent sample t-tests or Mann-Whitney u-tests. ANOVA and analysis of covariance (ANCOVA) were utilized to identify differences in means and account for initial values. All tests were two-sided with a significance level set at less than 0.05.

Results

Seventy-three patients were initially qualified to participate in the study, but the number decreased due to changing medications, or getting COVID-19 (Figure 1). At the end of the 8-week investigation, 61 patients completed the trial; 9 (14.8%) were females, and 52 (85.2%) were males. They were randomly assigned to the intervention group (n=30) and the placebo group (n=31) for eight weeks. The average age of the patients was 44.23 ± 8.03 years. The two groups had no significant differences regarding age, gender, or BMI (p=0.498, p=0.731, and p=0.129, respectively). Additionally, there were no significant differences between the two groups regarding the duration of disease, smoking, physical activity, type of antipsychotics used, or any medication regimen (Table 1).

In the intervention group, there was a significant decrease in BMI (p<0.001), WHR (p<0.001), total cholesterol levels (p=0.03), LDL concentration (p=0.009), and systolic blood pressure (SBP) (p=0.037) after eight weeks. Additionally, there was a notable increase in high-density lipoprotein (HDL) concentration (p=0.02). The mean AST level significantly increased from 18.43±4.94 to 21.37±5.81 (IU/L) (p=0.002) and the ALT level increased from 19.33±8.76 to 21.73±8.67 (IU/L) (p=0.008) after eight weeks in the intervention group. In the placebo group, the mean level of AST and ALT showed significant changes (p=0.04 and p=0.037), while the other measured variables did not change significantly in this period (for all p>0.05).
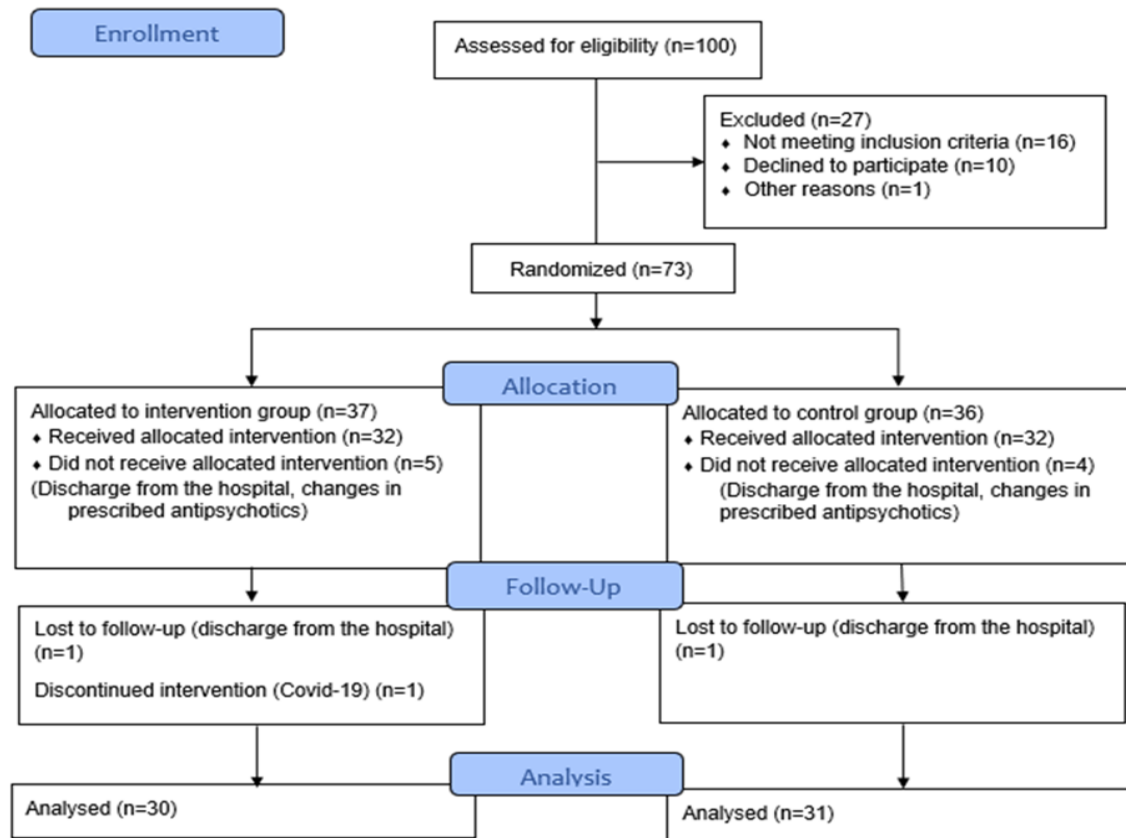
Herbal approach for antipsychotic weight gain

Figure 1. CONSORT Flow Diagram of the study

Table 1. Baseline characteristics of the participants.

	Intervention (n=30)	Placebo (n=31)	Total (n=61)	p-value
Age, years	43.40 ±8.24	45.03±7.88	44.23 ± 8.03	0.498 [d]
Gender, male	25 (83.3 %)	27 (87.1 %)	52 (85.2 %)	0.731 [b]
BMI (kg/m^2)	28.13 ± 2.07	28.91 ± 1.86	28.53 ± 1.99	0.129 [d]
Duration of disease (years)				
< 5	5 (16.7 %)	5 (16.1 %)	10 (16.4 %)	
5-10	16 (53.3 %)	13 (41.9 %)	29 (47.5 %)	0.289 [c]
>10	9 (30.0 %)	13 (41.9 %)	22 (36.1 %)	
Smoking	15 (50 %)	14 (45.2 %)	29 (47.5 %)	0.705 [a]
Sport	16 (53.3%)	16 (51.6 %)	32 (52.4 %)	0.893 [a]
Antipsychotic regimen				
Olanzapine	1 (3.3 %)	1 (3.2 %)	2 (3.3 %)	0.933 [a]
Clozapine	8 (26.7 %)	7 (22.6 %)	15 (24.6 %)	
Quetiapine	1 (3.3 %)	2 (6.5 %)	3 (4.9 %)	
Olanzapine-risperidone	3 (10.0 %)	2 (6.5 %)	5 (8.2 %)	
Clozapine-risperidone	7 (23.3 %)	9 (29 %)	16 (26.2 %)	
Risperidone-Quetiapine	3 (10.0 %)	4 (12.9 %)	7 (11.5 %)	
Olanzapine-clozapine	4 (13.3 %)	2 (6.5 %)	6 (9.8 %)	
Olanzapine-Quetiapine	1 (3.3 %)	3 (9.7 %)	4 (6.6 %)	
Clozapine-Quetiapine	1 (3.3 %)	1 (3.2 %)	2 (3.3 %)	
Olanzapine-clozapine-quetiapine	1 (3.3 %)	0 (0 %)	1 (1.6 %)	
Anti-diabetic agents				
Metformin	8 (26.7 %)	12 (38.7 %)	20 (32.8%)	0.316 [a]
Glibenclamide	3 (9.7 %)	1 (3.3 %)	4 (6.5%)	0.354 [b]
Pitoze	3 (9.7%)	0 (0.0 %)	4 (6.5%)	0.113 [b]
Anti-lipid agents				
Atorvastatin	17 (56.7%)	13 (41.9%)	30 (49.2%)	0.250 [a]
Gemfibrozil	2 (6.7%)	0(0.0%)	2 (3.2%)	0.238 [b]
Fenofibrate	1 (3.3%)	0(0.0%)	1 (3.3%)	0.492 [b]
Anti-hypertensive agents	3 (10.0%)	6 (19.3%)	9 (14.7%)	0.473 [b]
Cardiovascular drugs	2 (6.6%)	0 (0.0)	2 (3.2%)	0.238 [b]

Data are presented as mean ± standard deviation or number (%). Between group analysis was evaluated as follows: a. Chi-square test; b. Fisher's exact test; c. Mann-Whitney u test; and d. independent sample t-test. The level of significance was less than 0.05. BMI: body mass index.

The between-group analysis at week eight showed that the intervention group had significantly lower BMI, WHR, HbA1c, and LDL concentration, and SBP than the placebo group. However, the mean AST level was higher in the intervention group than the placebo group (Table 2).

The intervention group had significantly lower VAS scores than the placebo group at weeks four and eight (Table 3 and Figure 2). There were no significant differences between the groups regarding positive, negative, or psychological symptoms and the total score of PANSS at any time point. The Quality of Life scores showed differences in psychological and environmental health dimensions at week eight (Table 3). Smoking status and physical activity remained unchanged for both groups. No significant adverse effects were reported.
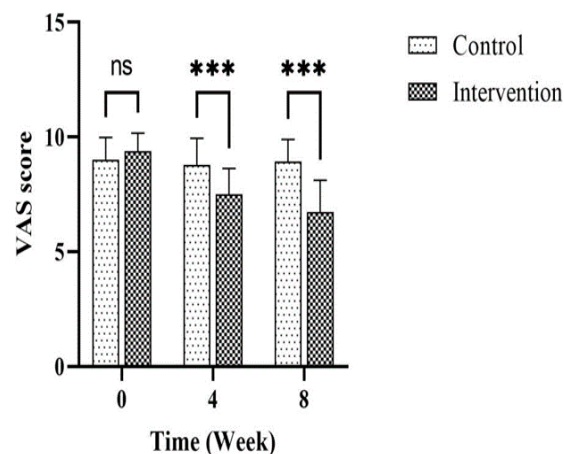

Figure 2. The effect of herbal compound on the appetite level of patients with a visual analog scale. Data are displayed as Mean±SD. Two-way Repeated Measures ANOVA (mixed model) and Bonferroni's post hoc test were used for statistical analysis. ns, Non-significant; ***$p > 0.001$ compared to the control group.

Table 2. Changes in BMI, anthropometric and clinical indicators, and biochemical parameters in intervention and placebo groups over time.

	Intervention (n=30)				Placebo (n=31)				**p-value
	Baseline	**Week 8**	**Mean difference**	*p-value	**Baseline**	**Week 8**	**Mean difference**	*p-value	value
BMI (kg/m^2)	28.13±2.07	27.13±1.98	-1.00	<0.001	28.91 ± 1.86	29.00±1.75	0.09	0.218	<0.001
WHR	1.01±0.07	1.00±0.07	-0.01	<0.001	1.01±0.08	1.01±0.08	0	0.36	<0.001
HbA1c (%)	5.77±0.57	5.72±0.58	-0.05	0.202	5.92±0.57	6.00±0.58	0.07	0.172	0.042
FBS (mg/dl)	88.23±18.24	87.93±15.97	-0.30	0.81	80.65±11.6	81.23±13.02	0.58	0.756	0.750
TG (mg/dl)	172.73±72.5	165.77±67.6	-6.96	0.12	119.65±50.7	120.94±56.9	1.29	0.762	0.504
Chol (mg/dl)	164.5±33.4	156.17±31.3	-8.33	0.03	136.94±21.01	139.81±25.02	2.87	0.283	0.215
LDL (mg/dl)	99.03±17.53	91.17±18.98	-7.87	0.009	86.77±22.98	88.35±25.18	1.58	0.38	0.021
HDL (mg/dl)	35.57±5.94	37.77±7.05	2.20	0.02	36.55±6.92	38.23±6.65	1.67	0.13	0.870
AST (IU/L)	18.43±4.95	21.37±5.82	2.93	0.002	21.71±6.03	20.03±6.52	-1.68	0.04	0.006
ALT(IU/L)	19.33±8.76	21.73±8.67	2.40	0.008	18.06±7.11	19.52±8.11	1.45	0.037	0.359
BUN (mg/dl)	22.73±7.52	21.80±4.31	-0.93	0.439	23.42±7.00	25.71±10.41	2.29	0.184	0.06
Cr (mg/dl)	0.99±0.13	0.95±0.13	0.04	0.053	0.97±0.11	0.97±0.17	0. 0	0.888	0.394
SBP (mmHg)	120.50±12.13	118.50±11.23	-1.066	0.037	121.29±14.60	121.13±13.70	-0.161	0.879	0.015
DPB (mmHg)	74.00±6.61	73.83±8.06	-0.167	0.920	72.58±9.11	73.71±7.84	1.129	0.467	0.475

Data are presented as mean ± standard deviation; BMI, body mass index; WHR, ratio of waist circumference to hip circumference; HbA1c, glycosylated hemoglobin; FBS, fasting blood sugar; TG, triglycerides; Chol, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BUN, blood urea nitrogen; Cr, creatinine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SBP, systolic blood pressure; DBP, diastolic blood pressure. Within-group analysis with Paired-samples t-test; **Between-group analysis with General linear model (multivariate) test. *The level of significance was less than 0.05.

Table 3. Changes in VAS score, PANSS score, and WHOQOL – BREF score in the intervention and placebo group at two or three time points.

	Intervention (n=30)	Placebo (n=31)	p-value
VAS score			
Baseline	9.47±0.68	9.00±1.00	0.58
Week 4	7.50±1.11	8.77±1.18	**<0.001**
Week 8	6.73±1.39	8.94±0.96	**<0.001**
PANSS score			
Positive score			
Baseline	25.0± 6.86	23.48± 5.36	0.340
Week 4	24.33± 6.69	23.48± 5.26	0.583
Week 8	24.23± 6.81	23.0± 5.1	0.428
Negative score			
Baseline	28.57± 6.12	27.84± 5.05	0.614
Week 4	28.67± 5.91	27.42± 4.87	0.372
Week 8	28.60± 5.75	27.29± 4.88	0.341
General score			
Baseline	62.83± 5.85	63.81± 5.90	0.521
Week 4	61.0± 6.42	63.16± 6.04	0.181
Week 8	60.53± 6.56	62.97± 6.06	0.138
Total score			
Baseline	116.40±12.65	115.13±11.73	0.685
Week 4	114.00±13.14	114.06±11.34	0.984
Week 8	113.37±13.06	113.26±11.76	0.973
WHOQOL – BREF score			
Physical health			
Baseline	27.62± 14.22	23.50± 12.63	0.236
Week 8	28.33± 14.43	24.07± 12.12	0.217
Psychological health			
Baseline	45.41± 9.68	39.9± 11.87	0.053
Week 8	52.08± 10.36	44.62± 12.13	**0.012**
Social relationships			
Baseline	22.50± 19.34	23.92± 18.22	0.768
Week 8	26.38± 21.11	23.65± 19.13	0.326
Environmental health			
Baseline	36.14± 7.18	32.15± 8.62	0.055
Week 8	36.14± 6.54	31.85 ± 7.88	**0.02**
General health			
Baseline	53.33± 15.02	49.19± 15.79	0.260
Week 8	53.3± 15.02	49.19± 15.79	0.260

Data were presented as mean ± standard deviation. VAS, Visual Analog Scale; PANSS, Positive, and Negative Syndrome Scale; WHOQL-BREF, World Health Organization Quality of Life Scale. Between-group analysis with independent sample t-test or its nonparametric equivalent (Mann-Whitney u test). The level of significance was less than 0.05.

Discussion

The present clinical trial tested an herbal combination, as an adjunct for weight control in schizophrenia patients. Results showed reduced BMI, WHR, cholesterol, HbA1c, systolic blood pressure, and appetite and improved HDL levels combined with antipsychotic treatment.

Antipsychotics are known to cause weight gain by increasing appetite, with the exact mechanism being still unclear. Serotonin receptors play a role in hyperphagia and weight gain induced by SGAs like olanzapine, clozapine, quetiapine, and risperidone, impacting obesity. Olanzapine and clozapine bind to 5-hydroxytryptamine receptor 2a (5HT2a) and 2c receptors, quetiapine blocks 5HT receptors, while risperidone inhibits 5HT2c receptors affecting appetite regulation (Mukherjee et al. 2022).

Research indicates that bioactive compounds in plants such as green tea, Persian borage, and purslane can positively affect metabolism and appetite, potentially offering an effective approach to managing weight gain associated with SGAs (Azizah et al. 2022; Golzar et al. 2023; Hasegawa et al. 2003; Hibi et al. 2018; Huang et al. 2014; Mahmoudi et al. 2015; Rains et al. 2011; Sabzghabaee et al. 2014; Uddin et al. 2014b).

The protective effects of green tea aqueous extract (GTAE) on olanzapine-related-metabolic changes were studied by Razavi et al. (Razavi et al. 2017). Their study on Wistar rats found that GTAE (25, 50, and 100 mg/kg/day, intraperitoneally.) significantly reduced body weight gain, improved lipid profile, and blood glucose, and lowered hyperleptinemia and hypertension. In a clinical study, Loftis et al. found that 150 mg of epigallocatechin gallate (EGCG) did not significantly decrease psychiatric symptoms in schizophrenia and bipolar disorder over 8 weeks (Loftis et al. 2013). In contrast, Ritsner et al. discovered that 400 mg/d of L-theanine improved positive symptoms, activation, and anxiety in patients with schizophrenia/schizoaffective disorder (Ritsner et al. 2011). Neither of these two studies examined metabolic changes or weight.

The antidepressant and anxiolytic effects of Echium amoenum have been found in studies, but research on its impact on psychosis is limited. A study by Sayyah et al. (Sayyah et al. 2006) using 375 mg of Echium amoenum aqueous extract reduced depressive symptoms. However, our study did not observe significant changes in patients' negative or positive symptoms. Zamansoltani et al. (Zamansoltani et al. 2008) found that administering an aqueous extract of Echium amoenum (100, 200, or 400 mg/kg/day) decreased serum levels of ALT and Alkaline phosphatase (ALP) in rats, while Zahedi et al. (Zahedi et al. 2004) showed that a methanolic extract of Echium amoenum (200 mg/kg) increased ALT and AST serum levels.

Purslane has the highest levels of omega-3 fatty acids among plants (Uddin et al. 2014a). Recent research suggests that schizophrenia patients lack omega-3 fatty acids, with supplementation improving positive and negative symptoms (Hsu and Ouyang 2021; Jamilian et al. 2014). In the Jamilian et al. study, 1000 mg/day omega-3 supplementation decreased the general psychopathologic score in PANSS in 60 schizophrenia patients (Jamilian et al. 2014).

In similar studies, a singular plant was analyzed; conversely, our research employed a triad of plants for enhanced efficacy. The synergistic interaction of these three plants may facilitate weight management. The catechins and caffeine present in green tea are posited to elevate metabolism and fat oxidation, while Persian borage and purslane contribute to inflammation management, nutrient absorption, and satiety enhancement. This integrative strategy may promote healthier weight by addressing energy expenditure and caloric intake. Moreover, the enhancement of insulin sensitivity, inflammation reduction, antioxidant properties, and the omega-3 and nutrient density of the herbal compound may aid in metabolic syndrome management.

Our research found that taking 700 mg of this herbal extract twice daily for eight weeks helped to manage weight gain in schizophrenia patients by controlling appetite and reducing cholesterol. Furthermore, herbal formula significantly decreased HbA1c levels within eight weeks. While it is ideal to compare changes in HbA1c levels over 12 weeks, the HbA1c test is more reliable than FBS for evaluating serum glucose levels due to its resistance to short-term influences like food intake, exercise, or stress.

Additionally, giving 700 mg of hydroalcoholic herbal extracts twice daily raised AST and ALT serum levels by 2-3 IU/L over eight weeks, within normal ranges. Still, caution is advised due to potential hepatotoxicity. Administering a safe dose of herbal medications is crucial to prevent liver issues and worsening of symptoms, although future studies should use more thorough tests to assess liver function.

The research sought to utilize herbal compounds for weight management and psychiatric symptom relief associated with SGAs. Nonetheless, the herbal compound did not demonstrate notable enhancements

in patients' quality of life or PANSS scores. Given dopamine's role in pleasure and motivation, it was hypothesized that the herbal compound could enhance patient outcomes by modulating dopamine levels. However, the limited results may stem from concerns regarding the side effects of higher dosages and the study's duration.

The herbs we utilized could be effortlessly integrated into the patients' diet as decoctions, herbal tea, or in food recipes.

Twice-daily use of herbal capsule, a compound of green tea, Persian borage, and Purslane extract, with antipsychotics can help manage weight in schizophrenia patients. It is recommended to combine these extracts with a balanced diet and regular exercise for best results.

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Conflicts of interest

The authors have confirmed no conflict of interest related to this manuscript.

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Ethical Considerations

This clinical trial has been conducted under the Declaration of Helsinki and approved by the ethics committees of Mashhad University of Medical Sciences. Informed consent was obtained from patients or their legal representatives after explaining the study's purpose.

Code of Ethics

IR.MUMS.REC.1400.075.

Authors' Contributions

M.R. Fayyazi Bordbar, R. Salari, and M. Yousefi led the study's conception and design. H. Naghibi, M.R. Ghanbarzadeh, and M. Kh-Rezaiyan prepared the herbal compound and conducted experiments, including data collection, analysis, and interpretation. H. Naghibi, R.Salari, and S.K. Farahmand drafted the article. All authors reviewed the manuscript critically and approved the final version.

References

Abed A, Minaiyan M, Ghannadi A, Mahzouni P, Babavalian MR (2012) Effect of Echium amoenum Fisch. et Mey a traditional Iranian herbal remedy in an experimental model of acute pancreatitis. Int Sch Res Notices 1(5):14-18

Abolghasemi A (2007) The relationship of meta-cognitive beliefs with positive and negative symptomes in the schizophrenia patients. Clin Psychol Personality 5(2):1-10

Azizah RN, Emelda A, Asmaliani I, Ahmad I, Fawwaz M (2022) Total Phenolic, Flavonoids, and Carotenoids Content and Anti-Obesity Activity of Purslane Herb (Portulaca oleracea L.) Ethanol Extract. Pharmacogn J 14(1):08-13

Azizi H, Ghafari S, Ghods R, Shojaii A, Salmanian M, Ghafarzadeh J (2018) A review study on pharmacological activities, chemical constituents, and traditional uses of Echium amoenum. Pharmacogn Rev 12(24):208-213.

Bekhradnia S, Ebrahimzadeh MA (2016) Antioxidant activity of Echium amoenum. Rev Chim J 67(2):223-6

Carrasco-Picazo JP, González-Teruel A, Gálvez-Llompart AM, Carbonell-Asins JA, Hernández-Viadel M (2023) Pain sensitivity in patients with schizophrenia: a systematic review and meta-analysis. Actas Esp Psiquiatr 51(1):29-40

Chen IJ, Liu CY, Chiu JP, Hsu CH (2016) Therapeutic effect of high-dose green tea extract on weight reduction: A randomized, double-blind, placebo-controlled clinical trial. Clinical nutrition (Edinburgh, Scotland) 35(3):592-9

Cho H, Kim K, Jang D-J, Kim HY (2019) Effect of six Korean plants on glucagon like peptide-1 release. Food Sci Biotechnol 28:1571-1576

Dong M, Lu L, Zhang L, et al. (2019) Quality of life in schizophrenia: A meta-analysis of comparative studies. Psychiatr Q 90:519-532

Drugs.com (2022a) Green Tea Uses, Benefits & Dosage. In. https://www.drugs.com/npp/green-tea.html Accessed 2021

Drugs.com (2022b) Purslane Uses, Benefits & Dosage. In. https://www.drugs.com/npp/purslane.html#dosage 2021

Duke JA, Bogenschutz-Godwin MJ, K. Duke P-A (2002) Handbook of Medicinal Herbs, 2nd edn. CRC Press, P:353-354., Boca Raton, United States of America

Ebrahimian Z, Razavi BM, Shaegh SAM, Hosseinzadeh H (2022) Effects of Portulaca oleracea L.(purslane) on the metabolic syndrome: A review. Iran J Basic Med Sci 25(11):1275

Flint A, Raben A, Blundell J, Astrup A (2000) Reproducibility, power and validity of visual analogue scales in assessment of appetite sensations in single test meal studies. Int J Obes 24(1):38-48

Ghahremanitamadon F, Shahidi S, Zargooshnia S, Nikkhah A, Ranjbar A, Soleimani Asl S (2014) Protective effects of Borago officinalis extract on amyloid β-peptide(25-35)-induced memory impairment in male rats: a behavioral study. BioMed research international 2014:798535

Ghamari Givi H, Moulavi P, Heshmati R (2010) Exploration of the factor structure of positive and negative syndrome scale in schizophernia spectrum disorder. J Clin Psychol 2(2):1-10

Girard L, Vohra S (2011) Ethics of Using Herbal Medicine as Primary or Adjunct Treatment and Issues of Drug-Herb Interaction. In: Benzie IFF, Wachtel-Galor S (eds) Herbal Medicine: Biomolecular and Clinical Aspects. CRC Press/Taylor & Francis, Boca Raton (FL)

Golzar M, Saghi E, Rakhshandeh H, Dehnavi Z, Esfehani AJ, Nematy M (2023) Evaluating the effect of an Iranian traditional medicine-based herbal candy on body composition and appetite in overweight and obese adults: A preliminary study. Avicenna J Phytomed 13(2):165

Hadi A, Pourmasoumi M, Najafgholizadeh A, Kafeshani M, Sahebkar A (2019) Effect of purslane on blood lipids and glucose: A systematic review and meta-analysis of randomized controlled trials. Phytother res 33(1):3-12

Hasegawa N, Yamda N, Mori M (2003) Powdered green tea has antilipogenic effect on Zucker rats fed a high-fat diet. Phytother Res 17(5):477-480

Hibi M, Takase H, Iwasaki M, Osaki N, Katsuragi Y (2018) Efficacy of tea catechin-rich beverages to reduce abdominal adiposity and metabolic syndrome risks in obese and overweight subjects: a pooled analysis of 6 human trials. Nutr Res 55:1-10

Hidese S, Ogawa S, Ota M, et al. (2019) Effects of L-Theanine Administration on Stress-Related Symptoms and Cognitive Functions in Healthy Adults: A Randomized Controlled Trial. Nutrients 11(10)

Hsu MC, Ouyang WC (2021) A Systematic Review of Effectiveness of Omega-3 Fatty Acid Supplementation on Symptoms, Social Functions, and Neurobiological Variables in Schizophrenia. Biol Res Nurs 23(4):723-737

Huang J, Wang Y, Xie Z, Zhou Y, Zhang Y, Wan X (2014) The anti-obesity effects of green tea in human intervention and basic molecular studies. Eur J Clin Nutr 68(10):1075-1087

Huang L-H, Liu C-Y, Wang L-Y, Huang C-J, Hsu C-H (2018) Effects of green tea extract on overweight and obese women with high levels of low density-lipoprotein-cholesterol (LDL-C): a randomised, double-blind, and cross-over placebo-controlled clinical trial. BMC Complement Altern Med 18:1-11

Hursel R, Viechtbauer W, Dulloo AG, et al. (2011) The effects of catechin rich teas and caffeine on energy expenditure and fat oxidation: a meta-analysis. Obesity reviews : an official journal of the International Association for the Study of Obesity 12(7):e573-81

Iranshahy M, Javadi B, Iranshahi M, et al. (2017) A review of traditional uses, phytochemistry and pharmacology of

Portulaca oleracea L. J Ethnopharmacol 205:158-172

Jafari H, Mokaberinejad R, Raeis-Abdollahi E (2018) Echium amoenum from viewpoint of Avicenna: a brief review. J Contemp Med Sci 4(4):187–190.

Jafari N, Shoaibinobarian N, Dehghani A, et al. (2023) The effects of purslane consumption on glycemic control and oxidative stress: A systematic review and dose–response meta-analysis. Food sci nutr 11(6):2530-2546

Jamilian H, Solhi H, Jamilian M (2014) Randomized, placebo-controlled clinical trial of omega-3 as supplemental treatment in schizophrenia. Glob. J. Health Sci 6(7):103-8

Javidi N, Mazloum Khorasani Z, Salari R, Niroumand S, Yousefi M (2024) Investigation the effect of a herbal composition based on blackseed on patients with primary hypothyroidism: A randomized controlled trial. Avicenna J Phytomed 14(3):325-337

Jung JH, Hwang SB, Park HJ, Jin GR, Lee BH (2021) Antiobesity and Antidiabetic Effects of Portulaca oleracea Powder Intake in High-Fat Diet-Induced Obese C57BL/6 Mice. Evidence-based complementary and alternative medicine : eCAM 2021:5587848

Kang HW, Lee SG, Otieno D, Ha K (2018) Flavonoids, Potential Bioactive Compounds, and Non-Shivering Thermogenesis. Nutrients 10(9): 1168.

Kh A, Siddiqui N (2024) An Insight into a therapeutically significant herbal drug, Gul-e-Gaozuban (Borago officinalis flower), from the treasures of Unani Medicine. IJUIM 8:112-118

Lardner AL (2014) Neurobiological effects of the green tea constituent theanine and its potential role in the treatment of psychiatric and neurodegenerative disorders. Nutr Neurosci 17(4):145-55

Li Y, Xiao L, Yan H, Wu M, Hao X, Liu H (2024) Nutritional values, bioactive compounds and health benefits of purslane (Portulaca oleracea L.): a comprehensive review. Food Sci Hum Wellness 13(5):2480-2501

Lin Y, Shi D, Su B, et al. (2020) The effect of green tea supplementation on obesity: A systematic review and dose-response meta-analysis of randomized controlled trials. Phytother Res 34(10):2459-2470

Liu K, Zhou R, Wang B, et al. (2013) Effect of green tea on glucose control and insulin sensitivity: a meta-analysis of 17 randomized controlled trials123. Am J Clin Nutr 98(2):340-348

Loftis JM, Wilhelm CJ, Huckans M (2013) Effect of epigallocatechin gallate supplementation in schizophrenia and bipolar disorder: an 8-week, randomized, double-blind, placebo-controlled study. Ther. Adv. Psychopharmacol. 3(1):21-7

Macêdo APA, Gonçalves MdS, Barreto-Medeiros JM, et al. (2023) Green Tea Induces the Browning of Adipose Tissue—Systematic Review. Obesities 3(3):193-206

Mahboob A, Samuel SM, Mohamed A, et al. (2023) Role of flavonoids in controlling obesity: molecular targets and mechanisms. Front Nutr 10:1177897

Mahmoudi M, Shahidi S, Golmohammadi H, Mohammadi S (2015) The effect of Echium amoenum hydro-alcoholic extract on blood glucose level, lipid profile and lipoproteins in streptozotocin-induced diabetic male rats. J Adv Med Biomed Res 23:72-81

Mancini E, Beglinger C, Drewe J, Zanchi D, Lang UE, Borgwardt S (2017) Green tea effects on cognition, mood and human brain function: A systematic review. Phytomedicine 34:26-37

Mas-Expósito L, Amador-Campos JA, Gómez-Benito J, Lalucat-Jo L (2011) The World Health Organization quality of life scale brief version: a validation study in patients with schizophrenia. Qual Life Res 20:1079-1089

Masoomi M, Shadloo B, Nedjat S, Bahrami Z, Sharifi V, Amini H (2018) Validity and reliability of the Persian version of the "Quality of Life Scale" in schizophrenia. Iran J Psychiatry Behav Sci 12(3): 1-5

Medeiros-Ferreira L, Obiols JE, Navarro-Pastor JB, Zúñiga-Lagares A (2013) Metabolic syndrome and health-related quality of life in patients with schizophrenia. Actas Esp Psiquiatr 41 17-26

Milkarizi N, Barghchi H, Belyani S, et al. (2024) Effects of Portulaca oleracea (purslane) on liver function tests, metabolic profile, oxidative stress and inflammatory biomarkers in patients with non-alcoholic fatty liver disease: a randomized, double-blind clinical trial. Front nutr 11:1371137

Miraj S, Kiani S (2016) A review study of therapeutic effects of Iranian borage (Echium amoenum Fisch). Pharm Lett 8(6):102-9

Mukherjee S, Skrede S, Milbank E, Andriantsitohaina R, López M, Fernø J (2022) Understanding the effects of antipsychotics on appetite control. Front Nutr 8:815456

Naghibi H, Salari R, Yousefi M, Khadem-Rezaiyan M, Ghanbarzadeh MR, Fayyazi Bordbar MR (2023) Herbal Therapies for Weight Gain and Metabolic Abnormalities Induced by Atypical Antipsychotics: A Review Article. Curr Drug Discov Technol 20(5):19-35

Nasri M, Taghian F (2020) Effect of high intensity interval training and use of Echium amoenum on serum ferritin and CRP levels in overweight and obese women. Iran J Psychiatry Behav Sci 23(1):79-87

Nouri M, Farajdokht F, Torbati M, et al. (2019) A Close Look at Echium amoenum Processing, Neuroactive Components, and Effects on Neuropsychiatric Disorders. GMJ 8:e1559

Onakpoya I, Spencer E, Heneghan C, Thompson M (2014) The effect of green tea on blood pressure and lipid profile: a systematic review and meta-analysis of randomized clinical trials. Nutr Metab Cardiovasc Dis 24(8):823-836

Patel KR, Cherian J, Gohil K, Atkinson D (2014) Schizophrenia: overview and treatment options. P & T : a peer-reviewed journal for formulary management 39(9):638-45

Potenza MA, Marasciulo FL, Tarquinio M, et al. (2007) EGCG, a green tea polyphenol, improves endothelial function and insulin sensitivity, reduces blood pressure, and protects against myocardial I/R injury in SHR. Am J Physiol Endocrinol Metab 292(5):E1378-E1387

Rabbani M, Sajjadi S, Vaseghi G, Jafarian A (2004) Anxiolytic effects of Echium amoenum on the elevated plus-maze model of anxiety in mice. Fitoterapia 75(5):457-464

Rahman T, Lauriello J (2016) Schizophrenia: an overview. Focus 14(3):300-307

Rains TM, Agarwal S, Maki KC (2011) Antiobesity effects of green tea catechins: a mechanistic review. J Nutr Biochem 22(1):1-7

Ramezani M, Amiri MS, Zibaee E, et al. (2020) A review on the phytochemistry, ethnobotanical uses and pharmacology of Borago species. Curr Pharm Des 26(1):110-128

Rani R, Nagpal D, Gullaiya S, Madan S, Agrawal S (2014) Phytochemical, pharmacological and beneficial effects of green tea. Int J Pharmacogn Phytochem Res 6(3):420-426

Razavi BM, Lookian F, Hosseinzadeh H (2017) Protective effects of green tea on olanzapine-induced-metabolic syndrome in rats. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 92:726-731

Ritsner MS, Miodownik C, Ratner Y, et al. (2011) L-theanine relieves positive, activation, and anxiety symptoms in patients with schizophrenia and schizoaffective disorder: an 8-week, randomized, double-blind, placebo-controlled, 2-center study. J Clin Psychiatry 72(1):34-42

Roy A, Khan A, Ahmad I, et al. (2022) Flavonoids a Bioactive Compound from Medicinal Plants and Its Therapeutic Applications. BioMed research international 2022:5445291

Sabzghabaee AM, Kelishadi R, Jelokhanian H, Asgary S, Ghannadi A, Badri S (2014) Clinical effects of Portulaca oleracea seeds on dyslipidemia in obese adolescents: a triple-blinded randomized controlled trial. Med Arch 68(3):195

Saiiah bargard M, Boostani H, Saiiah M, Fazileh F, Kamalinejad M, Akhondzadeh S (2005) Efficacy of aqueous extract of Echium amoenum L. in the treatment of mild to moderate obsessive – compulsive disorder. J Med plants 4(15):43-50

Salehsari A, Ghasemzadeh Rahbardar M, Razavi BM, Hosseinzadeh H (2024) Investigating the effect of zeaxanthin on olanzapine-induced metabolic disorders in rats. Avicenna J Phytomed 14(6):653-665

Salleh MR (2018) The burden of mental illness: An emerging global disaster. J Clin Health Sci 3(1):1-8

Sayyah M, Sayyah M, Kamalinejad M (2006) A preliminary randomized double blind clinical trial on the efficacy of aqueous extract of Echium amoenum in the

treatment of mild to moderate major depression. Prog Neuro-Psychopharmacol Biol Psychiatry 30(1):166-169

Shi X-J, Fan F-C, Liu H, et al. (2021) Traditional Chinese medicine decoction combined with antipsychotic for chronic schizophrenia treatment: a systematic review and Meta-analysis. Front Pharmacol 11:616088

Sirotkin AV, Kolesárová A (2021) The anti-obesity and health-promoting effects of tea and coffee. Physiol. Res 70(2):161-168

Smith J (2023) In. https://reference.medscape.com/calculator/860/positive-and-negative-syndrome-scale-for-schizophrenia-panss

Smith RC, Rachakonda S, Dwivedi S, Davis JM (2012) Olanzapine and risperidone effects on appetite and ghrelin in chronic schizophrenic patients. Psychiatry res 199(3):159-163

Srivastava R, Srivastava V, Singh A (2023) Multipurpose Benefits of an Underexplored Species Purslane (Portulaca oleracea L.): A Critical Review. Environ. Manag. 72(2):309-320

Stip E, Lungu O, Anselmo K, et al. (2012) Neural changes associated with appetite information processing in schizophrenic patients after 16 weeks of olanzapine treatment. Transl Psychiatry 2(6):e128-e128

Sultana A, Rahman K, Heyat MBB, Sumbul, Akhtar F, Muaad AY (2022) Role of Inflammation, Oxidative Stress, and Mitochondrial Changes in Premenstrual Psychosomatic Behavioral Symptoms with Anti-Inflammatory, Antioxidant Herbs, and Nutritional Supplements. Oxid Med Cell Longev 2022(1):3599246

Suzuki T, Pervin M, Goto S, Isemura M, Nakamura Y (2016) Beneficial Effects of Tea and the Green Tea Catechin Epigallocatechin-3-gallate on Obesity. Molecules 21(10):1305

Tschoner A, Engl J, Laimer M, et al. (2007) Metabolic side effects of antipsychotic medication. Int J Clin Pract 61(8):1356-1370

Uddin MK, Juraimi AS, Hossain MS, Nahar MA, Ali ME, Rahman MM (2014a) Purslane weed (Portulaca oleracea): a prospective plant source of nutrition, omega-3 fatty acid, and antioxidant attributes. Sci World J 2014:951019

Uddin MK, Juraimi AS, Hossain MS, Nahar MAU, Ali ME, Rahman M (2014b) Purslane weed (Portulaca oleracea): A prospective plant source of nutrition, omega-3 fatty acid, and antioxidant attributes. Sci World J 2014(1):951019

Wan C, Ouyang J, Li M, Rengasamy KR, Liu Z (2024) Effects of green tea polyphenol extract and epigallocatechin-3-O-gallate on diabetes mellitus and diabetic complications: Recent advances. Crit Rev Food Sci Nutr 64(17):5719-5747

Werneke U, Taylor D, Sanders TA (2013) Behavioral interventions for antipsychotic induced appetite changes. Curr Psychiatry Rep 15:1-10

Wong FY, Yang L, Yuen JWM, Chang KKP, Wong FKY (2018) Assessing quality of life using WHOQOL-BREF: a cross-sectional study on the association between quality of life and neighborhood environmental satisfaction, and the mediating effect of health-related behaviors. BMC public health 18(1):1113

Xu R, Bai Y, Yang K, Chen G (2020) Effects of green tea consumption on glycemic control: a systematic review and meta-analysis of randomized controlled trials. Nutr Metab 17(1):56

Yang CS, Zhang J, Zhang L, Huang J, Wang Y (2016) Mechanisms of body weight reduction and metabolic syndrome alleviation by tea. Mol Nutr Food Res 60(1):160-74

Yıldırım Ayaz E, Dincer B, Mesci B (2023) Effect of Green Tea on Blood Pressure in Healthy Individuals: A Meta-Analysis. Altern Ther Health Med 29(5):66-73

Zahedi M, Heidari M, Mohajeri M (2004) Study the effect of Valeriana Officinalis and Echium Amoenum on the liver and renal function tests in rats. J Kerman Univ Med Sci 10(1):22-27

Zamansoltani F, Nassiri-Asl M, Karimi R, Mamaghani-Rad P (2008) Hepatotoxicity effects of aqueous extract of Echium amoenum in rats. Pharmacologyonline 1:432-8

Zarshenas M, Dabaghian F, Moein M (2016) An overview on phytochemical and pharmacological aspects of Echium amoenum. Nat Rev Endocrinol 6(4):285-291

Zheng G, Sayama K, Okubo T, Juneja LR, Oguni I (2004) Anti-obesity effects of three major components of green tea, catechins, caffeine and theanine, in mice. In vivo 18(1):55-62 .