Chapter 6
Micronutrients and Depression: Is There Any Association?

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Abstract Scientific research have made significant advancement to the comprehension of nutritional status on depression. Nutrition can be a key contributor to the onset, severity, and progression of a depressive illness. Although no definite causal relationship is established, the association between nutritional deficiencies or excess of certain nutrients and depression has been recognised in some intervention studies that demonstrated the pathophysiological mechanisms of various dietary elements contributing to depression. Nutritional advice should be incorporated as an integral part of the management of a person with depression.

Keywords Nutrition · Depression · Dietary element · Dietary pattern

6.1 Nutrition and its Association with Depression

For more than a decade, scientific researches have made significant advancement to the comprehension of nutritional status on mental health, in particular for depression. The nascent field of nutritional psychiatry focuses on the use of essential nutrients and the effects of both individual nutrients and dietary patterns in the prevention and treatment of certain mental health (Logan and Jacka 2014; Jacka 2017). It is considered in general an alternative approach rather than being widely accepted as an integral part for the management of a person's mental well-being. Nutrition can be a key contributor to the commencement, seriousness, and progression of a depressive illness. Depression, being a common mental disorder with a major source of global disability, is characterised by sadness, amotivation, insomnia, hopelessness, and suicidal ideation in severe cases (Friedrich 2017). Even in subclinical depression, the condition can affect the mental well-being and functional capacity of a substantial community (Johnson et al. 1992). Treatment commonly involves pharmacotherapy and psychotherapy as well as treating any underlying diseases or

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causes that may contribute to depression, for example, hormonal imbalances due to dysfunction of thyroid or adrenal glands.

Although no definite causal relationship is established, the association between nutritional deficiencies or excess of certain nutrients and depression has been recognised in some intervention studies. Nevertheless, inconsistent findings from most researches were due to variable confounding factors, such as blinding issues, recall bias, type of intervention (for example, increase in vegetable consumption in comparison to decrease in fatty food), heterogeneity or size of study populations, variation in food nutritional content or multiple environmental stress (Thomson and Robinson 1980; Opie et al. 2015). Furthermore, the pathophysiology and cause-and-effect relationship at present are not clearly elucidated. Reverse causality is a possibility in some studies when depression itself posed as a risk factor for poor eating or dietary habits as a lack of appetite for food is a common symptom in depressed persons (Le Port et al. 2012). During the Coronavirus disease 2019 or COVID-19 outbreak and with the imposed restriction in movement and lockdown, certain nutritional deficiencies or over-indulgence in unhealthy food consumption could result from dysfunctional eating behaviour or emotional eating due to the negative psychological stress or depressive reaction to the pandemic (Cecchetto et al. 2021). In fact, lack of food intake such as the Mediterranean diet or overconsumption of ultra-processed food may result in lower immunity response due to the inflammatory and oxidative damage and increase vulnerability to COVID-19 with subsequent emotional sequelae (Evers et al. 2018; Di Renzo et al. 2020).

Studies on pathophysiology have demonstrated dietary elements of various sources can alter the mechanisms that result in inflammatory reaction contributing to depression. These include sympathetic overactivity with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, production of pro-inflammatory cytokines, activation of transcription factor nuclear factor kappa B (NF-κB), and oxidative stress. Interference by pro-inflammatory cytokines may disrupt the metabolism of neurotransmitters especially serotonin, alter messenger RNA, reduce levels of plasma tryptophan, and inhibit the brain derived neurotrophic factor (BDNF) from being expressed (Hayley et al. 2005; Anisman 2009). Inflammatory process can be induced by diets especially rich in refined sugars, saturated, and trans fats. During the metabolism of these foods, the production of oxidants such as hydrogen peroxide and superoxide radicals may initiate the NF-κB pathway and promote further inflammatory reaction (Calder et al. 2009).

Subsyndromal depression similarly in response to stress can further stimulate the sympathetic nervous system, induce oxidative stress, activate the NF-κB pathway, and increase production of pro-inflammatory cytokines (Pace et al. 2006). The food intake pattern that precedes the onset of depression may be similar to that in those who are depressed, for example, dieting, skipping meals, or making poor food choices with a dominant desire for sweet foods (Sathyanarayana Rao et al. 2008). By contrast, untreated chronic depression can induce directly long-standing modulation in the production of pro-inflammatory cytokines or indirectly the NF-κB pathway via oxidative stress (Steptoe et al. 2007).

6.2 Pathophysiological Mechanisms of Dietary Elements and Contribution to Depression

6.2.1 Serotonin

Depletion of serotonin or 5-hydroxytryptamine (5-HT) is a well-studied molecular mechanism for the etiopathogenesis of depression. Serotonin, a monoamine neurotransmitter produced in the brain, is involved significantly in mood amelioration, feeling of fullness after a meal or satiety, and sleep control. The pharmacological target of most antidepressant agents is to augment the brain's serotonin concentration (Willner et al. 2013). Although it is richly found in foods such as nuts (for example, walnuts), leafy green vegetables (for example, kale and spinach), fatty fish (for example, tuna and mackerel), and cheese, 5-HT is not readily available to the brain because of the presence of blood–brain barrier. The precursor for 5-HT, i.e. tryptophan, however, can easily penetrate the blood–brain barrier and then catalysed by tryptophan hydroxylase with coenzyme pyridoxal phosphate (derived from vitamin B6) to 5-HT (Dakshinamurti et al. 2003; Shabbir et al. 2013). Diet rich in vitamin B6 (found in fish, beef liver, potatoes) and tryptophan (present in plant-based sources which include pumpkin seeds, broccoli, peas, soybeans, and turkey) is therefore fundamental for serotonergic neurotransmission in patients with depression. For the biosynthesis of serotonin, tetrahydrobiopterin (BH4) is an essential cofactor. Tetrahydrobiopterin can be attained from methyl folate supplementation. It is utilised by phenylalanine hydroxylase in the conversion of phenylalanine into tyrosine and its subsequent conversion by tyrosine hydroxylase to dopamine and by tryptophan hydrolyse to generate serotonin. Tetrahydrobiopterin can be inactivated irreversibly and potently by oxidative stress induced by reactive oxygen species (ROS) produced from the inflammatory process. The consequent inactivation of the cofactor may further reduce the serotonin levels (Swardfager et al. 2016).

6.2.2 Polyunsaturated Fatty Acids

Omega-6 (n-6) polyunsaturated fatty acids (PUFAs) with its precursor linoleic acid (LA) are abundant in most plant seeds (for example, sunflower, soybean, and corn) and relatively low in coconut and palm. Linoleic acid is converted to arachidonic acid (AA) in the body. Fatty acids present in the phospholipids of cell membranes of animals that are grain-fed contain chiefly AA (Simopoulos 2016). While positive associations between LA and risk of severe depression in men have been generated (Wolfe et al. 2009), the findings were not consistent. Omega-3 (n-3) PUFAs with its precursor alpha-linolenic acid (ALA) is abundant in leafy green vegetables, walnuts, chia, and flax seeds. Alpha-linolenic acid is metabolised to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are present richly in the oils of fish, particularly fatty fish like salmons, sardines, and mackerels. In a longitudinal study,

the intake of n-3 PUFAs from fish among women who consumed at least 2 times per week had a 25 percent reduction of risk for depression compared to those who had fish less than 2 times per week (Smith et al. 2014). In fact, deficiency of dietary n-3 fatty acids concentration may modulate the fluidity and composition of the brain's phospholipid bilayer cell membranes causing altered structural and functional impairment to the embedded proteins especially those that are specifically involved in serotonin neurotransmission (Chalon 2006). The conclusion from most meta-analyses is that EPA supplements at higher doses may confer significant beneficial effects on persons with depression (Martins et al. 2012; Hallahan et al. 2016; Mocking et al. 2016). Eicosapentaenoic acid showed efficacy similar to that of the antidepressants (Turner et al. 2008; Martins et al. 2012). At a dose of 1000 mg per day, EPA had equivalent therapeutic effects to fluoxetine at 20 mg daily (Jazayeri et al. 2008).

Omega-3 and n-6 PUFAs generally have opposite effects on inflammatory modulation. Evidence from studies demonstrates the anti-inflammatory and antioxidant properties of n-3 PUFAs (Giacobbe et al. 2020), while omega-6 PUFAs act as pro-inflammatory modulators. Prostaglandins and leukotrienes, both mediators at the site of inflammation, are synthesised from the n-6 PUFAs arachidonic acid. As the brain grows and develops, it requires an n-6:n-3 PUFAs ratio of close to 1:1. Thus for proper human nutrition, the n-6:n-3 PUFAs ratio target should be between 2:1 and 1:1 (Massiera et al. 2010). However, in some countries with high consumption of Western diet, the deficiency of n-3 PUFAs has given rise to a higher n-6:n-3 PUFAs ratio from approximately 1:1 to 10:1, and some reaching up to 20–25:1 or higher (Simopoulos 2002). This high ratio is generally considered to have adverse effects on a person's mental health and in particular its higher correlation with depression due to the induced neuroinflammation (Simopoulos 2008; Jacka et al. 2010).

Depression and suicide risk have been implicated in n-3 PUFAs biosynthetic pathway involving DNA methylation of certain genes. DNA methylation is an epigenetic modulation that adds a methyl group to the DNA molecule (Moore et al. 2013). DHA, the final n-3 PUFAs product is synthesised endogenously in humans from ALA, involving the sequential enzymatic reactions of desaturation and elongation pathway catalysed by fatty acid desaturase 2 (Fads2) gene product, fatty acid desaturase 1 (Fads1) gene product and by the elongation of very long-chain fatty acids proteins (Elovl5 and Elovl2) gene products. Suicide attempters with major depression were correlated remarkedly with DNA methylation in the Elovl5 gene regulatory regions (Haghighi et al. 2015). EPA levels were detected low in washed red blood cells in suicide attempt cases compared to depressed non-attempters (Huan et al. 2004). DHA levels are found to be very low as well in suicide completers (Lewis et al. 2011). A prospective study determined that low DHA levels in depressed persons predicted risk of suicide attempt within two years (Sublette et al. 2006). Nevertheless, intervention trials with better methodology to ascertain causal direction are required for these studies.

6.2.3 Monosaturated Fatty Acids

Oleic acid accounts for approximately 72 percent of olive oil (Waterman and Lockwood 2007). This form of monounsaturated fats tends to be negatively correlated with depressive symptoms among women (Hamazaki et al. 2012). The Mediterranean diet with the commonly added fat of extra virgin olive oil, in particular, contains abundant biophenol tyrosol that has the capacity to repair the intracellular defences of antioxidants (Di Benedetto et al. 2007), found decreased among depressive patients.

6.2.4 Saturated Fatty Acids

Existing evidence suggests that the TLR4 receptors in the hypothalamic microglial cells are activated by saturated fatty acids, causing the cells to promptly change their structural and function as a phagocyte and correspondingly enhance their cytotoxic reactions with the secretion of nitric oxide, proteases, and cytokines (Kreutzberg 1996; Valdearcos et al. 2014).

Thus, food high in saturated fats, i.e. palmitic acid, lauric acid, and stearic acid, may promote neuroinflammation by stimulating astrocytes to secrete pro-inflammatory cytokines such as IL-1β, IL-6, and TNFα (Gupta et al. 2012). These cytokines may also induce the microglial expression of indolamine-2,3-dioxygenase, the heme-containing enzyme that catalyses tryptophan to kynurenine (Wichers and Maes 2004; Dantzer et al. 2008). Due to this alternative cascade, less tryptophan will be available for its conversion to 5-hydroxytryptophan (precursor for serotonin) and lower level of serotonin may then lead to depression. As kynurenine metabolism increased, more quinolinic acid is being produced in excessive concentration. Quinolinic acid is a pro-inflammatory mediator as well as a strong agonist on the N-methyl-D-aspartate (NMDA) receptor, which is correlated with depression (Müller and Schwarz 2007).

Palmitic acid specifically has been correlated positively with symptoms of depression (Tsuboi et al. 2013). When compared with controls, pathological findings from the amygdala of patients with major depressive disorder revealed a higher 6.5 percent of palmitic acid and a lower 6.2 percent of oleic acid (Hamazaki et al. 2012). Thus, a dietary change to the levels of certain saturated fats may be implicated to be partially responsible for the brain dysfunction in depression.

6.2.5 Trans Fatty Acids

The association between the consumption of trans fatty acids and inflammatory process is consistently found in controlled trials and observational studies

(Mozaffarian et al. 2009). Trans fatty acids are a form of unsaturated fatty acids produced when liquid vegetable oil is hydrogenated into solid oil at room temperature (Teegala et al. 2009). This partially hydrogenated oil is commonly found in baked products (for example, cakes and cookies), margarine, and fried foods. The Food and Drug Administration (FDA) in 2015 issued that trans fats are unsafe for use in food and subsequently establish a time period over three years for total elimination of these fats from all processed foods (Ginter and Simko 2016). A prospective cohort study in Spain showed a potentially harmful relation between intake of dietary trans fats from natural foods (mostly whole-fat milk and cheese) and risk of depression (Sánchez-Villegas et al. 2011). In another cohort study, the consumption of trans fats (majority from baked goods and margarines) had positive correlation with negative affect (which included an item of 'upset' using the Positive and Negative Affect Schedule or PANAS scale) (Ford et al. 2016).

6.2.6 Refined Sugars

Refined sugars can cause impaired insulin resistance and rapidly increase blood glucose concentrations (Giugliano et al. 2006). Consequently, the postprandial hyperglycaemia may increase release of free radicals as well as production of pro-inflammatory cytokines (Esposito et al. 2002). Also, excessive intake of additional fructose present in high concentration in sugar-sweetened beverages can potentially cause chronic dysregulation of the HPA axis (Harrell et al. 2015). The dysfunctional axis may be partially responsible for the emergence of obesity-induced heightened low-grade inflammation (McInnis et al. 2014). Danqing et al. (2019) demonstrated that study recruits who consumed the comparable 2 cups of cola per day may be at higher risk of depression by 5 percent and those who drank the comparable 3 cans of cola per day may be at estimated 25 percent increased risk of depression.

6.2.7 Gut Microbiome

Emerging evidence shows that the human gut microbiome is strongly associated with depression via the microbiome–gut–brain axis that emphasises the bidirectional relationship and interaction between the gut microflora and brain (DellaGioia and Hannestad 2010; Forsythe et al. 2010; Critchfield et al. 2011; Grenham et al. 2011; Messaoudi et al. 2011; Mayer et al. 2014). Gut microbiome or intestinal microflora promote gastrointestinal digestion and absorption of nutrients, regulate immunological defences, and maintain the intestinal structural integrity or gut barrier function (Clemente et al. 2012). The adult gut microbiota is predominantly members of the Bacteroidetes and Firmicutes phyla that accounts for approximately 90 percent of the adult microbiota (Tremaroli and Backhed 2012). As the brain function is influenced

by the composition and metabolic activity of the gut microbiota particularly from the humoral and neuronal mechanisms via the vagus nerve, the psychological stress from depression may reciprocally further disrupt the gut microbiota (Dash et al. 2015). These mechanisms through the vagal stimulation may result in inflammation, dysregulation of the HPA axis, or disruption of the neurotransmitter signalling with profound effect on the central and peripheral serotonergic system (O'Mahony et al. 2015; Yano et al. 2015a, 2015b). In fact, persons with depression have demonstrated alteration or dysbiosis in the composition of gut microbiome, commonly resulted from the decrease in richness or numbers and diversity of the microbiota (Kelly et al. 2016; Zheng et al. 2016a, b; Grochowska et al. 2018).

Alteration in the gut microbiome composition may also trigger the production of lipopolysaccharides (LPS), endotoxins that occur in the outer membrane of Gram-negative enterobacteria. LPS potently activate the inflammatory responses and alter neuronal activity in the limbic system (a region in the medial temporal lobe responsible for mood regulation) (Haba et al. 2012), as well as activate the afferent vagus nerve (de Lartigue et al. 2012). In patients with chronic depression, serum levels of IgA and IgM mediated immune response mounted against the Gram-negative enterobacteria-derived LPS are increased. This systemic immunological response is due to bacterial translocation from impaired intestinal permeability with consequential increase in the release of pro-inflammatory cytokines (Maes et al. 2012).

Although diet can highly influence the gut microflora, there is insufficient data to identify the depression 'gut microbiota profile', due to the different methodology administered to study the intestinal microbiome composition and variation in each person's gut microbiota (The Human Microbiome Project Consortium 2012). In depressed persons, there is a common observation of an increase in potentially harmful bacteria that induces inflammatory reaction, for example, Proteobacteria (which are present relatively less in non-depressed persons), and a reduction in commensal bacteria (which occur generally more substantial in non-depressed persons) (Naseribafrouei et al. 2014; Jiang et al. 2015; Aizawa et al. 2016; Zheng et al. 2016a, b; Valles-Colomer et al. 2019). Studies on persons with depression showed that modification of diet can increase the numbers of Enterobacteriaceae family and Alistipes spp. that cause a reduction in the availability of serotonin (Naseribafrouei et al. 2014; Jiang et al. 2015). Mediterranean dietary pattern when adhered to reduces the levels of inflammatory bacteria (for example, Escherichia coli) and increases commensal bacteria (for example, Bifidobacteria, Clostridiumcluster XVIa, and Faecalibacterium prausnitzii) (Gow and Yadav 2017; Gutiérrez-Díaz et al. 2017). The consumption of such diet also increases microbial metabolites that include the faecal SCFAs (short-chain fatty acids) (Mitsou et al. 2017), phenolic metabolites, benzoic acid, and 3-hydroxyphenylacetic acid (Gutiérrez-Díaz et al. 2017). Short-chain fatty acids are major metabolites that function as substrates or signalling molecules. In particular, butyrate decreases gut inflammation (Singh et al. 2014) and enhances gut epithelial integrity (Stilling et al. 2016). Short-chain fatty acids activate free fatty acid receptors which appear to have a direct anti-inflammatory effect on microglial activation (Erny et al. 2015), as well as stimulate the secretion of serotonin from enterochromaffin cells in the intestine

which then activates the vagus nerve (Fukumoto et al. 2003; Reigstad et al. 2015; Yano et al. 2015a, b).

A fast-food diet reduces Lactobacilli (Mitsou et al. 2017), while a high-fat diet, regardless of fat type, decreases total bacteria (Fava et al. 2013). A double-blind, placebo-controlled, randomised clinical study with probiotic formulation (Lactobacillus helveticus and Bifidobacterium longum) administered for 30 days alleviated psychological distress due to depression (and anxiety) in healthy human volunteers (Messaoudi et al. 2011). In another trial over a four-week period, healthy female volunteers were required to consume fermented milk product with probiotic containing a combination of Bifidobacterium animalis subsp. Lactis, Streptococcus thermophiles, Lactobacillus bulgaricus, and Lactococcus lactis subsp. Lactis. The result demonstrated the modulatory effect of probiotic on the brain regions that control central processing of emotion on the frontal, prefrontal, and temporal cortices (Tillisch et al. 2013). Although the use of supplemental probiotics has shown some favourable effects as a therapeutic treatment for depression, more research on mechanistic studies is needed to ascertain the probiotics' mode of action and side-effects (Mohajeri et al. 2018).

6.2.8 Micronutrients

The evidence for the role of micronutrient deficiencies in contributing to the pathophysiology of depression remains inconclusive with more rigorous randomised controlled trials required to establish clinically significant associations. Some elements of micronutrients are present at low levels in depressed persons or those at high risk for depression. These include vitamins B6, B12, C, D, and E, folate, magnesium, zinc, selenium, and iron (Alpert and Fava 1997; Jacka et al. 2012; Anglin et al. 2013a, b; Gougeon et al. 2016a, b; Vulser et al. 2016; Wang et al. 2018a, b). These micronutrients may contribute to the onset and progression of depression through the effects on the decreased production of monoamine neurotransmitters such as serotonin (Dakshinamurti et al. 1990; Hartvig et al. 1995; Partonen 1998; Paul et al. 2004; Coppen and Bolander-Gouaille 2005; Spedding 2014), inflammatory and oxidative stress (Rybka et al. 2013; Wang et al. 2018a), glutamatergic signalling (Wang et al. 2018b), or alterations to the HPA system (Wang et al. 2018a). A diet with vegetables and fruits may offer higher amounts of these micronutrients (Bouayed 2010; Zhang et al. 2011; Hurley et al. 2014; Chandrasekhar et al. 2017).

Based on a longitudinal community study on vitamin B intake and risk of depression by Gougeon et al. (2016a), the depression risk is lower among generally healthy older adult women with higher intake of vitamin B6 from food (dependent on total energy intake) and among men with higher intake of B12 (independent of energy intake). According to Dhiman et al. (2021), for women in the postpartum period, low vitamin B12 levels may precipitate depressive symptoms and as such vitamin B12 together with folic acid (vitamin B9) are to be given prophylactically

during pregnancy. Dietary sources of vitamin B6 include fish, poultry, starchy vegetables, and non-citrus fruits. Vitamin B12 is found only in animal foods like fish, eggs, and dairy produce.

With the recognition of neuromodulatory role of vitamin D and presence of vitamin D receptors on the brain limbic system that are implicated in emotional processing, studies showed that low vitamin D levels are correlated with depression and its supplementation may benefit patients with clinical depression. However, these findings need to be interpreted with caution due to the methodological limitation (Anglin et al. 2013a; Vellekkatt and Menon 2019). Fatty fish and fortified milk are the main sources of vitamin D.

Magnesium occurs in the neurotransmitters, enzymes, and hormones involved in the pathophysiology of depression (Serefko et al. 2013). Generally, most evidence supports an inverse association between magnesium levels and the development of depression (Wang et al. 2018a). Magnesium also acts on both the pituitary and adrenal glands. In the pituitary gland, it reduces the release of adrenocorticotrophic hormone (ACTH) and modulates the adrenal cortex adrenocorticotropic sensitivity to ACTH. Thus, magnesium maintains cortisol levels within a normal range and prevents hyperactivation of the HPA axis (Wang et al. 2018b). Green leafy vegetables, such as spinach, legumes, and whole grains are good sources of magnesium.

Zinc when administered as an adjunctive treatment to monoaminergic antidepressants appears to have a synergistic (additive serotonergic, cholinergic, or neurotrophic) or complimentary (glutamatergic, antioxidant) effects on patients with treatment-resistant depression (Swardfager et al. 2013). High dietary intake of zinc may potentially cause secondary copper deficiency (Scheiber et al. 2013). Thus, the intake of dietary zinc is to be restricted to the recommended amount or taken together with adequate copper supplementation. Zinc is mainly found in animal-based foods such as oysters, red meat, poultry.

Although selenium deficiency appears to correlate with depressive symptom, studies that examine the association between selenium deficiency and depression have been mostly inconclusive (Wang et al. 2018a). Selenium is incorporated into iodothyronine deiodinases, and is thus required essentially for the proper synthesis and metabolism of thyroid hormones. Selenium deficiency and the sequential dysregulation of thyroid function may result in clinical depression (Kohrle et al. 2005). Food with high selenium content includes eggs, poultry, and shellfish.

6.3 Dietary Pattern and Depression

For healthy adults, most researches showed that those who adhere to dietary patterns with predominant consumption of fruits, vegetables, legumes, unrefined cereals, nuts and with moderate quantities of eggs, dairy products, fish, and unsaturated fats had a lower rate of depression incidence (Lai et al. 2014). These dietary patterns include the Mediterranean diet (Crichton et al. 2013; Ford et al. 2013), Japanese diet (Nanri et al. 2010; Suzuki et al. 2013), and Norwegian diet (Jacka et al. 2011). Conversely,

Western diet has been increasingly shown to be one of the contributors to depression (Melo et al. 2019). The Western diet is the present-day pattern diet that contains mainly high quantities of processed meats, saturated fats, refined sugars, and omega-6 PUFAs with a decreased intake of vegetables, fruits, grains, legumes, fish, and food containing omega-3 PUFAs (Statovci et al. 2017).

According to a longitudinal community study on older adults, the left hippocampal volumes were smaller in correlation with those on lower consumption of foods with dense nutrients, i.e. fresh vegetables, salad, fruit, and grilled fish, as well as higher consumption of unhealthy Western foods, i.e. roast meat, sausages, hamburgers, steak, chips, crisps, and soft drinks (Jacka et al. 2015). Hippocampus, a major brain structure located in the medial region of the temporal lobe, is associated with learning, memory, and mood regulation. Unhealthy foods potentially promote oxidative stress with the release of pro-inflammatory cytokines to inhibit hippocampal neurogenesis (or accelerate hippocampal atrophy) and thus increase the risk of depression in healthy adults (Stangl and Thuret 2009). Furthermore, the hippocampal volume is demonstrated from MRI studies to be reduced in adults with depression (Videbech and Ravnkilde 2004).

6.4 Conclusion

In summary, apart from reduction of certain food in particular saturated or trans fats and refined sugar, specific nutritional components (for example, polyunsaturated fats and polyphenols) as well as the adoption of certain dietary patterns (for example, consumption of a Mediterranean diet) may offer anti-inflammatory effects to prevent or reduce the severity of depressive symptoms associated with a raised or intensely sustained inflammatory state (Borsini et al. 2017). In reality, a person does not consume single nutrients or individual foods but meals with complex combinations of multiple nutrients that interact with each other (Hu 2002). Thus, the objective or aim of some researches based on single nutrients or foods may provide an inadequate comprehension of the association between diet and depression. Accordingly, more attention needs to be emphasised on the influential impact of dietary patterns on depression. Furthermore, studies with prospective cohorts and interventional methodology are required to understand and examine the cause-and-effect relationship between nutrients and depression, as well as the potential pathophysiological mechanisms arising from the observed associations.

Clinically, it is recommended to incorporate nutritional advice as part of an integrative approach to the care of mental health. Although we may often identify an individual dietary component as the possible element contributing to depression, one may need to consider the multifactorial influence of dietary constituents or intricate interplay of multiple nutritional elements, and factors perpetuated by the environmental agents as well as a person's genetic inheritance to a depressive illness. As inflammatory process may be responsible for some clinically depressed persons,

the approach of dietary intervention as anti-inflammatory agents may benefit these group of individuals (Köhler-Forsberg et al. 2019).

Below are Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes on Mineral, Vitamins, and Macronutrients.

For recommended dietary allowances and adequate intakes on minerals, vitamins, and macronutrients, refer to Dietary Reference Intakes (DRIs) from http://www.nap.edu

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