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Functional Foods in the Management of Mental Illness

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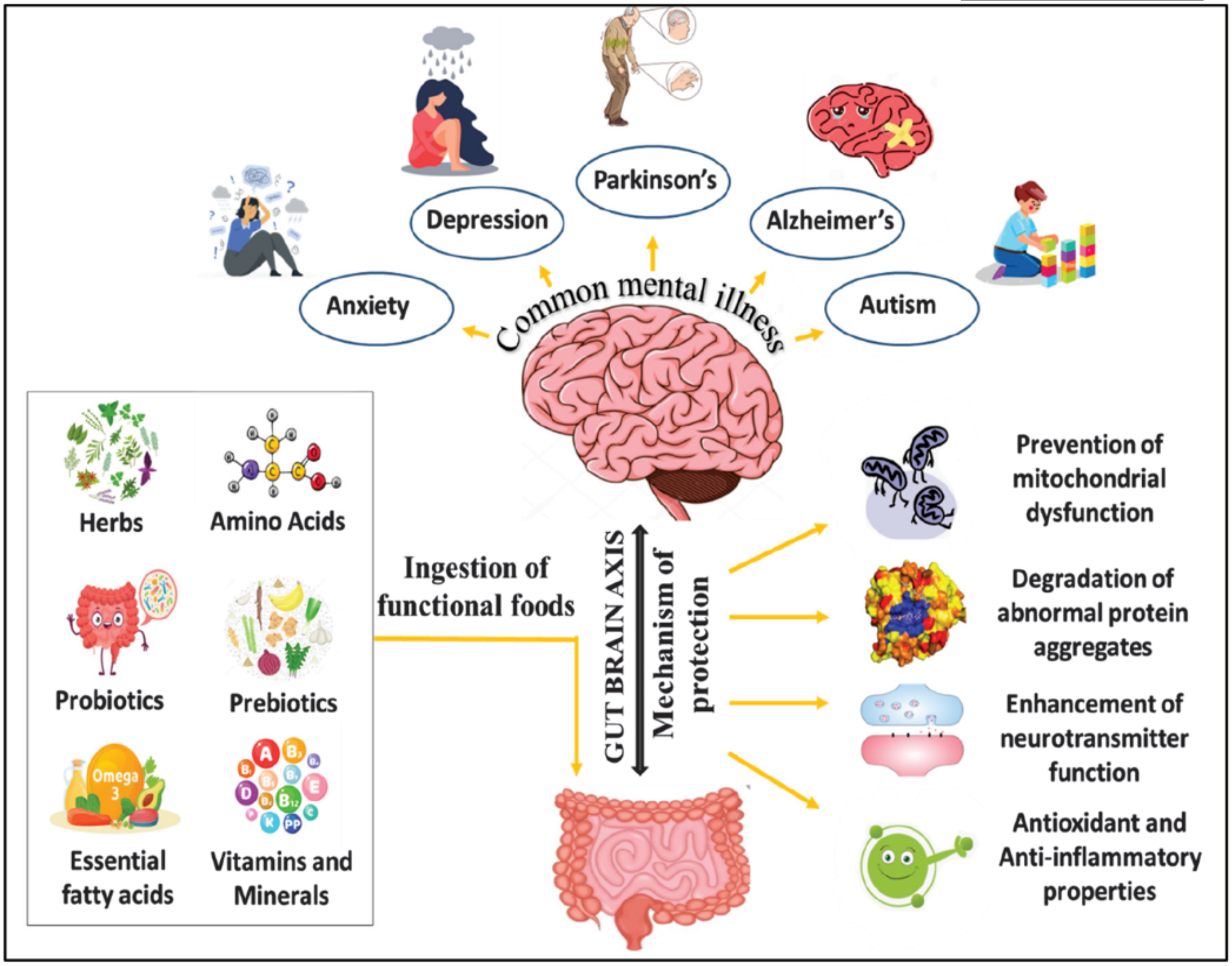
Graphical Abstract



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Abstract

Maintaining adequate mental health is critical for personal and social well-being. According to the latest UN statistical data, one billion people, including 14% of the world's adolescents are suffering from some form of mental illness. These illnesses progress inevitably leading to severe inability and death. An abundance of scientific evidence has demonstrated the relationship between mental health and nutrition, which has gained considerable interest in present-day consumers. Improper nutrition does not only contribute to low physical health but also affects mental well-being. Functional foods are enriched, fortified or augmented with specific nutrients and offer health benefits over and above their regular nutritional values. The ability of functional foods to affect the central nervous system (CNS) and its related functions and behaviours are presently reviewed by the scientific community for its potential applications in the treatment of mental illnesses. Emerging evidence demonstrates that these functional foods protect mental health positively via modulation of the gut-brain axis by preventing mitochondrial dysfunction, improving neurotransmitter production and function, degrading abnormal protein aggregates, and offering antioxidant and anti-inflammatory properties. Furthermore, preclinical and clinical trials have claimed the therapeutic efficacy of functional foods offering mental health protection. Despite the wide applications of these functional foods as health supplements, there is a limited understanding of the possible role of these as neuroprotective therapeutics. This review provides important insights into various functional foods with special emphasis on existing direct and indirect evidence of their therapeutic potential in offering neuroprotection in specific mental illness conditions.

Keywords: *Mental illness, Central nervous system, Functional foods, Neuroprotection, Mitochondrial dysfunction, Protein aggregates, Antioxidant, Anti-inflammatory*

1.0 Introduction

A societal ideal is to possess a sound mind and body. The World Health Organization (WHO) defines mental health as "a state of well-being, in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and can make a contribution to his or her community"[35]. The human brain consists of around 86 billion neurons, to create neural circuits to receive and transfer information[57]. Any disturbance in these neural communication networks can lead to the development of a variety of neurological and mental illnesses. Mental illnesses are disruptions in the state of mental health and disturbances of thoughts, experiences, and emotions which can cause functional impairment in humans (Ranna Parekh, 2018). All these mental illnesses eventually become worse, resulting in severe disability and even death. The most prevalent mental illnesses include anxiety, depression, autism spectrum disorder, bipolar disorder, Alzheimer's and Parkinson's, Obsessive Compulsive Disorder (OCD), and Post Traumatic Stress Disorder (PTSD). Anxiety disorders and depression are the most common type of psychiatric conditions[75]. Subclinical indications of depression and anxiety have an impact on the health and functioning of a significant section of the population even when no clinical symptoms exist[42]. The term "depression" is used to describe a variety of mental health issues marked by the lack of a positive affect (a loss of interest and enjoyment in commonplace things and events), a low mood, and a variety of accompanying emotional, cognitive, physical, and behavioural symptoms. People with anxiety disorder struggle to manage their worry and anxiety, which are frequently accompanied by restlessness, being easily tired, finding it difficult to concentrate, irritability, muscle tension, and having trouble sleeping (National Collaborating Centre for Mental Health & Health, 2011). Parkinson's and Alzheimer's are slowly progressive neurodegenerative conditions that have a significant impact on cognitive function[93]. Autism Spectrum Disorder (ASD) is a term used to describe a group of early-onset social communication deficits and repetitive sensory-motor behaviours with a strong genetic component and other causes[13]. Most of the mental illnesses begin before the age of 25, students, in particular, are at risk for depression, anxiety, drug use disorders, and mental health problems[78]. The discussion on the significance of mental health has particularly risen after the COVID-19 pandemic. People exhibit emotional instability, irritation, sleeplessness, sadness, and post-traumatic stress symptoms soon following the quarantine period. Long-term effects include anxiety, frustration, depression, post-traumatic stress symptoms, alcohol dependence, and behavioural changes such as avoiding crowded situations and washing hands diligently[10]. Social distancing and isolation have shown to have a synergistic negative effect on mental health.

To fulfil this expanding need due to the surge in mental illnesses, nutritional psychiatry research is now examining dietary therapies to prevent and cure mental diseases[62]. The links between diet and psychological health have received a lot of attention in recent years. Brain health is not just dependent on the body's general health status, and all measures that lead to good and maintained overall physical health will also be beneficial for overall brain wellbeing. Our understanding of the pathogenesis of chronic neurological illnesses has undergone a profound transformation. Historically, microorganisms were not thought to be main stakeholders in the cause or impact of neurological diseases, but bidirectional communications between the brain and the gut microbiome have lately emerged. This communication happens in both directions: the neural network governs gastrointestinal (GI) function through the gut nervous system (ENS), and the gut communicates with the CNS through sympathetic (prevertebral ganglia) and parasympathetic (vagus nerve) signaling[55]. The gut-brain axis (GBA) consists of bidirectional communication between the CNS and the ENS, linking the brain's emotional and cognitive centers with peripheral intestinal functions[12]. The human GI tract is a complex ecosystem that influences the production of neurotransmitters that constantly carry messages from the ENS to the CNS. Eating nutritious foods encourages the growth of "friendly" bacteria, which benefits neurotransmitter synthesis. Numerous factors influence the gut microbiota out of which diet is considered the most crucial factor causing an impact on the human gut microbiota. Hence, dietary interventions have the potential to modulate psychiatric symptoms associated with GBA dysfunction[76].

Specific neurotransmitters and networks between brain centers influence the signaling networks in the brain that are connected to mood and behaviour, such as depression, sleep and wakefulness, pain, and so on. Dietary components may also influence these networks by affecting the amounts and effects of the active neurotransmitters or by interfering with crucial receptors[9]. Memory and cognition are crucial for brain function; they rely on neural networks and other mechanisms that are currently poorly understood. Synaptic plasticity is a key idea in understanding how the brain works. There is proof that learning and novelty drive brain plasticity, and that food choices and aerobic activity make it stronger[48]. Energy supply is a prerequisite for cognition and memory; thus, both the health of the brain's circulatory system and the efficiency of its mitochondria will be crucial[21]. Synaptic plasticity, which is crucial for cognition and memory, will be affected by the intimidation of glucose and oxygen delivery to the brain and mitochondrial energy generation. The same holds for cells' capacity to handle the creation of unfolded or misfolded proteins and their elimination via proteasomes or autophagy. A growing body of research suggests that certain protein clumps that affect neuronal function are imported from remote sources. Chronic inflammation is generally harmful to the brain as it is to other sections of the body, hence numerous dietary elements with anti-inflammatory properties have been taken into consideration while creating neuroprotective diets. Different aspects of brain structure and function are strongly influenced by diet (Fig.1)[37].

Scientific evidence shows that consuming high saturated fatty meals over the long and short-term during adulthood results in a sensitive inflammatory phenotype in the hippocampus region of the brain via a surge in glucocorticoids, which creates vulnerabilities in learning and memory. Microglial activation is altered by imbalances in omega-3 and omega-6 polyunsaturated fatty acids (PUFA), which results in improperly constructed brain networks and activity, which in turn contributes to neuro-developmental issues. Reducing oxidative stress and inflammation, eating fruits and vegetables like grapes, cherries, berries, pomegranate and onions rich in polyphenols helps prevent and treat age-related cognitive impairment[5]. Collectively, these studies demonstrate the significance of dietary composition for long-term effects beyond metabolic effects and emphasize the possibility that dietary changes might help us maintain or perhaps improve our cognitive function as we age[81].

Functional foods are fortified, enriched, or augmented foods that give beneficial health effects in addition to providing vital nutrients when ingested in adequate amounts. There is no common agreement on what constitutes a functional food[88]. The idea was initially created in Japan in the 1980s when, in response to rising health care expenditures, the Ministry of Health and Welfare established a regulatory system to certify

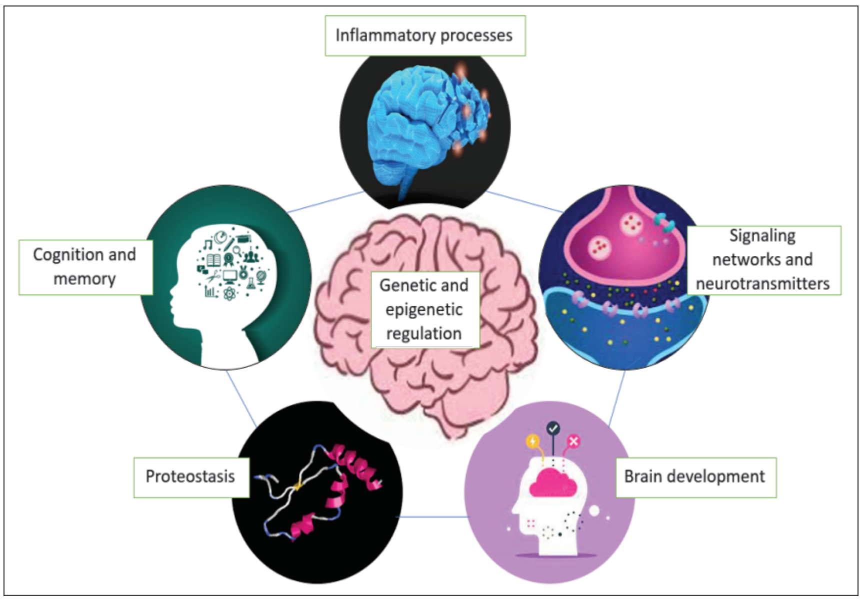

Figure 1: Various aspects of brain structure and function that may be influenced by diet

certain meals with established health advantages to improve the health of the country's elderly society[24]. The functional foods come from natural components and are thus not taken as pills or capsules, but rather as part of a balanced diet. They are said to improve immune function, keep against sickness, aid in the recovery from medical conditions, manage physical and mental ailments, and slow down the ageing process. Nutraceuticals and functional foods are frequently used interchangeably. Antioxidants, dietary supplements, fortified dairy products, citrus fruits, vitamins, minerals, herbal items, milk, and cereals are all examples of nutraceuticals[58]. The development of functional foods for improved mental health has been getting the spotlight lately and will be discussed in detail in this review.

2.0 Mental well-being and its Connection to a Healthy Diet

Keeping a healthy lifestyle contributes to both mental and physical well-being. Exercise, sleep, and consumption of a healthy diet are all beneficial to physical and mental health, including reduced risk of anxiety and increased psychological well-being. This healthy lifestyle may be especially important for the mental health of young adults[92]. One cannot emphasize how crucial it is to take care of one's mental well-being. Better diet quality is always linked to superior mental health, whereas poor diet quality is connected to declining psychological performance. A reduction in the quality of adolescents' diets over recent decades may be parallel to this possible increase in psychological disorders among adolescents[51]. A recent study indicated that although there is significant variation by population, adolescents rarely consume fruits and vegetables and regularly consume carbonated soft beverages[6].

Diet and its bioactive components have been identified by researchers as modifiable risk factors that may contribute to pathogenesis[45]. In recent years, it has become clear that nutrition and mental health conditions are linked. An improper diet carries a high risk of developing both physical and mental illnesses, including several malignancies, diabetes, and cardiovascular diseases. In terms of a healthy diet, research recommends that processed food intake should be kept to a minimum and that considerable amounts of nuts, whole grains, fruits, vegetables, seeds, and seafood should be consumed. The results of new clinical trials indicate that using dietary improvements as a strategy to prevent depression is possible. Several animal and human studies have also indicated that these mental illnesses may be modulated by diet, gut microbiota and by modifying inflammatory pathways[22].

Often called the "second brain," the GI tract has a close relationship with the brain, which explains the link between diet and emotions. Nutritional food consumption promotes the development of "good" bacteria (Probiotics), which in turn benefits the production of neurotransmitters. On the other hand, eating junk food frequently can cause inflammation, which lowers output. The brain receives these positive messages effectively when neurotransmitter production is strong, and the emotions reflect that. The link between diet and mental health has attracted a lot of attention in recent years. Epidemiological studies have shown that following healthy dietary patterns-consuming lots of fruits, vegetables, nuts, and legumes while consuming modest amounts of poultry, eggs, dairy products and occasionally red meat is linked to a lower risk of depression[18].

A study by[38] demonstrated the association between eating habits and depressive symptoms and perceived stress. Their study was clear enough to conclude the association between unhealthy food habits to increased depressive symptoms and perceived stress.

The practice of mindful eating is a factor that has just recently caught the attention of researchers, even though the idea of mindfulness is already being studied. Numerous research has looked at the advantages of mindfulness and meditation, but it has been necessary to investigate how these practices might be implemented into daily life and whether they have a substantial psychological impact when considered separately. After studies and experimentation, it was shown that mindful eating and mental health have a strong and beneficial association[72].

It has been seen that gut microbiota influence both GI and extra GI health. Probiotics are capable of restoring normal microbial balance, and therefore they have the potential in treating and preventing anxiety and depression[17]. An improvement in mental state, sleep quality, and gut microbiota under stressful circumstances was observed in healthy young adults in a randomised controlled trial with a 4-week trial of long-term use of Lactobacillus gasseri CP2305. This was accomplished by reducing the stress-induced decline of Bifidobacterium spp. and the stress-induced elevation of Streptococcus spp[52].

Current studies also indicate that we might have some control over our mental health through the foods we choose to eat, though more research is necessary for this area. But we must remember that eating is only one aspect of the far more complicated subject of mental health. Therefore, it is crucial for anyone who is exhibiting signs of depression or anxiety or has general worries about their mental health to collaborate with dependable healthcare professionals to create a customised treatment plan.

3.0 Functional Foods

If food has positive impacts on target bodily processes besides nutritional benefits in a way that is pertinent to health and well-being and/or the prevention of disease, then it can be said to be functional. When ingested at effective levels as a regular part of a mixed diet, functional foods can be defined as those enriched, complete, fortified, or enhanced foods that offer health advantages beyond the provision of necessary elements. A food must have a physiological effect on the body that is significant and goes beyond simple feeding for it to be deemed functional. Functional foods must, however, be consumed in the same way as regular foods - dietary supplements like vitamin pills or fish oil capsules are nutraceuticals, not functional foods.

Examples of functional foods include oily fish which contain high levels of omega-3 fatty acids and fruits, which may be rich in fibre and antioxidants, soy protein and oat bran fibre (Jones, 2002). Functional ingredients can be added to products that have had minimum processing, like orange juice that has been fortified with soluble fibre, or to foods that have undergone more extensive processing, like margarine that contain plant stanols[85].

For a food to be considered functional it must include:

1. Foods that have been added biologically active ingredients (for example, probiotics).
2. Supplementing traditional foods with derived food components (for example, prebiotics).
3. Common foods that naturally contain physiologically active compounds (for example, dietary fibre, dietary polyphenols, phytochemicals)[2].

3.1 Nutritional Demands of the Human Brain

It has been seen that the adult human brain represents only 2% of body weight but requires 20% of the body's resting energy needs[86]. The brain's nutritional demands are very complex and vary greatly with age. However, human physiology requires essential micro and macro nutrients for its proper functioning. Most of the human brain is made up of lipids, mostly in the form of phospholipids, with docosahexaenoic acid being the predominate omega-3 fatty acid and arachidonic acid being the predominate omega-6 fatty acid. Early-life DHA deficiency can impair cognitive function and negatively affect behavioural development[47]. The brain needs a steady flow of glucose from the bloodstream for its healthy activity. The total energy (45-60%) in a healthy diet should come from carbohydrates. The brain requires about 130 g of the 200 g of glucose that an adult of average weight needs each day (or roughly two-thirds of that total). However, a study also found that found dietary fibre, a carbohydrate nutrition factor, had a weak correlation with the frequency of depressed symptoms[46]. Consumption of specific amino acids such as tryptophan is reported to boost neurotransmitter (serotonin) production and uptake in the brain, with positive effects on mood, cognition, and hormone production[41].

Taurine, one of the most prevalent amino acids in the brain, has a variety of functions in the CNS[47]. Through a variety of mechanisms that enhance neuronal function, such as the modulation of inhibitory neurotransmission and, consequently, the promotion of an excitatory-inhibitory balance, the stimulation of antioxidant systems, and the stabilisation of mitochondria, these reported cytoprotective actions of taurine contribute to improvements in brain health in subjects with obesity and diabetes[77].

Consumption of vitamin B fortified foods is reported to alter cognitive performance, enhance memory during ageing, and uplift cerebral and cognitive functions in the geriatric population by lowering the levels of homocysteine. Supplementation of vitamin E (á-tocopherol, protects against oxidative stress-induced neuronal membrane damage. Furthermore, vitamin D is implicated in the prevention of neurodegenerative illnesses such as Parkinson's disease, Alzheimer's disease and stroke[67]. Fortification of foods with iron is also known to offer mental well-being. Iron helps with oxygenation, energy production, myelin synthesis and neurotransmitter synthesis in the cerebral parenchyma. Manganese, zinc, and copper lessen oxidative damage by participating in enzymatic mechanisms (Bourre, J.M, 2006). Calcium, potassium, and magnesium regulate sleep by ensuring that ion channels are functioning properly[45].

In addition, regular consumption of green leafy vegetables, nuts, berries and whole-grain cereals lowers cognitive deterioration[69]. The presence of functional ingredients viz., carotenoids, and lipophilic compounds in orange and red vegetables are known to improve cognitive performance[16]. Considering these factors, certain dietary habits have been studied and found to have a major impact on the brain, which include:

- Mediterranean diet: this includes plant-based foods and has been proven to lower the risk of dementia and mild cognitive impairment.
- DASH diet: This diet mainly made of fruits, whole grains and vegetables has been linked to a lowered risk of Alzheimer's disease or a slower loss in cognitive function.
- MIND Diet: This diet including fish, poultry, berries, nuts, olive oil and whole grain helps people who are most at risk maintain healthy brain function and prevents hypertension by combining Mediterranean and DASH diets.

The brain is the most influential organ in mental health, planning a diet with all the necessary ingredients will improve memory, mood, and focus and reduce the risk of certain cognitive disorders.

3.2 Functional Foods and Gut-Brain Axis (GBA)

The GBA refers to the 2-way communication that occurs between the brain and gut microbiome. The gut microbiota houses bacteria, viruses, protozoa, archaea, and fungi. It is well recognised that hormones, neurotransmitters, and immune components secreted from the gut communicate with the brain either directly or through autonomic neurons[12]. As we know that this intricate communication system between the GIT, the micro-organisms which inhabit it and the peripheral and CNS is termed the GBA and constantly transmits and interprets information from the periphery to the brain. The vagus nerve, the ENS, the hypothalamic-pituitary-adrenal (HPA) axis, and immunological (cytokine) pathways all play a role in this communication, though the precise mechanisms are still being studied. Significantly, the setting of psychiatric diseases frequently alters these pathways. A study that identified the altered stress response in germ-free mice made the case for the existence of the GBA. Along similar lines, germ-free mice not only confirmed the presence of GBA but also suggested that it encompasses immunological, endocrine, and neurological pathways systems[11].

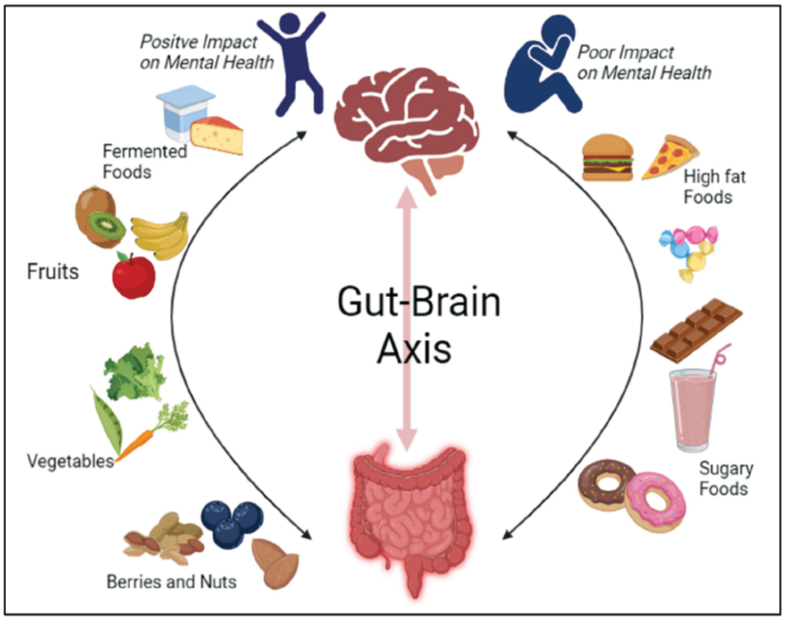

Figure 2: The Gut-Brain Axis (GBA) and the impact of Diet on Mental Health

In response to food consumption, the brain gets neuronal and endocrine inputs from the gut, which are combined with signals from other organs to coordinate physiological responses.

Microbiology and neuroscience have been intertwined more and more in recent decades. Although the idea of a microbiota-GBA is still relatively new, it is widely recognised that the host's resident microbiota can have a significant impact on behaviour. The ability of the microbiota and host to work together to access gut-brain signaling pathways and modify host brain and behaviour depends on bidirectional communication along the gut-brain axis[20].

Probiotics are live organisms, which when administered in adequate amounts, offer health benefits to the host. In 1910, it was first suggested that depression and anxiety could be treated using probiotics[62]. A study has shown that there are three key methods by which probiotics influence the gut microbiota, including indirect stimulatory or inhibitory impact, direct stimulatory or inhibitory impact, and trophic interactions[2]. In trophic interactions, numerous probiotics can quickly break down simple carbohydrates to create metabolites such as lactic acid, acetic acid, or propionic acid. While in direct stimulatory impact, due to the probiotics' inhibitory effects, the existence of some resident members of the gut communities is changed or inhibited. In the last one, indirect stimulatory impact includes modulating the gut microbiota because of the host's responsiveness to probiotic administration. It has been found that prebiotics, probiotics, synbiotics (combinations of pre-and probiotics), postbiotics (bacterial fermentation products such as short chain fatty acids (SCFAs), and faecal microbiota transplantation) are some methods for changing the GBA. All of these methods could be viewed as potential psychobiotics because they are said to have the ability to alter the microbiota, which is thought to benefit mental health[68].

The current increase in the consumption of functional foods demonstrates our ability to influence the human microbiota through dietary modifications, which have the potential to directly affect the host's physiology and lengthen their life span. Fig.2 shows the impact of the type of food on mental health, suggesting that functional foods impact positively. This will aid in the development of novel medications that can treat the issue and consequences caused by a gut imbalance with little to no adverse effects. This will aid in the development of novel medications that can treat the issue and consequences caused by a gut imbalance with little to no adverse effects[2].

3.3 Therapeutic Mechanism of Functional Foods in The Management of Specific Mental Illness

Functional foods have been reported to be beneficial in the treatment and prevention of specific mental illnesses. This can be attributed to their inherent antioxidant and anti-inflammatory properties[54]. They are also capable of degrading abnormal protein aggregates and halting mitochondrial dysfunction. Studies have shown the effectiveness of functional foods in improving neurotransmitter activity (acetylcholine and monoamine)[35].

3.3.1 Anxiety and Depression

An increase in inflammation due to stress, high levels of oxidative stress markers, abnormal gut microbiota, hypothalamic-Pituitary-Adrenal Axis dysfunction, mitochondrial dysfunction and irregulated tryptophan–kynurenine metabolism are common observations in people suffering from depression[65].

Studies reviewed by[89] indicated that ingestion of daily doses of probiotic supplements results in an improvement in mood, anxiety and other depressive symptoms. The most significant positive effects were observed with anxiety.

It has been observed that specific strains of probiotic organisms, Lactobacillus and Bifidobacterium secrete gamma-aminobutyric acid (GABA), a neurotransmitter that regulates psychological processes about anxiety and depression[26,27,44]. GABA produced in the gut may have a direct effect on the GBA[27]. It is known that Escherichia, Bacillus, and Saccharomyces can produce norepinephrine while Candida, Streptococcus, Escherichia, and Enterococcus can produce serotonin and GABA[43-44]. Recent studies indicate that Bacillus and Serratia have the potential to produce dopamine[25].

It has been hypothesized that deficiencies or imbalances in monoamine neurotransmitters (serotonin, dopamine and norepinephrine) are a major reason for major depressive disorders[60].

Manipulation of gut microbiota with specific prebiotics has shown a modulation in anxiety and behaviour[21]. It has been studied that milk oligosaccharides support normal gut microbiota and behavioural responses[84]. Mice models with anxiety when supplemented with prebiotics (3'Sialyllactose and 6'Sialyllactose) showed an improvement in their behaviour. The anxiolytic action of prebiotics may attribute to their anti-inflammatory properties. The manipulated gut microbiota showed an elevation of short-chain fatty acid levels and a reduction in plasma corticosterone levels hence regulating the HPA axis. This led to an improvement in depressive symptoms[83]. The probiotic strain, E. faceium CRF 3003 was able to produce 240 mg/L of GABA in the simulated GI conditions[30] and supplementation of this strain for 28 days to adult male mice with offered psychotropic effect by reducing the levels of oxidative markers and enhancing the activities of antioxidant enzymes[27]. The same strain was also successful in protecting the mice brain against the conditions of acrylamide induced neurotoxicity[29].

Fermented foods have been known to reduce inflammation in GI illness via the reduction in inflammatory cytokines and production of SCFA[60]. Fermented foods also have the potential to manipulate gut microbiota composition. Fermented foods can be modulated to produce GABA[30]. Hence, the potential of fermented foods as a therapeutic against anxiety and depression can be further evaluated[3].

Fermentation of nutrient-rich foods results in the production of novel bioactive compounds which have anti-inflammatory and immunity-enhancing properties. These indicate therapeutic ability against mood disorders[80].

Polyphenols (flavonoids and non-flavonoids) are known neuroprotective phytochemicals[70]. Flavonoids are anti-inflammatory and are capable of scavenging reactive oxygen species (ROS) and reactive nitrogen species (RNS). Phytochemicals protect mitochondria against toxicity by the accumulation of pathogenic amyloid beta and presynaptic protein α-synuclein. They can regulate mitochondrial membrane permeabilization. Phytochemicals function as neurotrophic factors which maintain the function and survival of neurons and hence have antidepressant activity[66].

Omega-3 fatty acid molecules enhance neurogenesis and inhibit the reuptake of monoamines during transmission and increase the fluidity in the membrane of cells. They can reduce inflammation[36].

S-adenosyl methionine participates in the biotransformation of neurotransmitters[14]. N-acetyl cysteine protects from mitochondrial toxicity and modulates the glutamate pathway. L-tryptophan is required to be converted into serotonin. These amino acids have been proven to have antidepressant properties.

Vitamin D is a neurosteroid compound which regulated neuron excitability by acting as a ligand for receptors in the hypothalamus, substania nigra and prefrontal cortex regions of the brain and by modifying gene expression[64].

3.3.2 Autism spectrum disorder (ASD)

Children diagnosed with ASD have a medical history of GI abnormalities. It has been reported that GI symptoms have a strong correlation with the severity of ASD. The various abnormalities include malabsorption, abnormal intestinal permeability, maldigestion and microbial overgrowth (fungal, bacterial, and viral). These abnormalities lead to symptoms like diarrhoea, constipation, gas, belching, probing and visibly undigested foods[50]. There have also been metabolic abnormalities such as methylation, oxidative stress, irregular concentration of plasma amino acids, abnormal sulphur metabolism, reduced concentrations of mammalian microbial co-metabolites and highly active nicotinic metabolism[87]. The gut microbiota plays an essential role in homeostasis[28]. The microbiota composition stabilizes between 6 to 36 months which is the window of time for synaptic formation and myelination. Throughout the course of life, the gut microbiota influences brain functions and the immune system by the secretion of protective active metabolites[1]. The normal microbiota consists of Bacteroidetes and Firmicutes phyla (70–90% of the total population), followed by Actinobacteria, Proteobacteria and Verrucomicrobia. It was observed that in autistic children, the population of Bifidobacterium and Enterococcus were reduced while the population of

Lactobacillus and Bacteroides were increased[21]. Potentially toxic Clostridium species were abundant. Recent studies indicate that the production of neurotoxins by Clostridium spp. contribute to the development of autistic symptoms[79]. Based on these findings, probiotics were studied as a potential therapeutic for autistic patients. It has been experimentally studied and reported that mice with autism spectrum disorder when treated with probiotic microbes (specified concentrations of Lactobacillus, Bifidobacteria and Streptococcus thermophilus) had improved behaviour and regulated neuron excitability[94].

While there is no confirmed mechanism for the role of probiotics in their therapeutic effect, there are multiple hypothesises. One of them is that probiotic supplements help restore the GI microbiota to its normal concentrations. It has been shown that probiotics can prevent the colonization of the toxic Candida species in the gut of autistic children. The stool samples of these children were analysed, and a reduction of the Clostridium species was reported. Another proposed mechanism is that the probiotic supplements act via the gut-brain axis to exert its therapeutic effect. Serotonin is known to be influenced by gut microbiota. Probiotics influence the production of numerous neuroactive compounds like serotonin and GABA[74].

Prebiotics are defined as non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and activity of one or a limited number of bacteria in the gut (probiotics), and thus provide health benefits. Fructo-oligosaccharides and galacto-oligosaccharides are known examples of prebiotics[23]. As prebiotics stimulate the growth of probiotics, it was hypothesised as a potential treatment. However, the studies conducted by[49] did not show a significant impact of the prebiotic treatment on GI symptoms and autistic behavioural symptoms. It was observed that a combined approach of prebiotics and exclusion diet (gluten and casein-free diet) led to improvement in antisocial behaviour. It was determined that further experimental studies are required to conclude.

Curcumin, a bioactive compound found in turmeric, has the potential to be therapeutic for autistic children as it has shown promise in rats induced with autism[63]. It improved symptoms by scavenging ROS and RNS, mitochondrial dysfunction, tumour necrosis factor-alpha (TNF-α) and matrix metallopeptidase 9 (MMP-9)[7]. Quercetin, resveratrol and sulforaphane have inherent antioxidant properties via which they exert a protective action on mitochondria. Phytochemicals from green tea and black pepper show neuroprotective effects. Various combinations of bioactive substances have been used to test for their effectiveness against autistic symptoms. Folinic acid (leucovorin), and methylcobalamin resulted in an improvement in the metabolic imbalance in autistic children. Methylcobalamin, folinic acid and sapropterin combination show potential therapeutic effects by affecting the folate, methylation and glutathione pathways hence showing an improvement in autistic symptoms. Further experimental studies are required for further understanding[19].

3.3.3 Parkinson’s and alzheimer’s disease

Neuro-inflammation is a process linked to the onset of several neurodegenerative disorders, and it plays an important role in the pathogenesis and progression of Alzheimer’s disease[16].

Parkinson’s disease is characterized by the accumulation of insoluble á-synuclein aggregates in the brain. The toxic, soluble, intermediate á-synuclein oligomers play a role in the pathogenesis of Parkinson’s disease by generating reactive oxygen species, promoting irregular calcium signaling, and causing mitochondrial dysfunction ultimately leading to neuronal cell death. The mechanisms of action by α-synuclein were experimentally studied by[15].

Quercetin has been proven to show neuroprotective properties which counter neuro-degradative effects in Alzheimer’s disease and Parkinson’s disease[16]. Consumption of sulforaphane, a bioactive compound found majorly in broccoli, impedes the NF-jB signaling cascade and pro-inflammatory cytokines which attribute to neuro-inflammation[82]. Mangiferin, a bioactive xanthone found in higher plants, has reactive oxygen species (ROS) scavenging ability and restorative ability of the mitochondrial membrane potential which attributes to its studied neuroprotective potential[34]. Lycopene, a bioactive carotenoid found in plants, possesses neuroprotective properties in the reduction of oxidative stress, inhibition of early apoptotic pathways in neurons and preventing depletion of dopamine, a neurotransmitter[40]. A known seafood-derived carotenoid astaxanthin has been documented to have mitochondrial protective functions, anti-inflammatory and antioxidant potential indicating its neuroprotective properties. Flavonoids and their metabolic products have shown neurological-modulating actions and have interacted with the neuronal-glial signaling pathway, which is essential in the survival and proper functioning of neurons. Mutations in mitochondrial DNA in dopaminergic neurons observed in patients with Parkinson’s Disease have been hypothesized as the mechanism that causes mitochondrial dysfunction. A known plant secondary metabolite, polyphenols can pass the blood-brain barrier and protect dopaminergic neurons and scavenges free radicals[64]. It is observed to retard the formation of beta-amyloid fibril formation from amyloid beta peptides while simultaneously destroying existing beta-amyloid fibrils[35].

Tryptophan is a known essential amino acid, i.e., it is not synthesized in the human body and must be obtained from the diet (primarily found in dairy products, meat, oats, etc). It occurs in D- and L-isomeric forms with the latter present in biological systems of higher organisms. Tryptophan is the precursor to important neuroactive molecules (E.g., serotonin, melatonin, niacin, tryptamine, quinolinic acid, kynurenic acid, nicotinamide adenine dinucleotide) which play a role in neuroimmune activity and mitochondrial function. In the kynurenine pathway, 3-hydroxy anthranilic acid is produced from activated 3-hydroxykynurenine. 3-hydroxy anthranilic acid performs a neuroprotective role during inflammation[91].

N-3 Poly Unsaturated Fatty Acids are essential lipids for human beings. They include á-linolenic acid (ALA), stearidonic acid (SDA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA). DPA, DHA and EPA are salient structural components in the phospholipid bilayers of the cell membrane. PUFAs have neuroprotective and antioxidant properties. They are precursors for endogenous cannabinoids which modulate dopaminergic activity in the basal ganglia, a part of the human brain[59]. N-3 PUFAs released within cells can encourage mechanisms of action against Parkinson's disease. The observed stimulation of brain-derived neurotrophic factor and glial cell-derived neurotrophic factor production by these n-3 PUFAs is being further studied. The PUFAs have a regulatory effect on genes associated with oxidative stress resulting in decreased levels of oxidized proteins, DNA damage and reactive oxygen species. The anti-inflammatory properties of n-3 PUFAs can be attributed to the observed hindrance of n-s PUFAs on arachidonic acid metabolism through enzymatic competition for cyclooxygenases leading to less production of potent proinflammatory eicosanoids such as 3-series prostaglandins[8].

Fat-soluble vitamin D was hypothesized to exert its action against Alzheimer's disease. Studies have reported that patients with Alzheimer's disease exhibit calcium dysregulation. Vitamin D stabilizes intra-neural calcium homeostasis by the regulation of the L-type voltage sensitive $Ca2+$ channel. Aβ plaques cause activation of these low-voltage calcium channels (LVCC)[4]. Alzheimer's disease is delineated by the accumulation of amyloid-â peptide (Aβ), which has neurotoxic properties. It is derived from amyloid precursor protein (APP)[33]. In-vitro studies have shown vitamin D reduces oxidative stress via activation of macrophages leading to Aâ plaque clearance[56].

4.0 Conclusions

There is no denying the benefits of a good diet for the brain, and it is interesting to consider how each dietary component affects how the brain functions and maintains one's mental health. These days mental illness is becoming a significant problem, and its treatment can be a challenging task. Functional foods being enhanced with dietary components, provide an added advantage in treating mental health disorders.

Further developments in creating functional food products that can support optimum mental health could benefit from the rapid growth of food technology industries.

5.0 References

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