

Review Article



Anti-Inflammatory Diets and Schizophrenia

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ABSTRACT

Schizophrenia is a mental illness characterized by symptoms such as hallucinations, delusions, disorganized speech, disorganized or catatonic behavior, and negative symptoms (emotional flatness, apathy, and lack of speech). It causes social and economic burdens to patients and their family. Although etiology of schizophrenia is still uncertain, dopamine dysregulation is traditionally considered as a main etiological factor of schizophrenia, which has been utilized to develop drugs for treating schizophrenia. Recently, inflammation has presented being a risk factor for schizophrenia in that neuroinflammation contributes to the pathophysiology of schizophrenia and the exacerbation of symptom severity. Various factors including diet can regulate inflammatory state. Specific foods or dietary patterns have anti- or pro-inflammatory potentials. Increased levels of pro-inflammatory cytokines and microglia activation have been reported in schizophrenia populations and were related to the pathogenesis of schizophrenia. Omega-3 fatty acids were often recommended to schizophrenia patients because of their anti-inflammatory activities. In this review, we investigate the inflammation-related pathogenesis of schizophrenia and summarize potential nutritional approaches to inhibit the manifestation of symptoms and to alleviate symptom severity using anti-inflammatory nutrients or functional components.

Keywords: Cytokines; Inflammation; Microglia; Omega-3 fatty acids

INTRODUCTION

Schizophrenia is a psychotic disorder with the prevalence of about 20 million people worldwide and has also affected about 450 thousand people in Republic of Korea [1,2]. The symptoms of schizophrenia are divided into positive symptoms (hallucinations, delusions, and racing thoughts, etc.) and negative symptoms (flat affect / inappropriate responses, apathy, and lack of speech). Although the causes of schizophrenia have not been evidently identified, interactions among genetic, environmental, and other psychological factors may involve with the development of schizophrenia [3,4].

The pathogenic mechanism of schizophrenia is not evidently elucidated, but the most leading hypothesis is the one that the altered dopamine levels in brain are involved with the development of schizophrenia [5]. Dopamine levels are high in patients with schizophrenia

with the dysregulation of dopamine synthesis and secretion [5]. Also, the role of glutamate dysfunction due to N-methyl-D-aspartate receptor hypofunction has also been suggested to induce symptoms of schizophrenia [6,7]. With dopaminergic and glutamatergic dysfunction, complicated symptoms such as delusion, hallucination, cognitive deficits, and oscillation are followed [6,8]. In addition, patients with schizophrenia suffer from negative symptoms, for example, social isolation and lethargy, as a compensatory response of dopamine overstimulation. Antipsychotic drugs are prescribed as a main treatment that alleviates symptoms, prevents relapse of schizophrenia, and regulates the dopamine level to the normal. However, usage of antipsychotic drugs often has the side effects of increasing appetite and body weights by interfering ghrelin and leptin, so disturbance of dopaminergic neurotransmission may change food intake and increase body weight in schizophrenia population [9-11]. Also, schizophrenia patients had poor dietary patterns with more saturated fats, sugar and alcohol as well as less intakes of fish, vegetables, and fruits, which may be related to impaired cognitive function [12,13]. It is assumed that the combination of antipsychotic drugs and poor dietary patterns increases a risk for obesity and metabolic syndrome.

Immune dysregulation and infection have been discussed as risk factors of schizophrenia [14]. In addition, chronic inflammation due to dietary and environmental factors may affect the development of schizophrenia, and aggravate or alleviate symptoms of schizophrenia [15,16]. Therefore, the management of dietary factors is important for schizophrenia patients.

The aim of this review is to investigate the possible inflammatory mechanisms that evoke pathogenesis of schizophrenia and to link dietary inflammation with the risk of schizophrenia. Furthermore, existing evidence for nutritional interventions and strategies that alleviate the symptoms of schizophrenia is discussed.

INFLAMMATION AND SCHIZOPHRENIA

Schizophrenia occurs by interactions between genetic variations and environmental factors, which affect neurotransmission and subsequent behavioral and intellectual changes [3,4]. Dysregulation of neurotransmission systems (e.g., dopaminergic and glutamatergic neurotransmission) has been considered as a primary hypothesis of schizophrenia [5,6,8].

In the central nervous system (CNS), inflammation may be neuroprotective or neurotoxic depending on the interactions among genetic variations, environmental factors, and inflammatory responses [17]. Recent evidence regarding inflammation and schizophrenia suggests that inflammation is a possible risk factor to induce schizophrenia and to aggravate its symptoms [16,18-20]. The levels of pro-inflammatory cytokines including interleukin (IL)-6, tumor necrosis factor (TNF)- α , IL-1 β , IL-12, and transforming growth factor (TGF)- β were elevated in subjects with schizophrenia [21,22]. Levels of pro-inflammatory cytokines in blood and brain and their relationship are not fully understood because pro-inflammatory cytokines are known to act in a paracrine way and blood brain barrier (BBB) protects brain from the influx of pro-inflammatory cytokines [15]. Nevertheless, excessive inflammatory responses could be a possible pathophysiological mechanism of schizophrenia. Increased microglia activation was observed in schizophrenia population, and activation levels of microglia increase the proportion to the severity of symptoms [23-26]. Microglia are neuronal support cells of CNS and play a crucial role in mediating neuroinflammation. Microglia induce inflammation in brain by low-level stimuli that let microglia produce

pro-inflammatory cytokines [27]. Moreover, inflammation or immune imbalance affect the neurotransmission system. Excesses in pro-inflammatory cytokines inhibit striatal dopamine synthesis and release [28,29].

Increased pro-inflammatory cytokines

Immune responses are categorized as innate and adaptive immunity. Innate immune response is a rapid reaction to injury or damaged cells; however, has relatively low specificity and diversity compared with acquired immunity. On the other hand, acquired immunity recognizes and memorizes the antigen and stimulates memory cells to produce specific antibody. Cytokines are small signaling molecules released from various types of cells and produced as a component of acquired immunity playing a role in communication between immune and neuronal cells. For example, cytokines activate other cells located on distant parts of the body or cytokine-secreting cells themselves to induce differentiation or alteration of activity by autocrine, paracrine, or endocrine manners. Cytokines are categorized further into 5 groups; 1) pro-inflammatory cytokines IL-1 β , IL-6, IL-8, and TNF- α are produced by activated macrophages and exacerbate inflammatory responses, 2) T helper 1 cytokines IL-2, IL-12, and interferon (IFN)- γ are involved in cell-mediated immunity, and have a function in protecting cells from parasites inside the cells while T helper 1 cytokines produce pro-inflammatory responses and function in especially autoimmune diseases like multiple sclerosis and rheumatoid arthritis, 3) T helper 2 cytokines IL-4, IL-5, and IL-13 play a role in humoral immunity and defense against parasites and allergic reactions outside the cells, 4) T helper 17 cytokines such as IL-17 and IL-23 are chief mediators of pro-inflammatory processes, and 5) IL-10 and TGF- β are classified as T regulatory cytokines that play a role in suppressing immune responses [22].

There are several hypotheses for the etiology of schizophrenia relating to inflammation. “Inflammation and two-hit hypothesis” for schizophrenia considers genetic susceptibility and inflammatory stimuli (infection and inflammation responses) during prenatal period as a first hit and developmental insults (environmental factors, physical and mental stresses, and endocrine disruption) inducing pro-inflammatory state during adolescence and adulthood as a second hit [30]. Another hypothesis “inflammation and neural diathesis-stress hypothesis” is that inflammation mediates neural damages to the stress-susceptible regions [31]. It is in part overlapped with the inflammation and two-hit hypothesis in that both hypotheses can be explained by first and second hits.

Increases in IL-6 levels are relatively consistent in schizophrenia subjects [32-34], which is accompanied by the concomitant upregulation of soluble IL-6 receptor [35]. In addition to IL-6, plasma levels of IL-1 β , IL-2, and IFN- γ were higher in schizophrenia subjects compared with controls [34]. In particular, IFN- γ and IL-12 levels were inversely correlated with whole-brain gray matter, and IL-1 β levels were positively related to psychotic symptoms assessed by Scale for the Assessment of Positive Symptoms in schizophrenia subjects [34]. And, increases in serum levels of IL-6, IL-18, TNF- α , and soluble IL-2 receptor were reported in subjects with depression and schizophrenia without overt inflammation having high C-reactive protein (CRP) concentrations (CRP > 6 mg/L) [32]. These findings suggest that pro-inflammatory cytokines are significantly stimulated in schizophrenia subjects regardless of obvious inflammation and that anti-inflammatory strategies using diet and drugs may be utilized as a potential adjuvant therapy. In fact, some anti-psychotic drugs (e.g., clozapine, olanzapine, and risperidone) reduced the levels of pro-inflammatory cytokines including IL-8 and IL-12 in first episode and relapse state schizophrenia patients [36,37]. Although there has

been inconsistency in alterations of cytokine levels and types of affected cytokines, several pro-inflammatory cytokines were relatively higher in schizophrenia subjects compared with controls, which was suppressed by the treatment of anti-psychotic drugs, resulting in alleviation of symptoms of schizophrenia.

Microglia activation

Microglia are immune cells in CNS, and play a role in mediating neuroinflammation. In normal condition, microglia regulate the homeostasis and resting state of neurons with the purpose of supporting neurons [38]. In a condition of brain damage, microglia rapidly shift into activated state by altering its phenotype, morphology, and even function. Along with these alterations, microglia release pro-inflammatory cytokines such as IL-1 β and TNF- α , neurotoxic substances, reactive oxygen species and nitric oxide [39]. Inflammation brings about response of M1 type of microglia, whereas M2 phenotype microglia respond in a way of ameliorating inflammatory processes. It has been indicated that microglial dysfunction has either neuroprotective or neurotoxic capacities depending on which microglia phenotype reacts. In the situation of microglia reacted to M1 phenotype peripheral monocyte, this type of microglia would impair neurons by releasing pro-inflammatory cytokines and lead to neuroinflammation. Neuroinflammation is the mechanism that protects CNS from external damage and infectious agents. As shown by the structural changes of brain including white matter and grey matter loss, it has been received mounting attention that neuroinflammation is a possible mechanism for morphological changes of brain [39].

Microglia are sensitized or primed by low stimuli such as neurodegeneration, aging process and stress [15]. When excessive immune processes begin, additional low-level stimuli let microglia proliferate and produce pro-inflammatory cytokines. Microglia activation-mediated CNS inflammation is one of the key features of various neurodegenerative diseases including Parkinson's and Alzheimer's diseases [40,41]. In post-mortem studies, increased microglia activation and density have been presented in schizophrenia population [24,26,42]. Immunohistochemical analysis showed that microglial cell numbers in anterior cingulate cortex and mediodorsal thalamus were increased in schizophrenia subjects committed suicide compared with controls [43]. Furthermore, elevated microglia activation in grey matter of schizophrenia subjects has demonstrated that it has similar manifestation with neurodegenerative dementia [25,44]. The inflammation and neural diathesis-stress hypothesis considers microglia activation-mediated inflammation as a key component triggering the onset of schizophrenia and aggravation of its symptoms [31].

Anti-inflammatory potential of anti-psychotic drugs

From numerous trials, anti-inflammatory potentials of anti-psychotic drugs on schizophrenia have paid attention [45-48]. The effects of anti-psychotic drugs on inflammation have been inconsistent because anti-psychotic drugs act in 2 ways on inflammatory processes, direct anti-inflammatory and indirect pro-inflammatory ways on alterations of cytokine levels. For example, risperidone, which is a second generation atypical antipsychotics, decreased the IL-1 β and IL-6 levels during the initial weeks of intervention; however, these levels rose again at six-month follow-up [48]. The result of this longitudinal study has indicated that anti-psychotics present both pro- and anti-inflammatory properties. Moreover, studies using anti-psychotic drugs and other medicines with anti-inflammatory properties (minocycline and non-steroidal anti-inflammatory drugs (NSAIDs)) have been conducted to investigate whether inflammation is a potential mechanism of pathophysiology of schizophrenia. Minocycline is a widely prescribed antibiotics that has anti-inflammatory potential on

microglia [49,50]. Minocycline can cross BBB by itself so that minocycline is able to act directly on microglia in accordance with improving the symptoms of schizophrenia [51-53]. Taking NSAIDs as adjunct to anti-psychotics in a randomized controlled trial showed ameliorative effect of symptom severity of schizophrenia spectrum disorder [54]. With these accumulating evidence, alleviation of inflammation has been suggested as adjunctive approach for treating schizophrenia [55].

DIETARY INFLAMMATION AND SCHIZOPHRENIA

Dietary inflammation

Dietary inflammatory index (DII) used in recent analyses is the literature-derived scoring tool that calculates inflammatory potentials on overall diet [56]. Developing DII involved the processes of reviewing and grading the weight of research articles regarding the effect of food parameters on inflammatory markers. Research articles were weighted by type of study (human, animal, and cell culture studies) and study design (experimental, prospective cohort, case-control, and cross-sectional studies), and the effect was calculated for each food parameter on inflammatory markers including CRP, IL-1 β , IL-4, IL-6, IL-10, and TNF- α . After grading articles, DII scores were standardized to world database for the 45 food parameters consisting of nutrients, whole foods and spices based on data from 11 countries [56]. Researches that examine the relationship between DII scores and inflammatory markers have been conducted to validate the DII [57,58]. DII has been proved its validity by linking several inflammatory markers including IL-1 β , IL-4, IL-6, IL-10, CRP, and TNF- α . For Korean adult population, validation analysis of the DII scores was conducted by making a comparison between DII scores and high-sensitivity CRP (hs-CRP) concentrations indicating that higher DII scores are positively related to hs-CRP levels [58].

Several case-control studies analyzed the association between DII and risk for diseases such as colorectal cancer, obesity, and metabolic syndrome. It has been demonstrated that the patients' diets with pro-inflammatory potentials increased the risk for the development of above-mentioned diseases compared with controls [59-61].

Dietary inflammation and schizophrenia

Evidence accumulated from previous studies indicates that inflammation has been noted for the etiology of schizophrenia. In addition to 2 major players in neuroinflammation, pro-inflammatory cytokines and microglia activation, pro-inflammatory diet aggravates neuroinflammation inducing the pathophysiological changes of schizophrenia and exacerbation of its symptom severity (**Figure 1**). Given the role that diets involve in the regulation of inflammatory markers, nutrients having anti-inflammatory properties such as omega-3 polyunsaturated fatty acids (PUFAs), vitamin D and vitamin B have been emphasized as adjunctive therapeutic means of improving either positive or negative symptoms of schizophrenia [41,62,63].

Gut-brain axis should be considered to explain the interaction between dietary inflammation and schizophrenia. Alterations in microbiota composition and microbial metabolites affect gut integrity and immune responses. Gut dysbiosis was observed in patients with schizophrenia, and the abundance of specific bacterial genera, *Succinivibrio* and *Corynebacterium*, were significantly associated with the symptom severity of schizophrenia [64]. The gut dysbiosis may affect the susceptibility to infection and inflammation, which

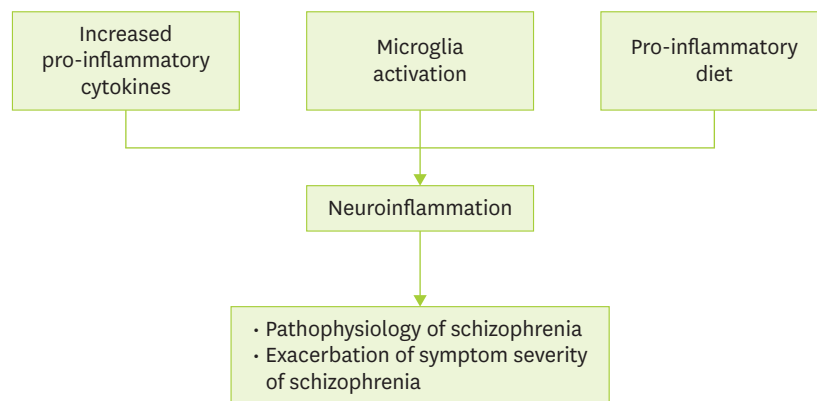


Figure 1. The suggested roles of inflammation in schizophrenia.

can accelerate the development of schizophrenia and aggravate its symptom severity. It is assumed that dietary components considered in schizophrenia exert their effects via, in part, gut-brain axis. However, the direct evidence to link dietary inflammation and schizophrenia in a context of gut-brain axis is limited so far.

A case-control study conducted in Bahrain aimed to examine the association between dietary inflammatory potential and schizophrenia using DII [65]. This study was performed using a 1:1 ratio matched design including 120 cases and 120 controls. Dietary intakes were estimated using a semi-quantitative food frequency questionnaire (FFQ), which can assess frequency and amounts of food consumption over a long period of time. Based on the FFQ results, each case and control's DII and energy-adjusted DII (E-DII) were calculated. The E-DII scores were significantly elevated in cases with schizophrenia compared with controls indicating that schizophrenia patients were more likely to have pro-inflammatory diets. Dietary intakes relevant to pro-inflammatory components such as energy, protein, carbohydrates, total fat, saturated fat, and cholesterol were elevated in 4th quartile of E-DII scores compared to 1st quartile. On the other hand, intakes of fiber, vitamins A and C, β -carotene, folic acid, Mg and Zn known as anti-inflammatory component tended to be increased in the 1st quartile of E-DII.

A population-scale study was conducted to explore the difference between severe mental illness population and general population on diet and inflammation using data from UK Biobank [66]. In this study, total eligible subjects for severe mental illness including schizophrenia, major depressive disorder and bipolar disorder were 69,843, and 262 subjects were classified as schizophrenia population. To compare severe mental illness and general population, 54,010 control data were also selected. Dietary intakes were calculated by computerized 24-hour recall method Oxford WebQ. Schizophrenia population among different types of severe mental illness had the biggest difference in dietary intakes in comparison with general population. Intakes of total energy, carbohydrates, protein, total fat, saturated fat, and sugar which are known as most pro-inflammatory components were higher in schizophrenia subjects compared to controls. Furthermore, statistical significance was observed in the finding that DII scores were increased in schizophrenia population.

Research related to DII and cognitive function was conducted using older Korean adult population [58]. DII and E-DII were calculated based on dietary intakes assessed by 24-hour dietary recall with trained interviewers. Cognitive function was assessed using Korean-adjusted version of the Mini-Mental State Examination (K-MMSE), which is a

screening tool that estimates the cognitive status for elderly population. E-DII scores were positively correlated with the K-MMSE scores suggesting that participants classified as normal condition had relatively higher anti-inflammatory diets rather than those who were diagnosed with boundary, mild, and moderate cognitive impairment. To investigate the relationship between DII and metabolic syndrome, the analysis using Health Examinees Cohort Study data from the Korean Genome and Epidemiology Study was conducted [67]. Participants over age of 40 years were selected, and definition of Modified National Cholesterol Education Program Adult Treatment Panel III from American Heart Association and National Heart, Lung, and Blood Institute were used to diagnose metabolic syndrome. It was observed that DII scores were significantly increased in metabolic syndrome group, meaning that participants with metabolic syndrome consume more pro-inflammatory foods than general population. The DII scores were significantly increased as the number of metabolic syndrome components increased, but only in women (p for trend < 0.01). Moreover, Korean version of DII (K-DII) was developed considering that Korean dietary pattern features not only high carbohydrates consumption because of rice, main meal in Korea but also soup or stew and side dishes. K-DII aimed to calculate the inflammatory potentials in Korean dietary pattern and to apply it in clinical settings in South Korea. Validation of K-DII was performed to analyze the association between K-DII and the incidence of metabolic syndrome [68]. The group of higher K-DII had significantly increased risk of metabolic syndrome compared to lower K-DII group after adjusting age and sex (odds ratio, 1.204; 95% confidence interval [CI], 1.123-1.290; $p = 0.002$) [68]. Above this, DII has been applied to many researches that investigate the correlation between inflammation in diet and diseases such as colorectal cancer and osteosarcopenic obesity in postmenopausal women [69,70].

Efforts to demonstrate the inflammatory potentials in schizophrenia population so far have focused mainly on the alterations of pro-inflammatory cytokine levels. However, few studies have been conducted to investigate the dietary inflammation in schizophrenia population using DII in Korea and even worldwide. Further researches should be carried out how dietary inflammatory potentials elicit the pathogenesis of neuropsychiatric disorders using DII as an indicator of assessing dietary inflammation.

ANTI-INFLAMMATORY NUTRITIONAL INTERVENTION FOR SCHIZOPHRENIA

Omega-3 fatty acids

Nutrients such as omega-3 fatty acids and vitamins having anti-inflammatory properties have been suggested to improve the symptoms of schizophrenia. Omega-3 fatty acids play a pivotal role in inflammation by suppressing of nuclear factor kappa B, which is a regulator of inflammatory responses [71], and exhibit anti-inflammatory potentials by reducing the levels of pro-inflammatory cytokines such as IL-1, IL-6, and TNF- α [72]. PUFAs are main components consisting of phospholipid structure of cell membrane. Structural abnormalities of cell membrane phospholipid can cause many types of mental illness [73]. Many studies have shown that docosahexaenoic acid (DHA) and α -linolenic acid (ALA) levels were reduced in the cell membranes of red blood cells of patients with schizophrenia [73]. Eicosapentaenoic acid (EPA) and DHAs can also be produced from essential fatty acid, ALA. EPA does not exist in the cell membrane of neuronal cells; however, one pilot study has revealed that EPA is superior to DHA in decreasing Positive and Negative Syndrome Scale

(PANSS) scores [74]. Improvements in PANSS ratings were significantly correlated with EPA, DHA, and arachidonic acid concentrations in erythrocyte membrane especially in EPA-treated subjects [74]. Omega-3 fatty acids treatment for 12 weeks decreased plasma TNF- α levels which were accompanied by the decline in triglycerides (TG) levels in schizophrenia patients with metabolic syndrome [75]. In a placebo-controlled trials of patients with schizophrenia, PANSS score was reduced in allocated to ethyl-EPA group [76]. In a randomized controlled study, decline in severity of symptoms and relapse rate was observed in young patients with first-episode schizophrenia who were randomly assigned to omega-3 fatty acids treatment for almost 6 months [77]. In addition to the traditional symptoms of schizophrenia, recent findings have focused other complications or side effects of the usage of antipsychotic drugs. Omega-3 fatty acids improved cognitive functions in subjects with schizophrenia and metabolic syndrome, which was accompanied by increased brain-derived neurotrophic factor and reduced levels of pro-inflammatory cytokines CRP, IL-6 and TNF- α [41].

Although ameliorative effects of omega-3 fatty acids for symptoms of schizophrenia have been demonstrated, inconsistent findings also exist. Even relatively high amount (3 g per day) of omega-3 fatty acids for 16 weeks did not show any significant effects on the symptoms of schizophrenia [78]. A possible reason for the inconsistencies in the effects is because of characteristics of the study subjects; 1) patients suffered from schizophrenia over 20 years and had symptoms despite taking new anti-psychotic drugs or clozapine may not respond well to the supplementation of omega-3 fatty acids, and 2) patients who exert the positive effects of EPA may be younger and their duration of schizophrenia may be shorter than those participated in the study with no effects from omega-3 fatty acids supplementations. Nevertheless, findings so far support the notion that omega-3 fatty acids ameliorate symptoms of schizophrenia, in part, by anti-inflammatory potentials (**Table 1**).

Vitamins, other nutrients, foods and dietary patterns

Vitamin D is involved with the relationship between inflammation-related markers such as CRP, IL-6, TNF- α , and the occurrence of schizophrenia at adolescence and early life as well

Table 1. Research evidence regarding the effects of omega-3 fatty acids on schizophrenia

References	Study design	Treatment	Main findings
[74]	Randomized double-blind placebo-controlled pilot study with 30 new or relapsed schizophrenic patients with no medication	2 g/day of EPA for 3 mo	· Lower PANSS scores
[79]	Randomized placebo-controlled, dose-ranging study, 45 outpatients with persistent schizophrenic symptoms and meeting DSM-IV criteria for schizophrenia, prescribed with antipsychotics (clozapine, typical and atypical drugs)	1, 2, and 4 g/day of E-EPA for 12 wk	· Improve PANSS scores, positive/negative/general symptoms, and MADRS scores · Positive relationship between rating scales and EPA, DHA, and AA levels in red blood cell membrane
[78]	Randomized double blind placebo-controlled trial with 87 patients with schizophrenia and schizoaffective disorder with residual symptoms	3 g/day of E-EPA for 16 wk	· No differences between groups
[76]	Randomized, parallel-group, double-blind, placebo-controlled, fixed-dose, add-on study with 40 patients diagnosed with schizophrenia according to DSM-IV criteria	3 g/day of E-EPA supplementation for 12 wk	· Reduce PANSS scores
[77]	Randomized placebo-controlled parallel group add-on, one-center trial with 82 patients with first episode schizophrenia according to ICD-10	2.2 g/day of n-3 PUFAs for 26 wk	· Decline in severity of symptoms and relapse
[75]	Randomized placebo-controlled trial, 80 patients with both schizophrenia and metabolic syndrome, received olanzapine only for a long period	Fish oil containing 720 mg EPA and 480 mg DHA for 12 wk	· Reduce TG levels · Decrease plasma TNF- α levels · Significant correlation between declines in TNF- α and decreases in TG

DHA, docosahexaenoic acid; DSM, The Diagnostic and Statistical Manual of Mental Disorders; EPA, eicosapentaenoic acid; E-EPA, ethyl-eicosapentaenoic acid; ICD-10, the 10th revision of the International Statistical Classification of Diseases and Related Health Problems; MADRS, Montgomery-Asberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; PUFA, polyunsaturated fatty acid; TG, triglyceride; TNF, tumor necrosis factor.

as symptom severity from first episode psychosis and chronic state of the disease [80]. Low vitamin D levels or vitamin D deficiency have been observed in schizophrenia population, which may influence brain development and its function [81]. The serum levels of vitamin D had negative correlation with symptom severity of psychosis. The higher the serum vitamin D levels, the lower the total PANSS and PANSS negative symptoms scores [82]. In a randomized, placebo-controlled trial examining the effects of vitamin D on chronic schizophrenia patients [83], 8 weeks of vitamin D supplementation significantly improved serum vitamin D concentrations and mean changes in Montreal Cognitive Assessment scores, which is a sensitive tool to detect cognitive impairment of schizophrenia [84]. Vitamin D supplementation for psychotic patients has been spotlighted because vitamin D is assured its safety, and relatively cheap and accessible rather than other substances. There has been an ongoing study in order to design practical approach and easily apply it to clinical field for first episode psychosis schizophrenia population [85]. In a randomized, placebo-controlled trial conducted in Iran, co-supplementation of vitamin D and probiotics had significant effects on improving total PANSS scores and inflammatory markers, hs-CRP as well as metabolic indicators including fasting plasma glucose, insulin, TG, very low density lipoprotein-cholesterol, and total-cholesterol [86]. This study demonstrated the synergistic potentials of vitamin D and probiotics suggesting that probiotics might improve inflammation via gut-brain axis by modulating gut microbiota.

Vitamin C has anti-oxidative properties that defense against damages from inflammation [87]. Male Korean schizophrenia patients had low dietary intakes of vitamin C, which was associated with increased risk for schizophrenia [88]. A prospective placebo-controlled study of vitamin C treatment (200 mg/day) for 8 weeks reported significant effects on the improvement of ascorbic acid levels and brief psychiatric rating scale (BPRS) score, a tool to promptly estimate and diagnose phase of psychopathology [89]. In addition, co-supplementation of vitamins C, E, and omega-3 fatty acids lowered several psychiatric scores including BPRS, Scale for the Assessment of Negative Symptoms, Simpson Angus Scale, and Barnes Akathisia Rating Scale [90]. Compared with previous studies with omega-3 fatty acids, analyses from interventions studies with vitamin C have focused on indices of oxidative stress rather than inflammatory markers.

Resveratrol (RSV) is a polyphenolic compound existing in grapes, berries, and red wine, and has received attention for anti-inflammatory function. RSV treatment (200 mg per day) for 4 weeks did not lead notable results on 19 male schizophrenia patients, except for the decline in the levels of TG in RSV treatment group [91]. Zortea et al. [92] also investigated the effect of RSV on cognition; however, 1 month of RSV treatment (200 mg/day) did not have any positive results on cognition. There were no differences between RSV and placebo groups on symptoms, inhibitory control, interference measurements, working memory, and attention.

The traditional Mediterranean diet is defined as dietary pattern that has high intakes of olive oil and plant foods including vegetables, fruits, legumes, low to moderate intakes of dairy products, and low intakes of animal foods such as red meat and poultry [93]. In a large-scale prospective survey, the high levels of adherence to Mediterranean diet lead to decline in inflammatory markers including CRP, IL-6, and TNF- α [94]. Attempts to investigate the role of Mediterranean diet on schizophrenia have been tried [95,96]; however, evidence is limited and unclear so far. Ketogenic diet is composed of low-carbohydrates and high-fat, and has got attention because of its effect on weight loss. Ketogenic diet induces the alterations of ratio of neurotransmitters, especially γ -aminobutyric acid (GABA)

Table 2. Research evidence regarding the effects of specific nutrients and food components on schizophrenia

References	Study design	Treatment	Main findings
[89]	Prospective, double-blind, placebo-controlled trial with 40 schizophrenia patients received atypical anti-psychotic drugs including olanzapine, quetiapine, and ziprasidone	500 mg/day of vitamin C for 8 wk	• Increase ascorbic acid levels and brief psychiatric rating scale scores
[91]	Randomized, double-blind controlled trial with 19 male schizophrenia patients	Resveratrol (200 mg/day) for 4 wk	• Decline in TG levels
[83]	Randomized, double-blind, placebo-controlled clinical trial with 47 schizophrenia patients who are prescribed with clozapine over 18 weeks, vitamin D levels < 75 nmol/L, and PANSS > 70	Oral vitamin D (14,000 IU) for 8 wk	• Increase the levels of vitamin D • Tend to improve cognitive function • No differences in psychotic, depressive or metabolic indicators
[86]	Randomized, double-blind, placebo-controlled trial with 60 schizophrenia patients with disease duration over 2 years, PANSS > 50, took chlorpromazine, anti-cholinergic medication at least 6 months	Vitamin D (50,000 IU) and 8×10^9 CFU/day of probiotics for 12 wk	• Improve PANSS scores • Reduce hs-CRP levels • Improve metabolic parameters (including fasting plasma glucose, insulin, and TG), and vitamin D levels

hs-CRP, high-sensitivity C-reactive protein; PANSS, Positive and Negative Syndrome Scale; TG, triglyceride.

and glutamate in brain [97]. The altered ratio of GABA and glutamate could be a potent therapeutic mechanism because these neurotransmitters get involved in the regulation of dopamine levels [98]. In addition, ketogenic diet has anti-inflammatory properties in that its pretreatment is associated with the reduced levels of TNF- α in plasma and IL-1 β in brain [99]. Dietary Approaches to Stop Hypertension (DASH) diet is originally designed to improve the control of blood pressure. The DASH diet could be described as high intakes of vegetables, fruits, whole grains, poultry and fish as well as low intakes of saturated fat, red meat, sweet beverages, and refined grains. A meta-analysis revealed that the levels of serum hs-CRP, a systemic inflammatory marker, were suppressed by the DASH diet [100]. So far evidence regarding the relationship between specific dietary pattern and schizophrenia has not been yet enough to suggest any dietary guideline linking the inflammation-mediating effects. Representative findings regarding the effects of vitamins, other nutrients, and food components on schizophrenia were summarized in **Table 2**.

CONCLUSION

The association between schizophrenia and inflammation, its possible etiological mechanism, has been supported by findings from epidemiological and experimental studies. Although it would not assert that inflammation is the definite mechanism that leads to schizophrenia, inflammation could be one of possible mechanisms for the onset of schizophrenia and the aggravation of its pathophysiology. The cost for treating schizophrenia is quite high, and many studies report that schizophrenia patients have poor dietary patterns. Schizophrenia patients are also likely to be overweight or obese, or to have metabolic syndrome due to the side effects of anti-psychotic drugs and poor dietary pattern. Therefore, recommendation of anti-inflammatory nutrients or foods as a part of balanced diet is beneficial in the long run to decrease the side effects of medication. Therefore, agents having anti-inflammatory potentials are helpful to ameliorate the symptom severity of diseases and to decrease risks triggering the onset of schizophrenia. Researches investigating the relationship between inflammation and schizophrenia so far performed mainly with tablets or a type of supplements, not with real foods or specific dietary patterns. Therefore, further researches should be conducted using anti-inflammatory nutrients, real foods, or specific dietary patterns. Moreover, considerable efforts should be focused on the identification of underlying mechanisms for the anti-inflammatory effects of specific dietary interventions. Because previous findings were limited to report relationship between a few inflammatory

markers and symptoms of schizophrenia, studies to identify underlying mechanisms relating to signaling networks of cytokines and microglia activation needed to identify molecular targets of anti-inflammatory diets or agents.

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