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Functional Food and Nutrition for the Management of Autism Spectrum Disorders and Schizophrenia

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Abstract

Autism spectrum disorder (ASD) and schizophrenia are two major neurodevelopmental disorders that differ in their age of onset and clinical profile. ASD and schizophrenia are characterized by varying degrees of brain dysfunction associated with behavioral abnormalities and differences in clinical outcomes. The causes of both disorders are unknown, but it is well recognized that their etiopathogenetic mechanisms involve an interaction between a strong genetic vulnerability and environmental factors. This combination then leads to epigenetic changes of gene expression and subsequent neuronal alterations responsible for synaptic plasticity and additional synapse formation. Additional pathogenetic mechanisms involve dysregulation of the immune system and brain-gut axis dysfunctions. Brain function analysis showed that individuals with ASD and schizophrenia have alterations in GABAergic and glutamatergic transmission. Gamma-Aminobutyric acid (GABA) and glutamate represent the major inhibitory and excitatory neurotransmitters in the brain, respectively. Preclinical and clinical studies have been investigating how an imbalance between the inhibitory (GABA) and excitatory (glutamate) neurotransmissions during early phases of neurodevelopment may be useful in discovering novel molecular targets for potential drug therapy. Current treatments for both ASD and schizophrenia include antipsychotic medications such as risperidone, olanzapine, clozapine, and aripiprazole, which target specific neurotransmitter receptors of the dopamine and serotonin systems. Despite the genetic vulnerability associated with ASD and schizophrenia, and the response (full or partial) to antipsychotic medications, treatments are still needed that can address the molecular mechanisms of the disorders in order to improve long-term overall health and quality of life. Recently, an emphasis has been put on environmental modifiable risk factors, including nutrition status and dietary patterns, which can play a role in disease prevention, treatment, and managing symptoms. Prenatal nutrition quality has been considered a candidate risk factor for both ASD and schizophrenia. For example, the inhibitory neurotransmitter GABA is derived from the decarboxylation of glutamate, which utilizes pyridoxal phosphate, the active form of vitamin B6.
as a cofactor. Vitamin deficiencies, such as low vitamin D, during early phases of life have been reported to be associated with both ASD and schizophrenia. In addition, alterations in vitamin D levels are associated with immune system dysregulations and systemic inflammation. This includes neuroinflammation, which has recently been considered one of the major pathogenetic mechanisms underlying both ASD and schizophrenia. Additionally, omega-3 polyunsaturated fatty acids such as α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) showed anti-inflammatory effects by regulating cytokine production and lowering pro-inflammatory activity of leukocytes. The anti-inflammatory effects of omega-3 fatty acids have recently been acknowledged as a mechanism for reducing psychosis severity amongst high-risk populations. In fact, the chronic low-grade systemic inflammation characterized by the hyper-production and activity of cytokines is involved in the development of mental illnesses including ASD and schizophrenia. Moreover, evidence showed that in subjects with schizophrenia, a diet rich in carotenoids found in fruit and vegetables caused an increase in the serum levels of brain-derived neurotrophic factor (BDNF), which is associated with brain plasticity and learning and memory mechanisms. Thus, we can speculate that adopting a functional, anti-inflammatory dietary pattern, rich in functional foods will help to support normal brain function and to ameliorate disease manifestation and progression in this specific population.

Introduction
The current definition of functional food, developed by the Functional Food Center (FFC) in 2012 at the FFC’s 10th International Conference in Santa Barbara, CA, is:

“Natural or processed foods that contain known or unknown biologically-active compounds; which, in defined, effective, and non-toxic amounts, provide a clinically proven and documented health benefit for the prevention, management, or treatment of chronic diseases.”

This definition, as explained in “A New Definition for Functional Food by FFC: Creating Functional Food Products Using New Definition” by Danik M. Martirosyan and Jaishree Singh [1], is unique because it highlights the role of food in a normal diet for optimized nutrition and emphasizes the importance of “bioactive compounds” which represent the effectors of functional food effectiveness. Examples of functional foods are grapes rich in resveratrol, blueberries rich in anthocyanins, flavonoids which have proven to be a powerful group of antioxidants, and walnuts rich in minerals and omega-3 fatty acids which have been shown to have anti-inflammatory properties. In recent years, several clinical trials have been conducted using bioactive compounds in the prevention, management, or treatment of both ASD and schizophrenia (see clinicaltrials.gov). They have also been utilized as supplementary compounds to potentiate conventional medications. Interestingly, 62 studies are currently listed on the clinicaltrials.gov website when searching “schizophrenia” and “diet” as keywords. These studies have focused on the role of different types of diets, such as the ketogenic diet or gluten-free diets, in addition to looking at how bioactive compounds can play a role in schizophrenia management. These studied bioactive components include omega-3 fatty acids, the antioxidant vitamins E and C, folate supplementation, curcumin and vitamin D. Several ongoing clinical trials are investigating the role of special diets and the supplementation of fatty acids (DHA, omega-3 FAs), antioxidants or minerals (clinicaltrials.gov: autism spectrum disorders and diet) in the management of ASD. It has
been suggested that nutritional supplementation can not only addresses the neuropsychiatric pathology of ASD and schizophrenia, but also the medical conditions often associated with the disorders such as cardiovascular diseases, obesity, and metabolic syndrome. These conditions are due to food selectivity, unhealthy dietary habits, or complications associated with the common medications used for treatment. Functional foods are strongly suggested for the overall prevention and management of cardio-metabolic disorders caused by unhealthy dietary habits. The onset of systemic medical conditions such as obesity and metabolic syndrome in patients with ASD or schizophrenia is largely caused by nutritional deficiencies and the adoption of diets rich in pro-inflammatory foods such as refined sugars and processed foods. Chronic low-grade systemic inflammation has been suggested to play a central role in a common pathogenetic mechanism found in both ASD and schizophrenia, leading to the activation of inflammatory cells (microglia cells) in the brain (neuroinflammation). Neuroinflammation causes alterations in neuronal cell communication and synaptic plasticity, which is considered to be the main mechanism underlying learning and memory processes. In addition, it has also been reported that neuroleptic drugs used to treat schizophrenia can cause oxidative stress and in turn neuronal damage [2]. In conclusion, clinicians, therapists, and mental care services should strongly consider the role of functional foods and bioactive compounds in preventing/limiting oxidative stress and systemic inflammation found in subjects with ASD or schizophrenia.

Recently, more emphasis has been put on examining the nutritional status of individuals with ASD and schizophrenia. In this chapter we will illustrate some of the current scientific evidence and studies that address the link between specific functional foods and bioactive compounds and the development and management of both ASD and schizophrenia. As there is a rapid increase in the scientific literature and studies in this field, the author would like to highlight that this chapter is not intended to be a comprehensive review covering all the scientific information available regarding all bioactive compounds and their correlation with neuropsychiatric disorders. It is rather intended to highlight the complexity of the pathogenetic hypothesis of these chronic and debilitating disorders and to show the potential role of some functional foods in managing these diseases.

**Functional Foods for the Management of ASD and Schizophrenia**

Oxidative stress, immune dysregulation, neuroinflammation, and microglia activation are the main underlying biological processes of ASD and schizophrenia. Figure 1 illustrates the molecular mechanisms involved in neuronal development. Functional Food, as mentioned above, is defined as “natural or processed foods that contain known or unknown biologically-active compounds; which, in defined, effective, and non-toxic amounts, provide a clinically proven and documented health benefit for the prevention, management, or treatment of chronic disease.” Importantly, the Functional Food Center defines functional food as “components of a normal diet for optimized nutrition.” This definition includes conventional whole foods, such as oranges or bran flakes, rather than pills, capsules, or supplements. The definition emphasizes that a diet based on unprocessed whole foods, especially of plant origin and rich in bioactive compounds, is essential for overall health and in the prevention, management, and treatment of chronic diseases. The mentioned bioactive compounds include flavonoids, essential fatty acids, minerals, vitamins, and phytonutrients, while the chronic diseases they can help treat include diabetes, cardiovascular diseases, hypertension, and diseases affecting the central nervous system, including ASD and
schizophrenia. ASD and schizophrenia are both neurodevelopmental disorders, with the age of onset of ASD occurring in the early phase of life (usually the diagnosis occurs around age of 2-3 years old, with a higher prevalence for males) while schizophrenia is usually first seen as an adolescent or young adult, depending on precipitating factors. In fact, it is well-established that both diseases are the result of an interaction between the individual’s genetic constitution and environmental factors which act as “second hit.” These environmental factors include psychological stressors and trauma, immunological stressors, infections, chemicals exposure, substance abuse, and nutritional deficiencies.

**Figure 1.** Dietary pattern and brain damage

High-fat diet promotes pro-inflammatory cytokines stimulation leading to microglia activation and neuronal damage (Fig. 1).

ASD is characterized by significant social, communication, and behavioral impairment. The Diagnostic and Statistical Manual for Mental Disorders (DSM-5) defines ASD as “a persistent deficit in social communication and social interaction across multiple contexts” and “by the presence of restricted, repetitive patterns of behavior, interests, or activities.” Although the cause of the disease is still unknown and under intensive clinical and preclinical research, it is well established that ASD is the result of genetic and environmental risk factors interaction. In contrast to genetic factors, environmental factors are modifiable factors, meaning that the identification of specific environmental factors, such as diet and nutritional deficiencies, can result in a suitable strategy for improving symptoms and managing the disease long-term. It has been reported that prenatal and perinatal exposure to environmental risk factors such as dietary habits, maternal diabetes, stress, medications, or infections are associated with a greater risk of developing ASD. This chapter will focus on specific functional foods that have been proven by scientific evidence to help brain functioning and the overall health of people affected by ASD or schizophrenia.

The pathogenesis of ASD is extremely heterogeneous and not fully understood [3], but new scientific evidence has suggested the possible role of abnormalities in synapse formation and maturation during early phases of neurodevelopment [4]. This process mainly involves the glutamatergic system, where alterations in the expression and function of AMPA receptors (ionotropic glutamate receptors) can affect synaptic plasticity as well as learning and memory processes [5, 6]. In addition, metabotropic glutamate (mGlu) receptors, such as mGlu5 receptors in specific brain regions such as the frontal cortex, hippocampus, striatum, and cerebellum, are crucial in the development of normal cognition and motor programming [7, 8]. Glutamate represents the major excitatory neurotransmission in the central nervous system and plays a key role in neuronal excitability, synaptic plasticity, immunity, and learning and memory mechanisms [9]. Glutamate is also involved in several different chemical reactions, including the formation of the inhibitory neurotransmitter, **γ-aminobutyric acid (GABA)**, which is catalyzed by the enzyme GAD (glutamate decarboxylase). GAD uses the B-vitamin P5P (itamin B6) as the cofactor for this
conversion. Glutamate is also involved in the synthesis of the potent antioxidant glutathione which is synthesized from glutamate, cysteine, and glycine using two enzymes. One of these enzymes is the glutathione synthetase that needs two magnesium molecules to carry out its function. Deficiencies in vitamin B6 or magnesium can lead to abnormalities in neurotransmitter synthesis and alterations in the physiological function of glutamate or GABA. Foods that are rich in magnesium include dark leafy greens, nuts and seeds, fish, soybeans, avocados, bananas, dark chocolate, and fat-free or low-fat yogurt. Magnesium deficiency induces an inflammatory response that results in leukocyte and macrophage activation, the release of inflammatory cytokines and acute-phase proteins such as CRP, and excessive production of free radicals [10] which cause cell damage. Neuroinflammation represents an important mechanism involved in the pathogenesis of ASD, although it is likely secondary to altered pathways of the so-called gut-microbiome-brain communication [11, 12]. Systemic inflammation can affect also the brain and its development [13]. Targeting the causes of inflammation can help to reduce the symptoms of ASD by addressing the abnormalities in the gut system and thus one’s dietary patterns. Several mechanisms are proposed for the gut-microbiota-brain axis including neural, hormonal, immunological, and metabolic [14, 15]. The hypothesis is based on the observation that the inflammation of the gastrointestinal (GI) tract causes an increase in the cytokines released that can cross the blood-brain barrier and trigger an immune response in the brain [16]. Neuroinflammation in early phases of life can alter the maturation of neurons and synaptic plasticity by altering the glutamatergic system. During development, microglia, the quiescent immune cell-type within the brain, regulates neurogenesis, synaptic plasticity and synaptic striping [17].

Different research groups have reported that maternal immune activation (MIA) during pregnancy is associated with neuronal defects, likely caused by microglia activation which leads to behavioral abnormalities in the offspring [18]. MIA induced by a high-fat diet represents a potential environmental risk for chronic pro-inflammatory programming during fetal development, allowing active microglia to negatively modulate synaptic pruning and neurogenesis [19]. Based on these observations, we can reasonably speculate that an anti-inflammatory functional food dietary pattern would be beneficial in improving the symptoms associated with neuroinflammation. The correlation between brain inflammation and intestinal microbiota alterations in ASD can be explained by the changes seen in gut microbiota after consuming a high-fat diet. This diet can induce an increase in intestinal permeability and the activation of immune cells causing systemic inflammation and metabolic disorder [20, 21]. In addition, inflammation processes lead to increased oxidative stress and consequent cell damage. Many functional foods have been proven to have anti-inflammatory and antioxidant properties. These include flavonoids contained in berries (blackberries, strawberries, blueberries, cranberries, mulberries, goji berries, and kumquats), red grapes, green tea, tomatoes, onions, garlic, cauliflower, broccoli, carrots, cabbages, and cocoa. Flavonoids are polyphenolic phytonutrients that have been extensively studied for their antioxidant and anti-inflammatory activities [22]. Several different subclasses of flavonoids are described based on their chemical structure, major sources and mechanism of action in Table 1.
<table>
<thead>
<tr>
<th>Phytochemical</th>
<th>Bioactive Compounds</th>
<th>Food Source</th>
<th>Physiological Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthocyanidins</td>
<td>malvidin</td>
<td>blueberries, black grapes, pomegranates</td>
<td>Antioxidant and anti-inflammatory activity, anti-carcinogenic, anti-inflammatory, antioxidant, and antiviral activities. Mitigation of microglia-mediated neuroinflammation</td>
</tr>
<tr>
<td>Flavonols</td>
<td>kaempferol, myricetin, quercetin</td>
<td>berries, kale, grapes, spinach, bell peppers, cocoa, broccoli, sweet potatoes, tomatoes</td>
<td></td>
</tr>
<tr>
<td>Flavanones</td>
<td>hesperetin, naringenin</td>
<td>citrus fruits (lemons and oranges), grapes</td>
<td>Antioxidant, anti-inflammatory</td>
</tr>
<tr>
<td>Flavones</td>
<td>apigenin, luteolin</td>
<td>celery, fresh parsley, olives, oregano, peppers, and rosemary</td>
<td>Suppression of oxidative stress via anti-inflammatory effects on NF-κB; offers brain support, protection, and increases in memory</td>
</tr>
<tr>
<td>Flavanols</td>
<td>epicatechin-gallates, procyanidins, catechin</td>
<td>Tea, grapes, lentils, cocoa, apples with peel on, apricots, cherries, peaches, blackberries, black grapes, strawberries, blueberries, and raspberries</td>
<td>Antioxidant, free radicals scavenging properties. Decrease of the hypothalamic inflammation and microglia overactivation. Improve cognition</td>
</tr>
<tr>
<td>Isoflavones</td>
<td>daidzein</td>
<td>grape seeds, soy products</td>
<td>Improves adipose inflammation, insulin resistance, and cognitive function.</td>
</tr>
<tr>
<td>Flavans</td>
<td>genistein</td>
<td>soybeans</td>
<td>Antioxidant and neuroprotective activities. Improves glucose metabolism and cognitive function.</td>
</tr>
<tr>
<td>flavonoid glycoside</td>
<td>rutin</td>
<td>Buckwheat, unpeeled apples, asparagus (specially the bottom part), grapefruit, lemons, orange juice, oranges</td>
<td>anti-inflammatory, antioxidant, neuroprotective, hepatoprotective effects. antioxidant and anti-inflammatory properties. Improve in cognition and neurodegeneration</td>
</tr>
<tr>
<td>Phenolic acids</td>
<td>caffeic acid, ferulic acid</td>
<td>apples, coffee beans, blueberries, oranges, peaches, potatoes, pears</td>
<td></td>
</tr>
<tr>
<td>Hydroxy-benzoic juice, longan seeds, gallic acids</td>
<td>grape and raspberry grape acids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trihydroxy-stilbenes</td>
<td>resveratrol</td>
<td>grape skin, peanuts, red wine, cranberries</td>
<td>anti-aging, chemopreventive, anti-carcinogenic, anti-inflammatory, and antioxidant effects antioxidant properties</td>
</tr>
<tr>
<td>Tannins/Proanthocyanidins</td>
<td>catechin, tannic acids</td>
<td>coffee, cocoa, lentils, peas, walnuts, berries, olives, plums, tea, chickpeas, herbs, and spices</td>
<td>antioxidant properties</td>
</tr>
<tr>
<td>Diferuloylmethane</td>
<td>curcumin</td>
<td>Turmeric plants</td>
<td>anti-inflammatory and antioxidant activities</td>
</tr>
</tbody>
</table>
Malvidin, one the larger diffused anthocyanidins, exhibits marked antioxidant and anti-inflammatory activity and has been reported to decrease inflammatory gene expression in human adipocytes [23]. Malvidin-3’-O-glucoside (Mal-gluc) also induces anti-inflammatory effects via epigenetic mechanisms and modulates brain synaptic plasticity and peripheral inflammation [24]. Quercetin showed a wide range of biological in vitro and in vivo actions including anticarcinogenic, anti-inflammatory, and antiviral activities, attenuation of lipid peroxidation (which represents one of the damaging effects of oxidative stress) [25], and mitigation of microglia-mediated neuroinflammation [26]. Hesperetin is a trihydroxyflavanone belonging to the flavanone class of flavonoids. In the form of its glycoside (hesperidin), hesperetin is the predominant flavonoid in lemons and oranges. A 2018 study showed that hesperetin induces ameliorative effects on social behavior deficits and oxido-inflammatory stress in animal models of autism [27]. It is well-established that a high calorie diet promotes oxidative stress and chronic systemic low-grade inflammation that predispose one to brain dysfunction and neurodegeneration. The degeneration particularly occurs in the hippocampus, a region that regulates important brain functions such as working memory and executive functions [28]. Apigenin, a bioactive flavone found in plants such as celery, parsley, and chamomile, shows benefits in reducing the risk of chronic diseases such as gastro-intestinal cancers [30]. It also has been shown to have anti-inflammatory properties and protective effects against neurodegeneration [31]. Recently, it has been reported that apigenin suppresses oxidative stress by reducing the activation of inflammatory biomarkers, such as NF-κB in the hippocampus, and consequently leading to neuroprotective benefits. In this study, rodents were treated with a high-fat, high-fructose diet [29]. The flavone luteolin has showed several beneficial effects including antioxidant and anti-inflammatory properties, microglia inhibition, neuroprotection, and an increase in memory [32]. Luteolin is found in different fruits, vegetables, and herbs such as thyme, chamomile tea, carrots, olive oil, peppermint, rosemary, oregano, basil, parsley, dandelion, and lemons. A recent clinical study showed that the anti-inflammatory properties of luteolin caused a decrease in interleukin-6 and TNF levels in children with ASD [33]. Theoharides et al. (2015) described the effects of luteolin on “brain fog,” which describes a constellation of symptoms that include reduced cognition, inability to concentrate and multitask, as well as short- and long-term memory loss [34]. Brain fog is seen in patients with ASD and is considered the result of inflammatory mechanisms [34]. Catechins, such as epicatechin gallate and epigallocatechin gallate (EGCG), are natural polyphenolic phytochemicals that are largely found in tea and provide antioxidant effects due to their free radical scavenging ability [35]. Other foods rich in catechins are unpeeled apples, apricots, cherries, peaches, blackberries, black grapes, strawberries, blueberries, and raspberries. An increasing number of studies have associated the intake of catechins-rich foods with the prevention and treatment of chronic diseases such as inflammatory bowel disease [36]. In addition, EGCG consumption significantly inhibited the development of high-fat diet-induced obesity and attenuated the hypothalamic inflammation and microglia overactivation by regulating the NF-κB and STAT3 signaling pathways in mice [37]. Another study showed that EGCG improved high-fat and high-fructose-induced cognitive defects by inhibiting the NF-κB pathway [38]. As a whole, these studies show the potential anti-inflammatory benefits of catechins and their potential application in preventing obesity-induced systemic inflammation. This finding is relevant
because obesity is very common in children with ASD. In fact, recent research suggested higher rates of obesity in children with ASD [39] due to their poor diet and nutritional patterns. Recent research showed that picky eating, food refusal, and food selectivity are characteristic of the dietary habits of the ASD population. In addition, food selectivity has been associated with worsening symptoms of ASD [40]. Daidzein, a naturally occurring compound found mostly in soybeans and soy products such as tofu, belongs to a class of compounds known as isoflavones. Various studies have been done to examine the effects of daidzein on adipose-induced inflammation which causes insulin resistance in obesity. The conclusion of a study published by Sakamoto et al. (2014) found that daidzein regulates adipokine expression through \(PPAR_\gamma\), thereby improving the adverse effects of adipose inflammation, such as insulin resistance, in those with obesity [41]. In addition, a recent study reported that a compound called 7,8,4'-THIF, a metabolized product of daidzein, improves cognitive function by activating the cholinergic system and the BDNF/ERK/CREB signaling pathway in mice [42]. This finding could be very promising for children with ASD and intellectual disabilities. Genistein is also found in soybeans and has shown antioxidant and neuroprotective properties. A recent study showed that genistein induced changes in gut microbiota, thus improving glucose metabolism and cognitive function in mice that were fed a high-fat diet [43]. Rutin, a biochemical compound found in buckwheat and many plants, exhibits various biological effects including anti-inflammatory, antioxidant, neuroprotective, nephroprotective, and hepatoprotective properties. A recent scientific article reported that rutin displays great antioxidant potential and could be beneficial in treating neurodegenerative disorders by counteracting the oxidative stress [44].

Another extensively studied flavonoid is resveratrol. Resveratrol exerts several physiological activities including anti-aging, chemo-preventive, anti-carcinogenic, anti-inflammatory and antioxidant effects. These effects have led to to the flavonoid being studied extensively in the past few years in relation to different chronic diseases [45]. Resveratrol is found largely in grape skin, with a major concentration found in dark grape extracts, and has been shown to display antioxidative effects [46]. In a recent study from China it was been reported that resveratrol ameliorates prenatal progestin-exposure-induced autism-like behavior through ER\(\beta\) activation [47]. Another study found that it prevents cellular and behavioral abnormalities in an animal model of autism induced by valproic acid [48]. In BTBR mice, a well-established animal model for studying ASD, resveratrol induced a marked decrease in pro-inflammatory biomarkers in the brain [49]. Curcumin is a bright yellow chemical produced by Curcuma longa plants. It is the principal curcuminoid of turmeric and together with resveratrol is the most phenolic compound studied for its anti-inflammatory and antioxidant activities. Curcumin lacks solubility in aqueous media and has poor bioavailability in biological systems, thus making it difficult for successful application. Researchers are focusing on creating new formulations using molecular technology to develop curcumin products with a higher absorption and bioavailability [50]. Despite its relatively low bioavailability, curcumin/turmeric has recently gotten the attention of several research groups and is still the most-used spice in everyday cooking. Studies have shown that combining curcumin/turmeric with piperine, the ingredient of black pepper, increased curcumin absorption [51]. Curcumin has been also studied in several clinical trials as being a cognitive enhancer in neurodegenerative disorders and for its potent anti-inflammatory property.
A recent study, conducted by Poulse et al. (2017) at the USDA-ARS Human Nutrition Research Center on Aging, reported that many dietary components such as curcumin and resveratrol, as well as caloric restriction and physical exercise, have been shown to induce neurogenesis in adult brains [52]. Recent studies found that curcumin has positive effects on cognitive function and ameliorates brain damages in the valproate-induced model of autism [53, 54]. Taken together, these studies show that foods rich in flavonoids might interfere with two major pathogenetic factors involved in ASD: oxidative stress and neuroinflammation. Flavonoids, then, may decrease the levels of both oxidation and inflammation thus causing ameliorative effects in overall brain functioning. Children with ASD have been described in several studies as picky eaters and as more prone to eating an imbalanced diet [55, 40]. An example of an imbalanced diet is one that lacks adequate dietary fibers.

Fibers are crucial to preventing cardiovascular disease, diabetes, and cancer, and promoting normal gastrointestinal health and mineral absorption in the intestinal tract. The FDA recently updated the official list of fibers and published two guidance documents on dietary fiber (for details see: fdasimplified.com). The 2016 definition of dietary fiber has two parts. First, it includes “non-digestible soluble and insoluble carbohydrates (with 3 or more monomeric units), and lignin that are intrinsic and intact in plants.” This part of the definition includes the fiber found in whole grains, fruits, vegetables, nuts, and seeds along with fibers in food ingredients that have been mechanically processed, chopped or ground. Only seven isolated or synthetic fibers were recognized as having physiological benefits in the updated nutrition labeling regulations of 2016:

1. Beta-glucan soluble fiber
2. Psyllium husk
3. Cellulose
4. Guar gum
5. Pectin
6. Locust bean gum

Regular consumption of foods rich in dietary fibers can improve overall health and prevent different conditions such as diabetes, atherosclerosis, diverticulitis, and obesity [56]. A diet rich in fibers is recommended for those with the above health conditions, as it has been shown to reduce inflammatory biomarkers such as C-reactive protein (CRP) and IL-6. Foods high in fiber include grains (barley, oats, rice), legumes (peas, beans, green beans), vegetables (potatoes, raw spinach, eggplants), fruits (grapes, oranges, kiwi), and nuts and seeds (almonds, sesame seeds, flaxseed). Dietary fiber can be also categorized into many different families based on their bioactive compounds. These families include arabinoxylan, inulin, lignin, psyllium, pectin, bran, cellulose, β-glucan and resistant starch, and guar gum. The different sources of dietary fibers, as well as their bioactive compounds and physiological effects, are shown in table 2.

Dietary fibers do not go through the digestion processes in the small intestine, but instead are fermented in the large intestine. This creates a bulk that helps the mass of food move along the intestine and stimulates intestinal contraction (peristalsis). This mechanism helps to keep the large
intestine clean and reduce the formation of pro-inflammatory byproducts. Fibers are also important in preventing constipation and colorectal cancer [57]. **Butyrate**, as a product of resistant starch and non-digestible oligosaccharide fermentation, is also considered to have a protective effect against colon cancer [57]. **Insoluble fibers** also are associated with a lower risk of diverticular disease and inflammatory bowel diseases [59].

**TABLE 14.2 Dietary Fibers and Food Sources**

<table>
<thead>
<tr>
<th>Food Group</th>
<th>Bioactive Compounds</th>
<th>Physiological Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grains</td>
<td>B-glucan, phytochemicals (phenolic acids, flavonoids, lignans, tocols, sterols, folate), cellulose</td>
<td>Boosting the immune system, immunostimulation, reducing the risk of colonic cancer, high blood pressure and gallstones</td>
</tr>
<tr>
<td>Legumes</td>
<td>Cellulose, gums, pectins</td>
<td>Improved blood sugar control and insulin sensitivity, laxation</td>
</tr>
<tr>
<td>Vegetables</td>
<td>Lignin, gums, inulin</td>
<td>Bulking capacity and stimulate the growth of intestinal bifidobacteria</td>
</tr>
<tr>
<td>Fruits</td>
<td>Pectin</td>
<td>Lipid reduction, GI benefits, blood sugar reduction</td>
</tr>
<tr>
<td>Nuts and Seeds</td>
<td>Lignans</td>
<td>Inflammatory diseases including intestinal inflammation, immune system, cancer, brain function</td>
</tr>
</tbody>
</table>

Gut microbiota, which is commonly defined as a collection of bacteria, viruses, and fungi, is crucial for immunologic, hormonal, and metabolic functions of the host [60]. Aberrations in the gastrointestinal (GI) microbiota of children with ASD have been reported to affect neurodevelopment by challenging the immune system and metabolism. Associations between specific microbial genera and some symptoms of ASD have been examined. Specifically, a lower ratio of Bacteroidetes-to-Firmicutes and a higher abundance of Clostridium and Desulfovibrio were positively associated with an increased severity of ASD symptoms [61]. In addition, differences in microbial products, such as volatile chain fatty acids (VFA), between children with ASD and unaffected controls have also been observed [62]. The end-products of microbial fermentation of complex carbohydrates in the colon are **short-chain fatty acids (SCFAs)** such as acetate, propionate, and butyrate. These products exhibit different health benefits to the host including the promotion of colon health. Butyrate, for example, is of interest because it has been shown to have anti-inflammatory properties on microglia and improve memory in mice when administered pharmacologically [63]. Butyrate plays a role in decreasing inflammation in the
brain. Increased levels of propionate caused developmental delay or seizures [63], and it has been reported that the administration of propionate in experimental animals caused ASD-like symptoms [64]. This was due to the translocation of propionate to the brain through the brain-blood barrier. Propionic acid is a metabolite of clostridia species, a bacterium found at higher levels in the feces of those with ASD in comparison to controls [62]. A diet poor in fermentable carbohydrates has been proposed to reduce the levels of propionate production in the gut. Bee pollen has been also reported to decrease the levels of propionic acid, which impairs the production of brain neurotransmitters such as serotonin, dopamine, and noradrenaline. Bee pollen was also found to be effective in

**Figure 2. Dietary Fibers and Brain function**

Dietary fibers help to reduce fat accumulation in the intestinal tract preventing local and systemic inflammation including brain inflammation (Fig.2)

ameliorating signs of PPA-induced brain toxicity [65]. We also know that autism is characterized by higher levels of glutamate, which leads to neurotoxicity through the activation of fast-mediating synapse transmission receptors (e.g., NMDA receptors). Glutamate excitotoxicity is clinically related to neuroinflammation, oxidative stress, and apoptosis. Furthermore, propionic acid impairs the physiological balance between glutamate and GABA (the major inhibitory and excitatory neurotransmitters in the brain) through oxidative stress mechanisms. Pollen is a significant source of vitamins such as vitamins E, A, D, B complex, folic acid, and biotin. Most of these components were individually effective in either improving behavior in valproic acid-induced autism (rat model) or clinically reducing symptoms of neurodevelopmental disorders (including autism) [66].

The management of the diet of children with ASD is further complicated due to strong preferences for snacks and processed foods and their low consumption of fruits and vegetables. This puts them at a higher risk of obesity and obesity-related disorders such as hypertension, early diabetes, and nutritional deficiencies. Although the data is not consistent regarding the type and severity of nutritional deficiencies amongst children with ASD, vitamin, mineral, and fatty acid deficiencies are the most commonly reported. Decreased vitamin D levels, for example, were associated with ASD [67] in either pregnancy or the postnatal period [68]. Vitamin D is a potent fat-soluble neurosteroid which is involved in many physiological mechanisms including calcium and phosphorus level regulation in the body and brain. In animal studies, it has been reported that vitamin D deficiency was associated with abnormalities in brain development and structural alterations such as enlarged brain at birth, enlarged ventricles, and neurotransmission changes [69, 70]. Early brain enlargement is due to increased gray matter and volume of ventricles and the
striatum, a brain region involved in motor programming and responsible for the stereotypic behavior observed in children with ASD and animal models. It has been reported that supplementation of vitamin D ameliorates the symptoms of ASD [71]. Based on these findings, it is possible that increased exposure to functional foods or fortified foods rich in vitamin D may improve ASD symptoms or reduce the risk of ASD when taken during pregnancy.

Foods rich in vitamin D include fatty fishes such as salmon and tuna, dairy-products such as milk and butter, almond milk, egg yolks, or shiitake mushrooms. Decreased levels of other vitamins such as vitamin C, folate, pantothenic acid, vitamin E, and B12 were also found in children with ASD [72]. Foods high in vitamin E include include sunflower seeds, almonds, spinach, avocados, squash, kiwifruit, trout, shrimp, olive oil, wheat germ oil, and broccoli. Recently, decreased levels of vitamin B12 and glutathione, which are involved in DNA methylation processes and antioxidant reactions, respectively, were found in the brains of those with autism or schizophrenia [73]. Vitamin B12 is only synthesized by certain bacteria and humans obtain it from animal source foods such as meat, dairy, eggs, fish, as well as nutritional yeast. Glutathione is an antioxidant in plants, animals, fungi, and some bacteria and archaea. Glutathione acts by preventing oxidative stress damages to important cellular components caused by reactive oxygen species such as free radicals, peroxides, lipid peroxides, and heavy metals. Glutathione is found mainly in fruits and vegetables such as blueberries, pomegranates, asparagus, avocados, and walnuts, but also in high-protein animal-based foods such as ricotta cheese, red meat, and poultry. In recent years, different diets have been suggested to treat ASD symptoms including the gluten-
free/casein-free diets, ketogenic diets, or supplementation with omega-3 fatty acids, minerals, and multivitamins. Studies have shown the importance of dietary omega-3 fatty acids in cognitive functioning and memory mechanisms [74]. Omega-3 polyunsaturated fatty acids (n-3 PUFAs) such as docosahexaenoic acid [DHA; 22:6 (n-3)] and eicosapentaenoic acid [EPA; 20:5 (n-3)] are found mainly in fatty fishes such as salmon, herring, sardines, mackerel, and cod liver oil. They play a major role in activity-dependent changes in the efficiency of synapses, or synaptic plasticity, which has been shown to be impaired in ASD [75]. DHA deficiency is associated with cognitive decline and supplementation during pregnancy has been reported to increase cognitive functions in children [76]. Dietary n-3 PUFA is relevant for the development of the glutamatergic system and for behavioral performance in adulthood [77]. As discussed earlier in the role of glutamatergic system abnormalities in ASD development, the role of PUFAs in synaptic plasticity and LTP, which is induced by the neurotransmitter glutamate, has been investigated recently [75]. In addition, preclinical studies found that chronic administration of DHA appears to enhance spatial memory-related learning ability, most likely due to the reduction of lipid peroxidation [78]. In humans, a higher proportion of total n-3 PUFAs is associated with a lower risk of cognitive decline [79].

Schizophrenia Spectrum Disorders (SSD)

Schizophrenia and related psychotic disorders are considered diseases of neurodevelopment with the onset of the disease usually coming after puberty or during adolescence or when the individual is a young adult. The principal schizophrenia symptoms include delusions and hallucinations, disorganized thinking and speech, negative symptoms such as affect flattening and avolition, and cognitive impairments which are considered the “core” of the disease (DSM-5). Scientific evidence has shown that a strong genetic predisposition, along with the interference of environmental factors later in life, lead to the manifestation of schizophrenia. This process is based on the so-called “second hit” model [80]. It has been reported that the life-expectancy of

![Figure 4. Role of Polyunsaturated Fatty Acids (PUFAs). Immunological effects induced by PUFAs and brain damages associated with cognitive decline (Fig. 4.)](image)

Immunological effects induced by PUFAs and brain damages associated with cognitive decline. Patients with schizophrenia is estimated to be shorter than the general population due an increased risk of mortality caused by low socioeconomic status, tobacco use, poor diet, physical inactivity, and metabolic syndrome [81]. Modifiable risk factors associated with schizophrenia include one’s dietary pattern and nutritional status [82]. Schizophrenia, like ASD, has a strong genetic vulnerability and is associated with abnormalities in synaptic plasticity, alterations in the release of neurotransmitters such as glutamate, dopamine, and serotonin, and abnormal activation of neuroinflammatory mechanisms. Strong evidence suggested that altered epigenetic mechanisms
in the glutamatergic/GABAergic systems (see the schematic representation below) play a key role in the pathogenesis of the disease which is characterized by cognitive dysfunctions associated with neurodegenerative and neuroinflammatory processes [83-85]. Recent scientific hypotheses of schizophrenia pathogenesis include gut microbiome abnormalities, blood sugar dysregulation, vitamin and mineral deficiencies, oxidative stress, alterations of methylation mechanisms, neuroinflammation, microbiome abnormalities, lack of essential amino acids or phytonutrients, fatty acids deficiencies, and food sensitivity [86].

**Figure 5.** Glutamatergic and GABAergic systems in brain.
A schematic representation of Glutamate, GABA and Dopamine neurotransmission systems in cortical-subcortical regions. Altered GABAergic function including the formation of GABA leads to an imbalance between Glutamate and GABA causing neurotoxicity and dopaminergic system dysfunction (Fig.5)

Thus, it has been suggested that nutritional interventions could help to improve both the mental and physical health of schizophrenic patients. As in ASD, prenatal nutritional deficits have been examined in cohorts of the population exposed to periods of famine. The results found that people born from mothers exposed to malnutrition during pregnancy had a higher risk of developing schizophrenia [87]. Additionally, as in ASD, low-grade inflammation has been suggested to play an important role in schizophrenia. It has been shown that chronic low-grade peripheral inflammation is associated with ultra-resistant schizophrenia [87]. Patients suffering from psychotic disorders are at a dramatically elevated risk of medical comorbidities, which have a significant impact on mortality and morbidity. In fact, schizophrenia patients have higher risk of developing metabolic syndrome, which is characterized by abnormalities in lipid profile, blood pressure, and diabetes, due to their lifestyle and antipsychotic treatment. Recent clinical studies suggest a potential role of anti-inflammatory drugs used in combination with antipsychotics to treat patients with schizophrenia [89]. It is suggested that inflammation starts in the gut and is associated with alterations in the absorption nutrients such as magnesium, omega-3 fatty acids, probiotics, vitamins and, minerals.
Omega-3 Fatty Acids
The clinicaltrials.gov website showed roughly 20 studies when searching for omega-3 fatty acids and schizophrenia as key words. These healthy fats may play a role in addressing the aggressive behavior, inflammation, oxidation mechanisms and the cardio-metabolic risk associated with schizophrenia. Polyunsaturated fatty acids (PUFAs), which are highly concentrated in neural phospholipids, are important components of the neuronal cell membrane and are crucial for synaptic plasticity and neuronal communication. Amongst the systemic effects of PUFAs, it is important to mention the cardio-metabolic effects of PUFAs in preventing heart diseases and diabetes. An imbalance between omega-6 and omega-3 fatty acids has been reported to cause an overproduction of inflammatory cytokines [90]. Omega-3 and omega-6 fatty acids play separate, defined functions in organisms. DHA and EPA acids, for example, exert different functions such as maintaining cell-membrane fluidity, inhibiting inflammatory processes, decreasing secretion of proinflammatory cytokines by monocytes/macrophages, improving functions of vascular endothelial cells, inhibiting blood platelet aggregation, and decreasing triglyceride synthesis in the liver [91]. Omega-3 fatty acids have anti-inflammatory and anti-allergic properties, predominantly through the inhibition of excessive immune response. Foods rich in omega-3 PUFAs are walnuts, sunflower seeds, flax seeds or oil, and fatty fishes, such as salmon.

Fruits and vegetables
Growing evidence has shown that individuals with psychosis consume lower amounts of fruits and vegetables. In addition, it has been shown that eating fruits and vegetables can help to decrease the risk of cardiovascular diseases, diabetes, and overall mortality. Fruits and vegetables are rich in antioxidants, mineral, and vitamins which promote overall health by decreasing age-related and inflammation-related cell damage [92]. Green tea, broccoli, onions, and berries contain a significant amount of phytonutrients derived from plants. Examples of phytonutrients include carotenoids, ellagic acid, flavonoids, resveratrol, glucosinolates, and phytoestrogens. Pumpkins and carrots are good sources of alpha and beta-carotene. Lycopene, the most potent antioxidant, is found in tomatoes, watermelon, and grapefruit. Spinach, kale and collard are good sources of lutein and zeaxanthin. Ellagic acid is found in various berries and other plant foods such as strawberries, raspberries and pomegranates. Catechins, hesperidin, and flavonols, such as quercetin, are excellent bioactive compounds that can help in limiting oxidation and inflammation. These components can be found in green tea, citrus fruits, apples, berries, kale, and onions. Resveratrol is found in grapes, red wine, and purple grape juice. Glucosinolates are found in cruciferous vegetables, including brussels sprouts, cabbage, kale, and broccoli. Good sources of lignans, a type of phytoestrogens, are sesame seeds and flaxseed. Supplementing phytonutrients into the diet of patients with psychosis can help them to manage inflammation and neuronal oxidation, both of which are associated with cell death, neurodegeneration, and cognitive impairments.

Minerals
Minerals, especially zinc, have also been considered to play a role in psychosis. Zinc is essential for all physiological systems, including neural functioning [93]. It is an essential trace mineral required for proper cellular function, including DNA replication, transcription, protein synthesis, maintenance of cell membranes, and cellular transport. Found mainly in red meat, poultry, fish and dairy, zinc also plays a role in the functioning of endocrine, immunological, and neuronal systems. The dysregulation of zinc is associated with reduced immunological functioning,
alterations in cognitive functions, and gastrointestinal complaints. Zinc insufficiency is also associated with neuropsychiatric manifestations [94]. A double-blind, placebo-controlled schizophrenia study showed that 220 mg of zinc sulfate TID, used as an adjuvant to 6 mg/day of risperidone, produced a statistically significant improvement of positive and negative symptomatology and reduced aggressive behavior [95]. It has been reported that zinc interferes with the glutamatergic system and, in particular, the ionotropic glutamate NMDA receptors which have been linked to the pathogenesis of schizophrenia. Zinc also stimulates the release of the inhibitory neurotransmitter GABA from interneurons, which results in the presynaptic inhibition of glutamate release. With less glutamate in the synapse, glutamate binding at the NMDA receptor is consequently reduced. Zinc inhibits the group I metabotropic glutamate receptors (mGluR1 and 5), diminishing Ca$^{2+}$ release from the internal neuron stores, which mediate calcium mobilization and its toxicity [93]. In addition, inflammation leads to a decrease in zinc levels, resulting in alterations in NMDA receptors and glutamate neurotransmission. Ultimately, this leads to excitotoxicity due to high levels of calcium in the neurons [96]. Lower zinc levels can be a consequence of inflammation, nutritional deficiencies or malabsorption. Subsequent zinc consumption will be helpful to modulate the hyper-glutamatergic state and reduce the symptoms of psychosis [97]. It has been speculated that increasing zinc intake will lead to decreasing glutamate mediated excitotoxicity and thus normalizing glutamatergic transmission [93].

**Vitamins**

Vitamins have also presented a potential protective role in psychosis, especially for vitamins B6, B12, and folate. These vitamins are involved in different mechanisms including homocysteine metabolism, neurotransmitter synthesis, and oxidative stress levels. Potential relevance of vitamin A, C, and E adequacy also has been considered to play a role in psychosis [86]. Foods containing vitamin B6 are bananas, pistachios, salmon, fortified tofu, and sweet potatoes. Foods rich in vitamin B12 are seafood, eggs, soy, meat, cheese, and fortified dairy products but also nutritional yeast and mushrooms. Taken together, these findings suggest that individuals with schizophrenia should consider decreasing their refined carbohydrate intake. This means limiting foods such as refined sugar, sugar-sweetened beverages, confectioneries, sweets, refined grain products (cereals, bread, pasta), as well pre-packaged and premade food. In contrast, foods that should be encouraged are whole fruits and vegetables, especially broccoli, onions, berries and grapes; high-fiber foods such as vegetables, fruit, whole grains, bran cereals, legumes, nuts, and seeds; foods rich in ω-3 fatty acids such as fish, seafood, walnuts, and flax seeds; foods rich in folate (essential for methionine metabolism) such as edamame, spinach, okra, artichokes, asparagus, broccoli, brussel sprouts, lettuce, and avocados; and foods rich in zinc such as oysters, wheat germ, liver, pumpkin seeds, baked beans, soy products, beef, and pork.

**Figure 6.** Role of Vitamin D and Brain.

Pleiotropic effects of vitamin D and brain function relevant for neuronal trophism and brain health (Fig. 6).
Conclusion
Functional food scientists strongly suggest the use of functional foods, especially those rich in antioxidants and anti-inflammatory properties, to help treat ASD and schizophrenia symptoms. A healthy dietary pattern based on whole functional foods, especially fruits, vegetables, unrefined grains, gluten-free grains, legumes, seeds, and nuts, can improve overall health and ameliorate the management of ASD and schizophrenia. Further clinical and pre-clinical studies are needed to investigate the cause-effect relationship between food and disease development.

Summary
- Functional foods are necessary to optimize nutrition intake. Examples of such foods are those rich in resveratrol, anthocyanins, and antioxidants.
- Recently, more emphasis has been placed on investigating the nutritional status of individuals with ASD and schizophrenia. Bioactive compounds have been used in clinical trials to help prevent, manage, and treat both ASD and schizophrenia; these compounds have also been utilized as supplements to potentiate conventional medications.
- Functional foods rich in antioxidants and exerting anti-inflammatory properties are recommended to help treat symptoms of ASD and schizophrenia.
- Healthy diets which center around whole functional foods have been found to improve overall health and ameliorate the management of ASD and schizophrenia.

Review Questions
1. What bioactive compounds are relevant for autism spectrum disorder?
   a. Carbohydrates
   b. Amino acids
   c. Flavonoids
   d. Triglycerides
   e. Lipids

2. Which neurotransmitter(s) is/are involved in autism spectrum disorder and schizophrenia?
   a. Glutamate
   b. Dopamine
   c. Serotonin
   d. GABA
   e. All the above

3. Which fatty acids possess anti-inflammatory effects?
   a. Saturated fatty acids
   b. Monosaturated fatty acids
   c. Trans fatty acids
   d. Omega-3 fatty acids

4. Which vitamin has been related with the development of schizophrenia?
a. Vitamin B1
b. Vitamin K
c. Vitamin B2
d. Vitamin D
e. Vitamin A

5. What are the bioactive compounds with antioxidant effects in green tea?
a. Catechins
b. Ellagic acid
c. Lutein
d. Quercetin

Answers: 1. (C); 2. (E); 3. (D); 4. (D); 5. (A)

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