

Black Seed (*Nigella sativa*) Efficacy in Improving Clinical Symptoms and Interleukin-6 Levels Schizophrenic Patients

by Saidah Syamsuddin

Submission date: 23-Jul-2022 07:06AM (UTC+0700)

Submission ID: 1873939283

File name: ed_*Nigella sativa*_Efficacy_in_Improving_Clinical_Symptoms.pdf (450.15K)

Word count: 7608

Character count: 40369



Black Seed (*Nigella sativa*) Efficacy in Improving Clinical Symptoms and Interleukin-6 Levels Schizophrenic Patients

Sri Purwatiningsih*, Saidah Syamsuddin³², Sonny T. Lisal, Kristian Liaury, Burhanuddin Bahar, Ika Yustisia

Department of Psychiatry, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia

Abstract

Edited by: Sasho Stoleski
Citation: Purwatiningsih S, Syamsuddin S, Lisal ST, Liaury K, Bahar B, Yustisia I. Black seed (*Nigella sativa*) Efficacy in Improving Clinical Symptoms and Interleukin-6 Levels Schizophrenic Patients. *Open Access Maced J Med Sci*. 2022 Feb 05; 10(B):374-382. https://doi.org/10.3889/oamjms.2022.7482
Keywords: Schizophrenia; PANSS; Interleukin-6; *Nigella sativa*; Liver function
***Correspondence:** Sri Purwatiningsih Sri, Department of Psychiatry, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia. E-mail: sripurwatiningsih20@gmail.com
Received: 25-Aug-2021
Revised: 18-Nov-2021
Accepted: 21-Feb-2022
Copyright: © 2022 Sri Purwatiningsih, Saidah Syamsuddin, Sonny T. Lisal, Kristian Liaury, Burhanuddin Bahar, Ika Yustisia
Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist
Open Access: This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0)

BACKGROUND: Schizophrenia with a global prevalence of 0.33–0.75% and one of the top 15 causes of disability. The etiology underlying this disease is still controversial. One of the causes is the Vulnerability Stress-Schizophrenia Inflammatory Model which shows an increase in pro-inflammatory cytokines, one of which is Interleukin-6 (IL-6).

AIM: It is hoped that through the adjuvant anti-inflammatory effect of black seed or *Nigella sativa* can improve the clinical symptoms of schizophrenia and reduce levels of Serum IL-6 as a marker of therapeutic efficacy, as well as observing the effect of treatment on liver function.

METHODS: The present study was conducted 22 schizophrenic patients hospitalized at the psychiatric hospital (*Rumah Sakit Khusus Daerah*) of South Sulawesi aged 20–45 years and received risperidone 4 mg/day therapy. Patients were divided into two groups, the control and treatment groups received *N. sativa* 1000 mg/d for 4 weeks. Each group was measured for baseline and week 4 clinical symptoms of schizophrenia with Positive and Negative Symptom of Schizophrenia (PANSS) and serum IL-6 levels. The analysis also measured serum IL-6 level in healthy people by assessing the side effects of *N. sativa* adjuvants by measuring liver function enzymes of Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvic Transaminase (SGPT).

RESULTS: Serum IL-6 levels of schizophrenic patients were higher than healthy controls. Administration of adjuvant *N. sativa* 1000 mg for 4 weeks significantly $p < 0.001$ improved PANSS value, decreased serum IL-6 levels 2.5 times faster in the treatment group and did not give a significant change in SGOT and SGPT values.

CONCLUSION: This study suggests that *N. sativa* may consider as an adjuvant therapy to improve clinical symptoms of schizophrenia and reduce levels of IL-6 was faster than control group and is safe for liver function.

Introduction

Schizophrenia can be understood as a neurodevelopmental disorder with onset usually in early adulthood [1]. A complex multidimensional syndrome characterized by positive symptoms (e.g., delusions and hallucinations), negative symptoms (e.g., motivational disturbances), affective dysregulation (e.g., depression, mania, or anxiety), and cognitive changes [2]. Schizophrenia is a multisystem disorder with a global prevalence of 0.33–0.75% and is one of the top 15 causes of disability. The etiology underlying the disease is still controversial and not fully understood [3].

Abnormal activation of the immune system over the years has been associated with schizophrenia. Inflammation may play a role in the pathogenesis of psychosis, based on the presence of immunological anomalies in schizophrenia through innate and acquired immune responses, and the consequent increase in specific cytokines and inflammatory mediators such as Interleukin (IL)-6 and CRP [2]. High levels of pro-inflammatory substances such as cytokines are found in the blood and cerebrospinal fluid of schizophrenic

patients. Further, the inflammatory hypothesis stems from the therapeutic benefits of anti-inflammatory drugs. Meta-analyses have demonstrated a beneficial effect of celecoxib and aspirin in schizophrenia. In addition, the anti-inflammatory and immunomodulatory effects of antipsychotics have been known for a long time [4].

Nigella sativa (black seed or black cumin), is an annual plant with many pharmacological properties. The use of *N. sativa* seeds and oil in traditional medicine has been used for more than 2000 years [5]. *N. sativa* has the most important active components, namely Thymoquinone (TQ) [6]. In the field of neuropsychiatry, it has been shown that *N. sativa* modulates mood, anxiety, and cognition in healthy young men [7]. *N. sativa* prevents depressive behavior in LPS-induced mice [8]. *N. sativa* is neuroprotective [9], [10], [11], nephroprotective [12], and hepatoprotective [13] in several animal studies. In a study of forty elderly *N. sativa* can improve memory, attention and cognition [14]. According to one study TQ reduces neutrophil accumulation, inhibits polymorphonuclear function *in vitro* and *in vivo*. In addition, it can inhibit inflammatory cytokines such as IL-1 and IL-6. TQ exerts anti-inflammatory properties by inhibiting their production [6].

Effects of TQ on hippocampal cytokine levels, oxidative stress, and cognitive memory impairments in rats produced by lipopolysaccharide (LPS). Protects against oxidative injury, antioxidant, anti-inflammatory, and acetyl cholinesterase inhibitory activities can induce memory impairment. As a result, study discovered that TQ boosts its anti-inflammatory and neuroprotective properties. *N. sativa* and TQ have traditionally and experimentally been used to treat a variety of degenerative disorders, including Parkinson's, Alzheimer's, and schizophrenia. TQ appears to improve learning and reduce LPS-induced memory impairment in mice, according to the findings of this study by reducing hippocampus cytokine levels and brain tissue oxidative damage [15].

TQ is an antioxidant phytochemical that has been found to reduce inflammation in the nervous system. TQ inhibited NF- κ B-dependent neuroinflammation in BV2 microglia by regulating an antioxidant pathway involving activation of nuclear erythroid 2 related factor 2/antioxidant response element, possibly leading to inhibitory neuroinflammation mediated by NF- κ B, according to one study. TQ reduced TNF, IL-6, and IL-1 mRNA levels in LPS-activated mice's primary microglia [16].

Another study evaluated at the anti-inflammatory effects of TQ in BV-2 murine microglial cells treated with LPS. TQ efficiently lowered NO₂ with an IC₅₀ of 5.04 μ M when compared to the specific iNOS inhibitor L-NIL-L-N6-(1-iminoethyl) lysine, according to the findings (IC₅₀ 4.09 μ M). Using the rayBio antibody protein array AAM-CYT-3 and 4 cytokines, the anti-inflammatory effect of TQ ninety-six (96) cytokines was also assessed. BV-2 cells generated a substantial increase in specific pro-inflammatory cytokines such as the chemokines IL-6, IL-12p40/70, CCL12/MCP-5, CCL2/MCP-1, and G-CSF in the presence of LPS (1 g/ml), which was decreased by the addition of TQ (10 μ M) [9].

Effects of *N. sativa* supplementation on inflammation and oxidative stress as indicators in a systematic review and meta-analysis of controlled clinical trials showed a significant reduction in CRP concentrations [17]. In addition, research on sepsis-affected mice found that TQ has an active inflammatory response in relation to early-stage biomarkers and can detect sepsis-related mortality. The information presented here indicates that TQ has the potential to be a therapeutic value in the treatment of sepsis. TQ 1 mg/kg post-dose infection aided significant inhibition of the levels of cytokines, namely TNF-, IL-1, IL-2, IL-6, and IL-10 [18].

In a systematic review and meta-analysis of controlled clinical studies, the effect of *N. sativa* supplementation on inflammation and oxidative stress as markers revealed a considerable reduction in CRP concentrations [17]. (Mohit et al., 2020) Furthermore, studies on sepsis-affected mice have discovered that TQ has an active inflammatory response in relation to early-stage indicators and can detect sepsis-related death. According to the information presented here, TQ

may have therapeutic utility in the treatment of sepsis. TNF-, IL-1, IL-2, IL-6, and IL-10 levels were significantly reduced by TQ 1 mg/kg i.p. after a dose of infection [18].

The pharmacological effect of crude *N. sativa* extract (and some of its active constituents, e.g., essential oil and TQ) is protection against nephrotoxicity and hepatotoxicity caused by disease or chemicals. The seeds/oil have anti-inflammatory, analgesic, antipyretic, antimicrobial, and antineoplastic activities. The oil lowers blood pressure and improves breathing. Treatment of mice with *N. sativa* extract for up to 12 weeks has been reported to cause changes in hemograms that increase packed cell volume and hemoglobin, and decrease plasma concentrations of cholesterol, triglycerides, and glucose. Seeds are characterized by a very low level of toxicity. Two cases of contact dermatitis in two persons have been reported following topical use. Administration of the seed extract or its oil has been shown to cause no significant side effects on liver or kidney function. The beneficial effects of the use of whole grains and TQ are related to their cytoprotective and antioxidant actions, and their effects on several mediators of inflammation [19]. In one study, *N. sativa* up to 1 g kg⁻¹ was added for 28 days, resulting in no change in liver enzymic levels and no toxic effect on liver function [20]. In addition, the toxicity of NSFO in mice and rats was tested, through LD50 assessment and examination of possible biochemical, hematological and histopathological changes. No changes were observed in the levels of major liver enzymes, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and GGT and histopathological modifications (heart, liver, kidney, and pancreas) in mice [21].

According to one study, co-administration of TQ or TQ-containing compounds with medicines metabolized by CYP enzymes, specifically CYP2C9, may cause a pharmacological interaction. In human liver microsomes, the effects of TQ on the metabolic activity of four key drug-metabolizing enzymes: Cytochrome P450 (CYP) 1A2, CYP2C9, CYP2D6, and CYP3A4. TQ inhibits CYP enzyme activity by incubating usual substrates with it (phenacetin for CYP1A2, tolbutamide for CYP2C9, dextromethorphan for CYP2D6, and testosterone for CYP3A4) [22]. The extract of *N. sativa* inhibits cytochrome P-450 3A4, 2C9, 3A5, and 2D7 in humans through cDNA-mediated inhibition of cytochrome P-450 3A4, 2C9, 3A5, and 3A7, which can impact and/or decrease the metabolism of numerous medications, according to *in vitro* investigations. Both methanol extract and *Nigella hexana* considerably boosted amoxicillin permeability *in vitro* (p 0.001) compared to controls. At the same dose level, permeation was found to be substantially higher for the hexane extract (p 0.001) than for the methanol extract (p 0.001). In both *in vivo* and *in vitro* experiments, *Nigella* boosted amoxicillin levels [23]. Hence, it is necessary to pay attention to its long-term effect on the metabolism of risperidone in the liver which is inhibited by TQ.

The [42] is one study looking at the role of TQ on day 28 after administration of TQ (20 mg/kg, i.p.) alone or in combination compared to control, it can reduce dopamine (DA) levels in experimental animals through induction of apomorphine and scopolamine [24]. In a preliminary study conducted in 2020 regarding *N. sativa* as an adjuvant therapy that improves clinical, cognitive, and extrapyramidal symptoms in schizophrenic patients receiving risperidone therapy in 20 research subjects, where clinical symptom improvement was significant [71] in the administration of 1000 mg *N. sativa* through Positive and Negative Syndrome Scale (PANSS) for schizophrenia assessment which was expected to [82] reduce length of stay. There has never been a study to improve symptoms of schizophrenia by administering *N. sativa* as adjuvant to schizophrenia patients by measuring changes in IL-6 cytokine levels as a marker of therapeutic effectiveness.

Methods

Sample

[44] This research is an experimental research that was conducted at the Regional Special Hospital of [18] South Sulawesi Province in March to May 2021. The population in this study were [13] new schizophrenic patients who were hospitalized at the Regional Special Hospital of South Sulawesi Province for the period of March to May 2021 who met the inclusion criteria.

Inclusion criteria, in this study, namely, patients aged 20–45 years who met the criteria for schizophrenia according to PPDGJ III, new or recurring schizophrenic patients with acute exacerbations of at least a PANSS value of 100, who received the antipsychotic drug risperidone 2–4 mg tablets/day. Exclusion criteria for patients suffering from general medical disorders, pregnancy, and a history of being using anti-inflammatory drugs and antibiotics. Samples were dropped out when they returned home at the request of themselves or their families before the study was completed or died.

Procedure

Every patient who met the criteria for schizophrenia according to PPDGJ III who matched the inclusion and exclusion criteria in the study group was recorded and a history of past disease was analyzed. The researcher then explained to the family and research subjects the aims and objectives of the study [56]. If agreed, the subject will be included in the research. Subjects were divided into two groups, namely, the control group which was treated only risperidone and the group treated with risperidone accompanied by giving *N. sativa*. The PANSS

score and serum IL-6 levels were determined in both groups at baseline before giving *N. sativa* 1000 mg/day and 4 weeks later. Giving *N. sativa* by called one by one before lunch by the nurse to immediately take the *N. sativa* capsules that had been given. Risperidone 2 mg is given twice in the morning and evening in the same manner as for *N. sativa*. The measurement of the PANSS value is based on interviews with patients and nurse observations. In addition, assessing body mass index (BMI), taking blood for examination of IL-6 and liver function in the treatment group. Then perform data analysis to determine differences in PANSS values and serum IL-6 levels at week 0 and week 4. Healthy control hired by interviews of people who did not have severe mental disorders according to the PPDGJ III diagnostic criteria. Not suffering from illness, fever, and taking anti-inflammatory drugs, antibiotics, antioxidants, and psychotropics age range 30–40 years.

IL-6 serum

3 cc of venous blood was taken using the phlebotomy technique and centrifuged to obtain serum fluid. The tool used to measure serum IL-6 levels is the human IL-6 ELISA assay kit. Has a size of 1 × 96 wells, sensitivity 0.96 ng/L, standard curve range: 2–600 ng/L, with a sample of 20 µL serum. Examination of serum IL-6 levels was carried out at the Research Laboratory of the Hasanudin University Central Hospital. The procedure with prepare all reagents, standard solutions and samples as instructed. Bring all reagents to room temperature before use. The assay is performed at room temperature [6]. After doing all the procedures, then determine the optical density value of each plate well immediately using a microplate reader set to 450 nm within 10 min after adding the stop solution.

Statistical analysis

Data were entered into Microsoft Excel. Collecting demographic data and analysis descriptive research subject analyzed the difference in PANSS and IL-6 values in the two groups and measuring the percentage of the speed of decreasing the effect of treatment on PANSS and IL-6 levels.

Results

Characteristics of patients [18]

This research was conducted in the inpatient room of the Regional Special Hospital of South Sulawesi Province March to May 2021. The sample that met the research inclusion criteria were 22 people which were divided into 2 groups, namely, ten subjects

Table 1: Socio-demographic characteristics by frequency (n = 22)

Variable	Variable Group	n	%	p
Gender	Man	22	100	
Age (years)	17–25	6	27.27	0.451
	26–35	8	36.36	
	36–45	8	36.36	
Marital status	Marry	3	13.6	0.304
	Not married yet	16	72.7	
Work	Divorced	3	13.6	0.341
	Work	7	31.8	
	Does not work	15	68.2	
Level of education	Elementary School	7	31.8	0.306
	Junior high school	5	22.7	
	Senior High School	10	45.5	
	1 time	5	22.7	
Inpatient	2–10 times>10 times	12	54.6	0.488
	< 5 years	5	22.7	
Disease Onset	< 5 years	12	54.5	0.451
	5–10 years>10 years	3	13.6	
	7	31.8		
BMI week 0	Underweight	2	9.1	0.571
	Normal	15	68.2	
BMI week 4	Overweight	5	22.7	0.387
	Underweight	3	14.6	
	Normal	14	63.6	
	Overweight	5	22.7	

BMI: Body mass index.

treatment groups who received 1000 mg black cumin adjuvant and 12 subjects controls. In the descriptive statistics (Table 1), the research subject the research subjects (n = 22) were all male (100%), most of them were unmarried (72.7%), and did not work (68.2%). The highest education level of the research subjects was high school (45.5%). The research subjects averaged 2–10 times of hospitalization (54.6%) and the most disease progression was <5 years (54.5%). BMI was mostly normal, 15 (68.2%) subjects in the 1st week, and 14 people with normal BMI (63.6%) at week 4.

68 Positive and negative symptoms scale (PANSS)

Improvements in the PANSS value in the research subjects are shown in Table 2. The median PANSS value in the treatment group in the 1st week of 112 decreased to 60 and in the control group the median PANSS value of 110 became 79. Changes in the PANSS value week 0 and week 4 obtained significant results for both groups p < 0.05.

Table 2: Comparison of Improvements in PANSS

Group	PANSS value		p
	Week 0 (Minimum–Maximum)	Week 4 (Minimum–Maximum)	
Treatment	115 (100–121)	60 (53–68)	0.005
Control	109 (100–125)	79 (67–93)	0.002

Figure 1 shows the comparison of the PANSS baseline and week 4 were showing a significant difference in the PANSS value in the treatment group compared to the treatment with p < 0.001.

Table 3 shows a comparison of the rate of decline in the value of each PANSS dimension. The decrease was significantly different in positive,

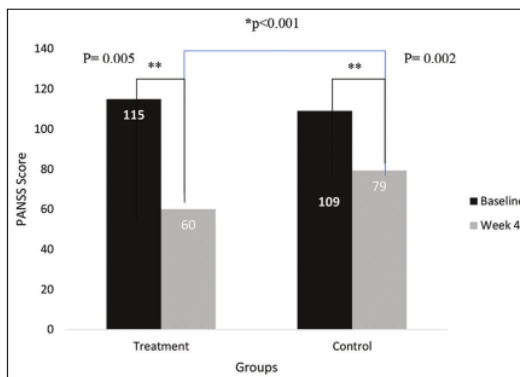


Figure 1: Comparison of PANSS values week-0 and week-4

negative and general symptoms in both the treatment group and the control group. Positive symptoms in the treatment group showed the greatest decrease in the 4th week compared to other symptoms with a significance <0.001.

75 Table 3: Percentage of change rate of PANSS value (n=22)

Group	Positive Symptoms		Negative Symptoms		General Psychopathology Scale	
	(%)	p	(%)	p	(%)	p
Treatment	-50.63 ± 5.41	<0.001	-48.17 ± 8.29	0.001	-42.43 ± 9.16	0.001
Control	-29.03 ± 9.24*		-28.76 ± 16.24*		-27.15 ± 9.02	

67 Serum IL-6 level

On examination, the serum levels of IL-6 at week 0 showed that the mean in 14 healthy people was 26.36 ± 21.78 ng/L, lower than the schizophrenia group with the range of serum IL-6 levels from 0 to 77.15 ng/L. Meanwhile, in the research subjects, the mean serum IL-6 level in the treatment group was 39.6 ± 43.54 ng/L, the IL-6 value ranged from 10.24 to 158.50 ng/L, and the control group was 51.59 ± 84.51 ng/L with a value range of 0–312.17 ng/L. Changes in serum IL-6 levels at week 0 and week 4 were not significant in both groups with a significance of treatment p = 0.241 and control p = 0.433 (p > 0.05) (Table 4).

The difference in serum IL-6 levels at week 4 was also not significant in the control group compared to the treatment group with p = 0.83 (>0.05). The mean levels of IL-6 in the treatment group were lower than the control group, 45.74 ± 44.59 ng/L compared 47.20 ± 45.15 ng/L in the control group. The serum IL-6 level in the treatment group was 8.1–167.41 ng/L and 9.1–180.7 ng/L in the control group.

Table 5 shows that the percentage rate of change in IL-6 levels in the treatment group of 36.44 ± 66.46 and the control group was 92.88 ± 168.24. This indicates that the biological effect of *N. sativa* on IL-6 in the treatment group was able to inhibit the increase in IL-6 better than the control group. Although statistically

Table 4: The levels of IL-6 healthy groups, treatment, and control

Group (n)	Serum IL-6 Level (ng/L)		Week 4	Range	p
	Week 0	Range			
Healthy (14)	26.36 ± 21.78	0–77.26			0.83 ^b
Treatment (10)	39.6 ± 43.54	10.24–158.50	45.74 ± 44.59 ^a	8.1–167.41	
Control (12)	51.59 ± 84.51	0–312.17	47.20 ± 45.15 ^a	9.1–180.7	

Mean ± SD Significant P < 0.05. ^aTreatment P = 0.241 3 decreased (5.3), 7 increased (5.7), control b = 0.433 4 decreased (7.25), 8 increased (6.13). IL: Interleukin.

significant, there was no significant difference with a t-test of significance of 0.940 (p > 0.05).

Table 5: Percentage of change in serum IL-6 levels (n = 22)

Group	Serum IL-6 Level (nmol/L)		p
	Week 0	Week 4	
Treatment	36.44 ± 66.46		0.940
Control	92.88 ± 168.24		

IL: Interleukin.

In the treatment group, liver function tests were performed at week 0 and week 4. To determine the effect of adjuvant *N. sativa* on changes in liver function, it is shown in Table 6. The SGOT examination at weeks 0 and 4 had the same results. A total of 9 people with normal levels (90%) and 1 person increased (10%). Meanwhile, the SGPT examination at week 0 and week 4 were all normal (100%).

Table 6: Results of liver function tests for treatment subjects

Variable	Referral Value (U/L)	Week 0		Week 4	
		n = 10	% = 100	n = 10	% = 100
SGOT	<35	9	90	9	90
	>35	1	10	1	10
SGPT	<45	10	100	10	100
	>45	0	0	0	0

SGOT: Serum Glutamic Oxaloacetic Transaminase, SGPT: Serum Glutamic Pyruvic Transaminase.

Discussion

This study was conducted based on several literatures which state that the etiology of schizophrenia is caused by inflammation. That is on hypothesis vulnerabilities–stress–inflammation schizophrenic [25] and associated with abnormal cytokine levels the Schizophrenia [3]. Hence, it is hoped that the presence of anti-inflammatory agents as adjuvants can reduce the etiology of schizophrenia so that clinical symptoms of schizophrenia can be improved which are assessed using the PANSS scale and reduce the cytokine, namely, IL-6.

In this study showed a decrease in the value of PANSS at week 4, both the control group and the treatment group. The decrease in PANSS value was significant at p = 0.05 in the treatment group and p = 0.02 in the control group. The decrease in PANSS values in both groups was the effect of the antipsychotic drug risperidone 4 mg/day which was used as therapy in both study groups. Risperidone is an atypical antipsychotic that can improve positive and negative symptoms in schizophrenia [26]. There was a significant difference in the comparison of the PANSS values in the treatment

and control groups at week 4 with p < 0.001. These results indicate a significant decrease in PANSS values in the treatment group after receiving adjuvant *N. sativa* 1000 mg/day at week 4. This condition was associated with the anti-inflammatory and antioxidant properties of *N. sativa* [17].

The anti-inflammatory agent used in this study was *N. sativa* of 1000 mg. Nature pharmacy from *N. sativa* especially in quinone constituents. It was disclosed that thymol, TQ, dimmer, and thymohydroquinone are the main pharmacologically active ingredients of *N. sativa* [27]. *N. sativa* has one of the most important active components, namely, TQ. TQ exerts anti-inflammatory properties by inhibiting its production [6]. One study showed that administration of TQ significantly decreased the expression of inflammatory cytokines, IL-2 = 38%, IL-4 = 19%, IL-6 = 83%, IL-10 = 23%, and IL-17 = 29%, in activated microglia compared with untreated. TQ increased neuronal protein expression while decreasing cytokine expression and expression of the pro-inflammatory gene NFκB signaling pathway target in BV-2-activated LPS/IFNγ microglia cells [9].

N. sativa which has anti-inflammatory properties [19] and antioxidants [28] through its active substance, TQ is estimated to improve clinical symptoms of schizophrenia as seen in the significant improvement in the PANSS value in the treatment group compared to the control group. The results of a meta-analysis of sixty double-blind randomized clinical trials (RCTs) studying 2914 patients with schizophrenia showed that anti-inflammatory agents significantly reduced the total score with positive and negative symptoms in PANSS scores [29]. Significantly on anti-inflammatory agents reduced the total score, positive and negative symptoms in PANSS scores [29]. In 22 RCTs of varying quality and sample size studying Ginkgo biloba, N-acetyl cysteine, allopurinol, dehydroepiandrosterone, Vitamin C, Vitamin E, or selegiline. There were three studies with short-term data for this outcome (there was a 20% improvement in PANSS scores) and in 7 RCTs lower psychotic symptoms based on PANSS scores in subjects taking antioxidants [30]. The results also showed that positive symptoms showed the fastest decrease in week 4 based on the rate of symptom reduction in the treatment group compared to negative and general symptoms with a significance of < 0.001.

In healthy controls taken in this study as many as 14 people had an average serum IL-6 level 26.36 ± 21.78 ng/L with a range of serum IL-6 levels of 0–77.26 ng/L lower than the mean of the schizophrenia group. In some literature, it is said IL-6 in healthy condition, the level is < 4 pg/ml, but when there is stress such as infection or injury. Serum IL-6 levels increase to several tens to hundreds of pg/ml, depending on infection or injury [31], [32]. Many factors can increase IL-6 levels, including BMI, depression [33], [34], after stress [34], immune reaction [35], and smoking. One

study showed differences in the range of IL-6 levels, healthy controls who smoked at 1.51–27.6 pg/ml [61] and did not smoke 0.09–19.1 pg/ml [36]. Where the healthy controls were not screened for the presence of stress and depression disorders, when IL-6 blood samples were taken. In a study of depressed (n = 12) and schizophrenic (n = 32) patients during the acute state of illness and after remission approximately 8 weeks after admission and compared with healthy controls (n = 12), concentrations of cytokines such as IL-6 plasma have been reported to be elevated in depressed and schizophrenic patients and in healthy individuals, after stress [34].

The mean serum IL-6 levels of schizophrenic patients in this study tended to be higher than healthy controls. These results are in accordance with several studies that discussed the relationship of elevated serum IL-6 levels with clinical symptoms of schizophrenia patients. Schizophrenia and people who experience brief or mild symptoms (classically described as the prodromal stage) are considered to be at clinical high risk for the disease. For FEP, significant increases in serum IL-1 β , sIL-2r, IL-6, IL-12, TNF-, TGF, and IFN- γ together with decreased IL-10 in acute relapse. In a meta-analysis, IL-1 β , IL-6, and TGF- β could be markers, given their elevated levels in acute episodes followed by normalization under antipsychotic treatment [37]. In this study, serum IL-6 levels were examined. The significance of the difference in serum IL-6 levels in the treatment and control groups was $t=0.83$, the results were not significant. This may be due to the small size of the sample included in this study and the relatively short study period of 4 weeks.

Observation week 4 on the mean serum IL-6 levels in the control group tended to decrease from 51.59 \pm 84.576 ng/L to 47.20 \pm 45.15 ng/L. This decrease in serum IL-6 levels is in accordance with previous studies that in patients treated with risperidone, serum levels of IL-6 and IL-2 decreased after 4 weeks compared to levels before antipsychotic therapy [38]. In another study after 2 months of treatment with a typical or atypical antipsychotic (such as risperidone), IL-6 levels appeared to decrease. [3] One study showed that risperidone normalized the increase in inflammatory mediators (cytokines and prostaglandin) [39]. The presence of antipsychotic anti-inflammatory effects suggests a major role for inflammation in schizophrenia [4]. A meta-analysis showed a significant reduction in serum IL-6 after risperidone treatment. In some cases, changes in IL-6 levels can be affected by region or duration of treatment. Treatment with risperidone on FEDN significantly suppressed the immune response system in particular, the inflammatory marker IL-6 was significantly reduced. In that study, risperidone affected astrocytes and C6 astroglia, by reducing the release of IL-6. In addition, risperidone inhibits IL-6-induced S100B secretion, reducing the level of secretion below the basal level. Risperidone can attenuate microglia

activation in the brain, which may decrease IL-6 levels [26]. Serum IL-6 levels may also increase after 3 months of taking risperidone and clozapine in patients with the metabolic syndrome [40].

In the treatment group, the mean serum IL-6 level was seen to increase by 39.6 \pm 43.54 ng/L becomes 45.74 \pm 44.59 ng/L. However, serum IL-6 levels treatment group at week 4 almost the same compared to the control group at 47.15 \pm 45.15 ng/L. The percentage rate of change in serum IL-6 levels indicates a biologic effect of *N. sativa* as adjuvant therapy. The results showed that the percentage increase in serum IL-6 levels in the treatment group was 36.44 \pm 66.46 and the control group was 92.88 \pm 168.24. These results indicate that the treatment group in the presence of *N. sativa* adjuvants was able to inhibit the increase in serum IL-6 levels were better than the control group. In line with studies in septic mice show that TQ suppresses the acute inflammatory response by significantly inhibiting levels of cytokines, including TNF-, IL-1 α , IL-2, IL-6, and IL-10 [18].

Changes in IL-6 levels may be well visible after 3 months of treatment. According to one study, changes in cytokines differed in various clinical conditions that increased in first-episode psychosis and acute relapse, and were normalized by antipsychotic treatment and decreased markedly after 3 months of treatment antipsychotic and minocycline adjuvants [41]. In other studies, there has been no study on the dose of *N. sativa* as an adjuvant therapy that will decrease IL-6 levels in schizophrenic patients, so there is no precise reference to the dose of *N. sativa*. In another study with human research subjects using *N. sativa* on 94 patients with type 2 diabetes mellitus took *N. sativa* 1000, 2000, and 3000 mg/day for 3 months. Result a dose of 2000 mg/day significantly reduced fasting blood sugar, 2 h postprandial and HbA1c. Doses of 1000 mg/day showed an improvement trend but not significant. Lack of response at a dose of 3000 mg/day [42] so that in future studies can observe the use of larger doses.

Risperidone 4 mg was used as antipsychotic therapy in schizophrenic patients in this study, in which an adjuvant *N. sativa* added to the treatment group. Risperidone is metabolized by cytochrome P450 (CYP) 2D6. In addition, the literature highlights the inhibitory effect of CYP2D6 drugs that interact with risperidone [43]. One of the studies show that there is a high probability of drug interactions and co-administration of TQ or TQ-containing substances with drugs metabolized by CYP enzymes. Inhibition of CYP enzyme activity by TQ was evaluated by incubating typical substrates (phenacetin for CYP1A2, tolbutamide for CYP2C9, dextromethorphan for CYP2D6, and testosterone for CYP3A4) [22]. Hence, it is necessary to pay attention to its long-term effect on the metabolism of risperidone in the liver which is inhibited by TQ.

To observe the side effects of adjuvant *N. sativa* in the treatment group (n=10) receiving risperidone antipsychotic therapy, liver function tests were performed, namely, Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvic Transaminase (SGPT). At week 0 of the SGOT examination, nine people had normal levels (90%) and one person increased (10%). At week 4, the results of the liver function test category did not change the category of liver function test results. Similarly, in the SGPT examination of 10 (100%) research subjects in the treatment group, the category of the results of the SGPT examination did not change at week 4, it was still within the normal reference value.

The results of liver function tests are in accordance with one of the studies conducted on twenty-seven male Sprague Dawley rats. The results showed that *N. sativa* supplement up to a dose of 1 g/kg for 28 days did not cause changes in liver enzyme levels and did not cause a toxic effect on liver function as indicated by the absence of significant changes in serum ALT and AST between the treatment groups [24]. In another study assessed the protective effect of TQ against Acrylamide (AA)-induced toxicity in forty-eight male Wistar. Administration of TQ normalized AA-induced changes in most serum parameters and increased antioxidant capacity in liver, kidney, and brain tissues [45]. Administration of *N. sativa* 1000 mg/day for 9 weeks in 40 male subjects aged around 55 years showed that biochemical markers of heart, liver, and kidney function were significantly unchanged [14]. However, in the period of more than 4 weeks, it is necessary to re-examine liver function to determine the side effects of adjuvant *N. sativa* in patients receiving risperidone therapy.

Conclusion

The value of PANSS in both the treatment and control groups decreased by week 4. Both trial groups showed an improvement in clinical symptoms. When schizophrenic patients on 4 mg risperidone were given adjuvant *N. sativa* 1000 mg, the PANSS score in the treatment group was considerably higher improvement than in the control group. Healthy controls had lower baseline serum IL-6 levels than schizophrenia subject. The treatment and control group's serum IL-6 levels were not substantially different at week 4. The treatment group had a faster percentage response to the drop in serum IL-6 levels, indicating that *N. sativa* had a biological effect on IL-6 levels. The decrease in PANSS values was negatively linked with serum IL-6 levels, and the mechanism that assisted in the reduction of PANSS values was faster in the group. At week 4, the treatment was compared to the control group. Giving adjuvant *N. sativa* 1000 mg to the treatment group for 4 weeks had no effect on the liver function tests,

SGOT and SGPT, indicating that it was safe to use as adjuvant therapy.

References

1. Uptegrove R, Khandaker GM. Cytokines, oxidative stress and cellular markers of inflammation in schizophrenia. *Curr Top Behav Neurosci*. 2020;44:49-66. https://doi.org/10.1007/7854_2018_88
PMid:31115797
2. Stojanovic A, Martorell L, Montalvo I, Ortega L, Monseny R, Vilella E, et al. Increased serum interleukin-6 levels in early stages of psychosis: Associations with at-risk mental states and the severity of psychotic symptoms. *Psychoneuroendocrinology*. 2014;41:23-32. <https://doi.org/10.1016/j.psyneuen.2013.12.005>
PMid:24495605
3. Momtazmanesh S, Zare-Shahabadi A, Rezaei N, Garcia-Gutierrez MS, Schiavone S, Arsenijevic NN. Cytokine alterations in schizophrenia: An updated review. *Front Psychiatry*. 2019;10:892. <https://doi.org/10.3389/fpsy.2019.00892>
PMid:31908647
4. Müller N, Weidinger E, Leitner B, Schwarz MJ, Powell S. The role of inflammation in schizophrenia. *Front Neurosci*. 2015;9:372. <https://doi.org/10.3389/fnins.2015.00372>
PMid:26539073
5. Tavakkoli A, Mahdian V, Razavi BM, Hosseinzadeh H. Review on clinical trials of black seed (*Nigella sativa*) and its active constituent, thymoquinone. *J Pharmacopuncture*. 2017;20(3):179-93. <https://doi.org/10.3831/KPI.2017.20.021>
PMid:30087794
6. Ahmad A, Husain A, Mujeeb M, Khan SA, Najmi AK, Siddique NA, et al. Review on therapeutic potential of *Nigella sativa*: A miracle herb. *Asian Pac J Trop Biomed*. 2013;3(5):337-52. [https://doi.org/10.1016/S2221-1691\(13\)60075-1](https://doi.org/10.1016/S2221-1691(13)60075-1)
PMid:23646296
7. Shahdaat M, Sayeed B, Shams T, Hossain SF, Rahman R, Mostofa AG, et al. *Nigella sativa* L. seeds modulate mood, anxiety and cognition in healthy adolescent males. *J Ethnopharmacol*. 2014;152(1):156-62. <https://doi.org/10.1016/j.jep.2013.12.050>
PMid:24412554
8. Hosseini M, Zakeri S, Khoshdast S. The effects of *Nigella sativa* hydro-alcoholic extract and thymoquinone on lipopolysaccharide induced depression like behavior in rats. *J Pharm Bioallied Sci*. 2012;4(3):219-25. <https://doi.org/10.4103/0975-7406.99052>
PMid:22923964
9. Cobourne-Duval MK, Taka E, Mendonca P, Soliman KF. Thymoquinone increases the expression of neuroprotective proteins while decreasing the expression of pro-inflammatory cytokines and the gene expression NF- κ B pathway signaling targets in LPS/IFN- γ -activated BV-2 microglia cells. *J Neuroimmunol*. 2018;320:87-97. <https://doi.org/10.1016/j.jneuroim.2018.04.018>
PMid:29759145
10. Hobbenaghi R, Javanbakht J, Sadeghzadeh S, Kheradmand D, Abdi FS, Jaber MH. Neuroprotective effects of *Nigella sativa* extract on cell death in hippocampal neurons following experimental global cerebral ischemia-reperfusion injury in rats. *J Neurol Sci*. 2014;337(1-2):74-9. <https://doi.org/10.1016/j.jns.2013.11.019>
PMid:24314720
11. Kanter ML, Kalayci M, Buyukbas S, Cagavi F. Neuroprotective

- effects of *Nigella sativa* on experimental spinat cord injury in rats. *Hum Exp Toxicol*. 2006;25(3):127-33. <https://doi.org/10.1191/0960327106ht608oa>
PMid:16634331
12. Yazdi S, Noorbakhsh H, Foad M, Farkhondeh T. An overview on renoprotective effects of thymoquinone. *Kidney Dis*. 2018;2018:9318614139.
 13. Adam GO, Rahman M, Lee SJ, Kim GB, Kang HS, Kim JS, et al. Hepatoprotective effects of *Nigella sativa* seed extract against acetaminophen-induced oxidative stress. *Asian Pac J Trop Med*. 2016;9(3):221-7. <https://doi.org/10.1016/j.apjtm.2016.01.039>
PMid:26972391
 14. Sayeed MS, Asaduzzaman M, Morshed H, Hossain MM, Kadir MF, Rahman MR. The effect of *Nigella sativa* Linn. seed on memory, attention and cognition in healthy human volunteers. *J Ethnopharmacol*. 2013;148(3):780-6. <https://doi.org/10.1016/j.jep.2013.05.004>
PMid:23707331
 15. Bargi R, Asgharzadeh F, Beheshti F, Hosseini M, Sadeghnia HR, Khazaei M. The effects of thymoquinone on hippocampal cytokine level, brain oxidative stress status and memory deficits induced by lipopolysaccharide in rats. *Cytokine*. 2017;96:173-84. <https://doi.org/10.1016/j.cyto.2017.04.015>
PMid:28432986
 16. Velagapudi R, Kumar A, Bhatia HS, El-Bakoush A, Lepiarz I, Fiebich BL, et al. Inhibition of neuroinflammation by thymoquinone requires activation of Nrf2/ARE signalling. *Int Immunopharmacol*. 2017;48:17-29. <https://doi.org/10.1016/j.intimp.2017.04.018>
PMid:28458100
 17. Mohit M, Farrokhzad A, Nooreddin S, Heidarzadeh-esfahani N, Kafeshani M. Complementary therapies in medicine effect of *Nigella sativa* L. supplementation on inflammatory and oxidative stress indicators: A systematic review and meta-analysis of controlled clinical trials. *Complement Ther Med*. 2020;54:102535. <https://doi.org/10.1016/j.ctim.2020.102535>
PMid:33183658
 18. Alkharfy KM, Ahmad A, Jan BL, Raish M. Thymoquinone reduces mortality and suppresses early acute inflammatory markers of sepsis in a mouse model. *Biomed Pharmacother*. 2018;98:801-5. <https://doi.org/10.1016/j.biopha.2018.01.028>
PMid:29571249
 19. Ali BH, Blunden G. Pharmacological and toxicological properties of *Nigella sativa*. *Phytother Res*. 2003;17(4):299-305. <https://doi.org/10.1002/ptr.1309>
PMid:12722128
 20. Hamed MA, El-Rigal NS, Ali SA. Effects of black seed oil on resolution of hepato-renal toxicity induced by bromobenzene in rats. *Eur Rev Med Pharmacol Sci*. 2013;17(5):569-81.
PMid:23543440
 21. Zaghlool DA, Kamel ES, Mohammed DS, Abbas NH. The possible toxic effect of different doses of *Nigella sativa* oil on the histological structure of the liver and renal cortex of adult male albino rats. *Egypt J Histol*. 2012;35(1):127-36. <https://doi.org/10.1097/01.EHX.0000411396.11951.02>
 22. Albassam AA, Ahad A, Alsultan A, Al-Jenoobi FI. Inhibition of cytochrome P450 enzymes by thymoquinone in human liver microsomes. *Saudi Pharm J*. 2018;26(5):673-7. <https://doi.org/10.1016/j.jsps.2018.02.024>
PMid:29989011
 23. Ali B, Amin S, Ahmad J, Ali A, Ali M, Mir SR. Bioavailability enhancement studies of amoxicillin with *Nigella*. *Indian J Med Res*. 2012;135(4):555-9.
PMid:22664507
 24. Rashid AK, AbulKN, Arshad HK, Darpan G, Mohd A. Ameliorating effects of thymoquinone in rodent models of schizophrenia. *Afr J Pharm Pharmacol*. 2014;8(15):413-21.
 25. Müller N. COX-2 inhibitors, aspirin, and other potential anti-inflammatory treatments for psychiatric disorders inflammation and depression risk. *Front Psychiatry*. 2019;10:375. <https://doi.org/10.3389/fpsy.2019.00375>
PMid:31214060
 26. Feng Z, Zhang Y, You X, Zhang W, Ma Y, Long Q, et al. Effects of risperidone on blood levels of interleukin-6 in schizophrenia: A meta-analysis. *Medicine*. 2020;99(15):e19694. <https://doi.org/10.1097/MD.00000000000019694>
PMid:32282724
 27. Mazaheri Y, Torbati M, Azadmard-Damirchi S, Savage GP. A comprehensive review of the physicochemical, quality and nutritional properties of *Nigella sativa* oil a comprehensive review of the physicochemical, quality and nutritional properties of *Nigella sativa* oil. *Food Rev Int*. 2019;35(4):342-62.
 28. Nagi MN, Mansour MA. Protective effect of thymoquinone against doxorubicin induced cardiotoxicity in rats: A possible mechanism of protection. *Pharmacol Res*. 2000;41(3):283-9. <https://doi.org/10.1006/phrs.1999.0585>
PMid:10675279
 29. Cho M, Lee TY, Kwak YB, Yoon YB, Kim M, Kwon JS. Adjunctive use of anti-inflammatory drugs for schizophrenia: A meta analytic investigation of randomized controlled trials. *Aust N Z J Psychiatry*. 2019;53(8):742-59. <https://doi.org/10.1177/0004867419835028>
PMid:30864461
 30. Magalhães PV, Dean O, Andreazza AC, Berk M, Kapczinski F. Antioxidant treatments for schizophrenia. *Cochrane Database Syst Rev*. 2016;2:CD008919. <https://doi.org/10.1002/14651858.CD008919.pub2>
PMid:26848926
 31. Tanaka T, Narazaki M, Masuda K, Kishimoto T. Regulation of IL-6 in immunity and diseases. In: Ma X, editor. *Regulation of Cytokine Gene Expression in Immunity and Diseases*. Berlin: Springer Science; 2016. p. 79-88.
 32. Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R, Jones PB. Inflammation and immunity in schizophrenia: Implications for pathophysiology and treatment. *Lancet Psychiatry*. 2015;2(3):258-70. [https://doi.org/10.1016/S2215-0366\(14\)00122-9](https://doi.org/10.1016/S2215-0366(14)00122-9)
PMid:26359903
 33. Lee ST. Inflammation, depression, and anxiety disorder: A population-based study examining the association between Interleukin-6 and the experiencing of depressive and anxiety symptoms. *Psychiatry Res*. 2020;285:112809.
 34. Frommberger UH, Bauer J, Haselbauer P, Fräulin A, Riemann D, Berger M. Interleukin-6-(IL-6) plasma levels in depression and schizophrenia: Comparison between the acute state and after remission. *Eur Arch Psychiatry Clin Neurosci*. 1997;247(4):228-33. <https://doi.org/10.1007/BF02900219>
PMid:9332905
 35. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol*. 2014;6(10):a016295. <https://doi.org/10.1101/cshperspect.a016295>
PMid:25190079
 36. Siagian D. Perbedaan Kadar Serum Interleukin-6 pada Kanker Paru Perokok dan Tidak Perokok. *Sumatera Utara*; 2018.
 37. Trovão N, Prata J, Vondoellinger O, Santos S, Barbosa M, Coelho R. Peripheral biomarkers for first-episode psychosis-opportunities from the neuroinflammatory hypothesis of schizophrenia. *Psychiatry Investig*. 2019;16(3):177-84.

- <https://doi.org/10.30773/pi.2018.12.19.1>
PMid:30836740
38. Lü LX, Guo SQ, Chen W, Li Q, Cheng J, Guo JH. Effect of clozapine and risperidone on serum cytokine levels in patients with first-episode paranoid schizophrenia. *Di Yi Jun Yi Da Xue Xue Bao*. 2004;24(11):1251-4. PMID:15567770
39. Leza JC, García-bueno B, Bioque M, Arango C, Parellada M, Do K, *et al*. Neuroscience and biobehavioral reviews inflammation in schizophrenia: A question of balance. *Neurosci Biobehav Rev*. 2015;55:612-26. <https://doi.org/10.1016/j.neubiorev.2015.05.014> PMID:26092265
40. Saidah S, SonnyLT, Liliik H, Burhanuddin B, Haerani R, Wempy T. Levels of interleukin 6 as a predictor of metabolic syndrome in schizophrenic patients receiving combination therapy of typical and atypical antipsychotics. *Open Access Maced J Med Sci*. 2021;9:600-7. <https://doi.org/10.3889/oamjms.2021.6378>
41. Kosten TR, Zhang L, Zheng H, Wu R, Zhu F, Zhang X, *et al*. Minocycline adjunctive treatment to risperidone for negative symptoms in schizophrenia Association with pro-inflammatory cytokine levels. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;85:69-76. <https://doi.org/10.1016/j.pnpbbp.2018.04.004> PMID:29678772
42. Bamosa AO, Kaatabi H, Lebda FM, Al Elq AM, Al-Sultan A. Effect of *Nigella sativa* seeds on the glycemic control of patients with Type 2 diabetes mellitus. *Indian J Physiol Pharmacol*. 2010;54(4):344-54. PMID:21675032
43. De Leon J. CYP2D6 genetic polymorphisms and risperidone pharmacokinetics: A systematic review and meta-analysis. 2020;40(7):632-47. <https://doi.org/10.1002/phar.2434> PMID:32519344
44. Dollah MA, Parhizkar S, Latiff LA, Hassan MH. Toxicity effect of *Nigella sativa* on the liver function of rats. *Adv Pharm Bull*. 2013;3(1):97-102. <https://doi.org/10.5681/apb.2013.016> PMID:24312819
45. Abdel-Daim MM, Abo El-Ela FI, Alshahrani FK, Bin-Jumah M, Al-Zharani M, Almutairi B, *etal*. Protective effects of thymoquinone against acrylamide-induced liver, kidney and brain oxidative damage in rats. *Environ Sci Pollut Res*. 2020;27(30):37709-17. <https://doi.org/10.1007/s11356-020-09516-3> PMID:32608003

Black Seed (Nigella sativa) Efficacy in Improving Clinical Symptoms and Interleukin-6 Levels Schizophrenic Patients

ORIGINALITY REPORT

20%
SIMILARITY INDEX

11%
INTERNET SOURCES

18%
PUBLICATIONS

6%
STUDENT PAPERS

PRIMARY SOURCES

1 onlinelibrary.wiley.com **2%**
Internet Source

2 Mohamed M. Abdel-Daim, Fatma I. Abo El-Ela, Fatima K. Alshahrani, May Bin-Jumah et al. "**Protective effects of thymoquinone against acrylamide-induced liver, kidney and brain oxidative damage in rats**", Environmental Science and Pollution Research, 2020 **<1%**
Publication

3 Norbert Müller. "**What role does inflammation play in schizophrenia?**", Expert Review of Neurotherapeutics, 2016 **<1%**
Publication

4 "**Regulation of Cytokine Gene Expression in Immunity and Diseases**", Springer Science and Business Media LLC, 2016 **<1%**
Publication

5 Submitted to Tikrit University **<1%**
Student Paper

Submitted to University of Kufa

6

Student Paper

<1 %

7

Zahra Gholamnezhad, Shahrzad Havakhah, Mohammad Hossein Boskabady. "Preclinical and clinical effects of Nigella sativa and its constituent, thymoquinone: A review", Journal of Ethnopharmacology, 2016

Publication

<1 %

8

bioinfo.uth.edu

Internet Source

<1 %

9

www.cureus.com

Internet Source

<1 %

10

Ali Shahraki, Roodabe Sarabandi, Mohsen Kianpour, Zahra Zakeri. "Elevated Serum Interleukin-23 and Interleukin-6 Levels in Schizophrenic Patients Compared to Those in Healthy Controls", Shiraz E-Medical Journal, 2016

Publication

<1 %

11

Mehmet Burak Ates, Mustafa Ortatati. "Phase-1 bioactivation mechanisms of aflatoxin through AhR, CAR and PXR nuclear receptors and the interactions with Nigella sativa seeds and thymoquinone in broilers", Ecotoxicology and Environmental Safety, 2021

Publication

<1 %

12

Internet Source

<1 %

13

Andi Jayalangkara Tanra, Hawaidah Hawaidah, Yazzit Mahri, Saidah Syamsuddin, Andi Nilawati Usman, Sonny Teddy Lisal. "The Side Effect of Haloperidol in Schizophrenic Patients: Analysis of Red Blood Cell Distribution Width (RDW) and Mean Platelet Volume (MPV) Values", Global Journal of Health Science, 2019

Publication

<1 %

14

Mukhtar Ikhsan, Nurul Hiedayati, Kazutaka Maeyama, Fariz Nurwidya. "Nigella sativa as an anti-inflammatory agent in asthma", BMC Research Notes, 2018

Publication

<1 %

15

Xin Zhou, Bo Tian, Hai-Bin Han. "Serum interleukin-6 in schizophrenia: A system review and meta-analysis", Cytokine, 2021

Publication

<1 %

16

cyberleninka.org

Internet Source

<1 %

17

ircmj.com

Internet Source

<1 %

18

amrsjournals.com

Internet Source

<1 %

19

www.journal.ac

Internet Source

<1 %

20

Michele Fornaro, Martino, Florinda Battaglia, Colicchio, Perugi. "Increase in IL-6 levels among major depressive disorder patients after a 6-week treatment with duloxetine 60 mg/day: a preliminary observation", *Neuropsychiatric Disease and Treatment*, 2011

Publication

<1 %

21

Muhammad Fakhar-e-Alam Kulyar, Rongrong Li, Khalid Mehmood, Muhammad Waqas, Kun Li, Jiakui Li. "Potential influence of *Nagella sativa* (Black Cumin) in reinforcing immune system: a hope to decelerate the COVID-19 pandemic", *Phytomedicine*, 2020

Publication

<1 %

22

Yusra Al Dhaheri, Adil Farooq Wali, Imra Akbar, Saiema Rasool, Maryam Razmpoor, Salma Jabnoun, Summya Rashid. "Nigella sativa, a cure for every disease: Phytochemistry, biological activities, and clinical trials", Elsevier BV, 2022

Publication

<1 %

23

eprints.kums.ac.ir

Internet Source

<1 %

24

"Immuno-Psychiatry", Springer Science and Business Media LLC, 2021

Publication

<1 %

25

Aziz A. Fallah, Elham Sarmast, Tina Jafari. "Effect of dietary anthocyanins on biomarkers of glycemic control and glucose metabolism: A systematic review and meta-analysis of randomized clinical trials", Food Research International, 2020

Publication

<1 %

26

Submitted to Hebron University

Student Paper

<1 %

27

Mohammad Rashidmayvan, Sarvenaz Vandyousefi, Meisam Barati, Shokoofeh Salamat et al. "The effect of nigella sativa supplementation on cardiometabolic outcomes in patients with non-alcoholic fatty liver: A randomized double-blind, placebo-controlled trial", Complementary Therapies in Clinical Practice, 2022

Publication

<1 %

28

repub.eur.nl

Internet Source

<1 %

29

research-information.bris.ac.uk

Internet Source

<1 %

30

Submitted to University of Northampton

Student Paper

<1 %

31	Submitted to Yeungnam University Student Paper	<1 %
32	e-journal.unair.ac.id Internet Source	<1 %
33	pbsrc.mums.ac.ir Internet Source	<1 %
34	www.spandidos-publications.com Internet Source	<1 %
35	Jaśmina Arabska, Dominik Strzelecki, Elżbieta Kozłowska, Ewa Brzezińska-Błaszczyk, Adam Wysokiński. "The association between serum levels of TNF-α and IL-6 in schizophrenic patients and their metabolic status – A case control study", Journal of Neuroimmunology, 2020 Publication	<1 %
36	journals.squ.edu.om Internet Source	<1 %
37	pure.hud.ac.uk Internet Source	<1 %
38	www.jidmr.com Internet Source	<1 %
39	www.nhaa.org.au Internet Source	<1 %

40 Müller, Norbert, Elif Weidinger, Bianka Leitner, and Markus J. Schwarz. "The role of inflammation in schizophrenia", *Frontiers in Neuroscience*, 2015.

Publication

<1 %

41 T Fujioka. "Effect of methylprednisolone on the kinetics of cytokines and liver function of regenerating liver in rats", *Hepatology Research*, 2001

Publication

<1 %

42 academicjournals.org

Internet Source

<1 %

43 biomedres01.blogspot.com

Internet Source

<1 %

44 innovareacademics.in

Internet Source

<1 %

45 www.thieme-connect.com

Internet Source

<1 %

46 Matej Ľupták, Danica Michaličková, Zdeněk Fišar, Eva Kitzlerová, Jana Hroudová. "Novel approaches in schizophrenia-from risk factors and hypotheses to novel drug targets", *World Journal of Psychiatry*, 2021

Publication

<1 %

47 Mohamed Mohamed Soliman, Saqer S. Alotaibi, Samy Sayed, Mohamed M. Hassan et

<1 %

al. "The Protective Impact of Salsola imbricata Leaf Extract From Taif Against Acrylamide-Induced Hepatic Inflammation and Oxidative Damage: The Role of Antioxidants, Cytokines, and Apoptosis-Associated Genes", *Frontiers in Veterinary Science*, 2022

Publication

48

Submitted to University of Birmingham

Student Paper

<1 %

49

www.mossnutrition.com

Internet Source

<1 %

50

www.springermedizin.de

Internet Source

<1 %

51

"Posters", *Clinical Microbiology and Infection*, 4/2007

Publication

<1 %

52

Ayuob, Nasra N., Hanem S. Abdel-Tawab, Soad S. Ali, Mohammad A. Saeed Al-Hegami, Mohamed B. Al-Salahy, and Hossam Eldin M. Omar. "Comparative study on the effect of antioxidants α -lipoic acid and N-acetyl cysteine on the structure of the renal tubules of diabetic rabbits :", *The Egyptian Journal of Histology*, 2014.

Publication

<1 %

53

Marcela Lascsáková. "IMPACT OF DIFFERENT PRICE MOVEMENTS ON THE ACCURACY OF

<1 %

NUMERICAL PRICE FORECASTING", Acta logistica, 2021

Publication

54

Milica Milovan Borovcanin, Ivan Jovanovic,
Gordana Radosavljevic, Jelena Pantic et al.
"Interleukin-6 in Schizophrenia—Is There a
Therapeutic Relevance?", Frontiers in
Psychiatry, 2017

Publication

<1 %

55

docplayer.com.br

Internet Source

<1 %

56

fik.umpr.ac.id

Internet Source

<1 %

57

www.coursehero.com

Internet Source

<1 %

58

www.scielo.br

Internet Source

<1 %

59

www.tandfonline.com

Internet Source

<1 %

60

"Neuroimaging in Schizophrenia", Springer
Science and Business Media LLC, 2020

Publication

<1 %

61

"Proceedings of the British Thoracic Society",
Thorax, 1994

Publication

<1 %

62 Ahmed M. El-Shehawi, Samy Sayed, Mohamed M. Hassan, Saad Al-Otaibi, Fayez Althobaiti, Mona M. Elseehy, Mohamed Soliman. "Taify Pomegranate Juice (TPJ) Abrogates Acrylamide-Induced Oxidative Stress Through the Regulation of Antioxidant Activity, Inflammation, and Apoptosis-Associated Genes", *Frontiers in Veterinary Science*, 2022

Publication

<1 %

63 Al-Saleh, I.A.. "Levels of selenium, dl-@a-tocopherol, dl-@c-tocopherol, all-trans-retinol, thymoquinone and thymol in different brands of *Nigella sativa* seeds", *Journal of Food Composition and Analysis*, 200603/05

Publication

<1 %

64 David Baumeister, Simone Ciufolini, Valeria Mondelli. "Effects of psychotropic drugs on inflammation: consequence or mediator of therapeutic effects in psychiatric treatment?", *Psychopharmacology*, 2015

Publication

<1 %

65 Farajollah Adib-Hashemi, Farshad Farahmand, Shamim Fattah Hesari, Bijan Rezakhaniha et al. "RETRACTED ARTICLE: Anti-inflammatory and protective investigations on the effects of Theranekron® "an alcoholic extract of the *Tarantula cubensis*" on wound healing of

<1 %

peritoneal in the rat: an in vivo comparative study", Diagnostic Pathology, 2015

Publication

66

Farimah Beheshti, Milad Hashemzahi, Mahmoud Hosseini, Narges Marefati, Sara Memarpour. "Inducible nitric oxide synthase plays a role in depression- and anxiety-like behaviors chronically induced by lipopolysaccharide in rats: Evidence from inflammation and oxidative stress", Behavioural Brain Research, 2020

Publication

<1 %

67

Frydecka, Dorota, Błażej Misiak, Edyta Pawlak-Adamska, Lidia Karabon, Anna Tomkiewicz, Paweł Sedlaczek, Andrzej Kiejna, and Jan Aleksander Beszłej. "Interleukin-6: the missing element of the neurocognitive deterioration in schizophrenia? The focus on genetic underpinnings, cognitive impairment and clinical manifestation", European Archives of Psychiatry and Clinical Neuroscience, 2015.

Publication

<1 %

68

Hee Yun Cha, Soo Jin Yang. "Anti-Inflammatory Diets and Schizophrenia", Clinical Nutrition Research, 2020

Publication

<1 %

69

Lulu Zhang, Hongbo Zheng, Rengrong Wu, Furong Zhu, Thomas R. Kosten, Xiang-Yang

<1 %

Zhang, Jingping Zhao. "Minocycline adjunctive treatment to risperidone for negative symptoms in schizophrenia: Association with pro-inflammatory cytokine levels", Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2018

Publication

70

Nawal Al-Rasheed, Nouf Al-Rasheed, Yieldez Bassiouni, Laila Faddah, Azza M Mohamad. "Potential Protective Effects of Nigella Sativa and Allium Sativum Against Fructose-Induced Metabolic Syndrome in Rats", Journal of Oleo Science, 2014

Publication

<1 %

71

journals.plos.org

Internet Source

<1 %

72

www.jurnalrespirologi.org

Internet Source

<1 %

73

"Abstract", Drug Metabolism Reviews, 2016

Publication

<1 %

74

Ann-Kristin Evers, Julia Veeh, Rhiannon McNeill, Andreas Reif, Sarah Kittel-Schneider. "C-reactive protein concentration in bipolar disorder: association with genetic variants", International Journal of Bipolar Disorders, 2019

Publication

<1 %

75

Anzalee Khan, Christian Yavorsky, Stacy Liechti, Mark Opler, Brian Rothman, Guillermo DiClemente, Luka Lucic, Sofija Jovic, Toshiya Inada, Lawrence Yang. "A rasch model to test the cross-cultural validity in the positive and negative syndrome scale (PANSS) across six geo-cultural groups", BMC Psychology, 2013

Publication

<1 %

76

Salome, N.. "Immune challenge induces differential corticosterone and interleukin-6 responsiveness in rats bred for extremes in anxiety-related behavior", Neuroscience, 20080219

Publication

<1 %

77

Zhou, H.R.. "Kinetics of lipopolysaccharide-induced transcription factor activation/inactivation and relation to proinflammatory gene expression in the murine spleen", Toxicology and Applied Pharmacology, 20030315

Publication

<1 %

78

hdl.handle.net

Internet Source

<1 %

79

"Proceedings of the World Molecular Imaging Congress 2020, October 7-9, 2020: General Abstracts", Molecular Imaging and Biology, 2022

Publication

<1 %

80

Alex J. Murray, Jack C. Rogers, Mohammad Zia Ul Haq Katshu, Peter F. Liddle, Rachel Upthegrove. "Oxidative Stress and the Pathophysiology and Symptom Profile of Schizophrenia Spectrum Disorders", *Frontiers in Psychiatry*, 2021

Publication

<1 %

81

Gladys Honein-AbouHaidar, Imad Bou-Hamad, Suzanne Dhaini, Patricia Davidson et al. "The validation of the Arabic Version of the Resilience Scale 14 (RS-14)", *Research Square Platform LLC*, 2022

Publication

<1 %

82

Kroken, Rune A., Else-Marie Løberg, Tore Drønen, Renate Grüner, Kenneth Hugdahl, Kristiina Kompus, Silje Skrede, and Erik Johnsen. "A Critical Review of Pro-Cognitive Drug Targets in Psychosis: Convergence on Myelination and Inflammation", *Frontiers in Psychiatry*, 2014.

Publication

<1 %

83

M Kido. "Differential induction of serum interleukin-6 and -12 by interferon- α and - β administration in chronic hepatitis C patients", *Hepatology Research*, 2003

Publication

<1 %

84

Magdalena Zielińska, Katarzyna Dereń, Ewelina Polak-Szczybyło, Agnieszka Ewa

<1 %

Stępień. "The Role of Bioactive Compounds of Nigella sativa in Rheumatoid Arthritis Therapy —Current Reports", Nutrients, 2021

Publication

85

Maiara Camotti Montanha, Andréa Diniz, Nuno Miguel Elvas Neves Silva, Elza Kimura, Paulo Paixão. "Physiologically-Based Pharmacokinetic Model on the Oral Drug Absorption in Roux-en-Y Gastric Bypass Bariatric Patients: Amoxicillin Tablet and Suspension", Molecular Pharmaceutics, 2019

Publication

<1 %

86

Masashi Narazaki, Tadimitsu Kishimoto. "The Two-Faced Cytokine IL-6 in Host Defense and Diseases", International Journal of Molecular Sciences, 2018

Publication

<1 %

87

Saeed Samarghandian, Mohsen Azimi-Nezhad, Hassan Mehrad-Majd, Seyed Reza Mirhafez. "Thymoquinone Ameliorates Acute Renal Failure in Gentamicin-Treated Adult Male Rats", Pharmacology, 2015

Publication

<1 %

88

Shahid Akbar. "Handbook of 200 Medicinal Plants", Springer Science and Business Media LLC, 2020

Publication

<1 %

89

lume.ufrgs.br

Exclude quotes On

Exclude matches < 5 words

Exclude bibliography On