Review Article

Kill Depression by Nutrition

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ABSTRACT

Depression is a multifaceted disorder with profound global health implications, impacting mental and physical health well-being. It is influenced by genetic, biological, environmental and lifestyle factors. The major risk factors include medical co-morbidities, social stressors, cognitive vulnerabilities, personality traits and so on. The etiology of depression is complex, involving deregulation of the hypothalamic-pituitary-adrenal (HPA) axis, neurotransmitters imbalance, structural abnormalities in the brain regions such as amygdala and prefrontal cortex. This article utilizes a comprehensive literature review and data synthesis approach including reported clinical trials and meta-analysis to explore the relationship between depression and nutrition. The illustration is also made to focus the interplay between depression, neurotransmitters, dietary influences, key nutrients, their roles and dietary patterns. The data analysis focuses on identifying patterns in nutritional impact on mental health. Comparative evaluations of the processed foods & sugary products and Mediterranean diets and whole foods are narrated to assess their implications for mental health. The article also explores the gut-brain axis, emphasizing probiotics impact on mood regulations. The review incorporates research findings, emphasizing dietary strategies as suitable and conventional treatments for preventing and managing depression through nutritional interventions.

Keywords: Depression, Neurotransmitter, Nutrition, Mood Regulation.

INTRODUCTION

Let's start with a story. Depression, depression, depression!! Anil's wife is nowadays so frustrated to carry forward the responsibility of her family almost alone due to the depression of Anil, occurred since one year back with the reason of death of Anil's father and mother in together in a car accident, as when Anil was driving their family car. Actually, Depression is a complex and multifaceted disorder with significant global health implications. Depression impacts mental and physical health through complex interactions of physical, social and biological dimensions with a 1.5 to 6 fold risk to develop various other health conditions including cardiac disease, diabetes, obesity and so on.[1-7] It is projected to become the 2nd leading cause of disability according to World Health Organization.[8]

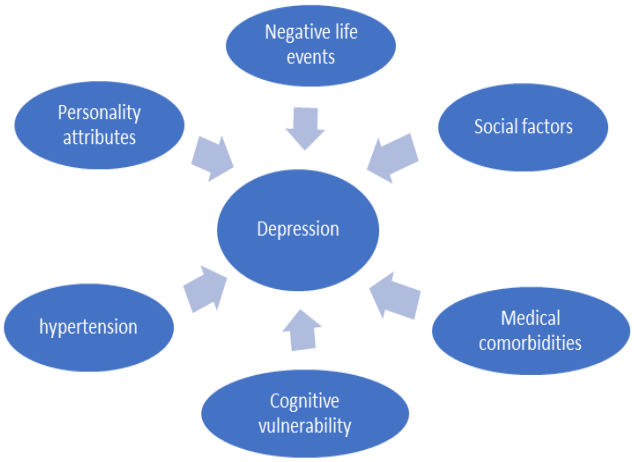


Figure 1: Factors of Depression

Depression manifests through a range of psychological and physical symptoms including persist sadness, fatigue, sleep disturbance, and change in appetite or weight, lack of interest, difficulty in daily functioning. Research indicates that its onset may be influenced by a variety of interrelated factors, including biological predispositions, lifestyle choices, medical co-morbidities, and social stressors. For instance, some studies suggest that gastric predisposition—possibly related to gut-brain interactions- can play a role in triggering depressive symptoms, particularly when combined with environmental stressors. Lifestyle factors such as diet, exercise, and overall daily habits have also been shown to significantly impact mental well-being, potentially mitigating or exacerbating the risk of depression. Moreover, medical co-morbidities, especially vascular diseases, not only heighten the likelihood of depressive symptoms but also increase the risk of vascular dementia, obesity.[9] Patients suffering from diabetes,[10] myocardial infarction and coronary heart disease, for example, are found to be more vulnerable to developing depression later in life. Finally, life stressors and social factors—including chronic stress, social isolation, and interpersonal conflicts—further contribute to the development and severity of depression.[11,12,13] Together, these diverse influences underscore the importance of a holistic approach to understanding and managing depression.

Factors

The key factors which are associated with severe depression are discussed below:

a. Medications-

Medications used to treat high blood pressure, cancer, chronic pain, diabetes, obesity, increased basal metabolic index, some psychiatric medications can lead to depression as a side effect. About 20% to 25% of individuals with heart disease report experiencing major depression.[14]

b. Hypertension –

The PAQUID study highlighted that man with hypertension and depression has a 50% increased risk of developing dementia compared to their non-hypertensive depressed counterparts.[15]

c. Personality attributes –

Kendler and colleagues[16] have found that neuroticism, characterized by emotional instability and frequently negative effect, low level of mastery are the key contributors to depression.[17] Also women are twice as likely to become depressed as men, making female gender a factor that increase the vulnerability of it.

d. Cognitive vulnerability –

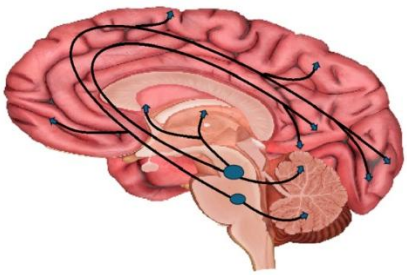
It includes pessimistic thinking styles, dysfunctional attitudes and tendencies towards self-criticism[18] or rumination,[19] depressogenic inferential styles[20,21,22]. The cognitive vulnerabilities interact with negative life events, influencing the development of depressive symptoms.

Neurotransmitter *Systems Involved for Depression*

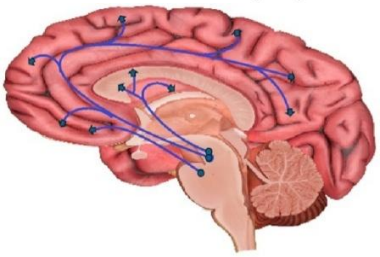
a. Monoaminergic system

Serotonin (5-HT), synthesized from amino acid L-tryptophan, its production is influenced by neuronal activity and calcium-dependent phosphorylation. It regulates sleep, mood, appetite, stress response. Research studies carried out at the University of Pisa in Italy confirm that serotonin deficiency plays a significant role in the development of depression. Deficiencies in serotonin levels are linked to major depressive disorder (MDD) and postpartum depression (PPD).

Dopamine (DA), synthesized from L-tyrosine, modulates motivation, pleasure and reward processing. Dysfunction of dopaminergic pathways, particularly the mesolimbic pathway contributes to anhedonia, reduced motivation in depression. Norepinephrine (NE), it is derived from dopamine via dopamine β- hydroxylase (DBH) in locus coeruleus. Norepinephrine is involved in the stress response, arousal and cognitive function. Dysregulated NE signaling in the prefrontal cortex (PFC) and limbic system are linked to depressive symptoms such as fatigue, impaired concentration, emotional instability. The sites of action of serotonin and dopamine are summarized with the help of diagram.



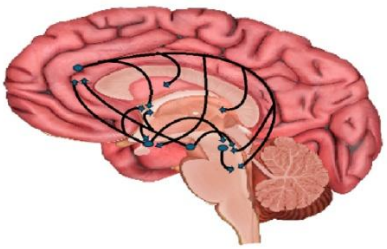
Serotonin pathway



Dopaminergic pathway

b. Glutamatergic System

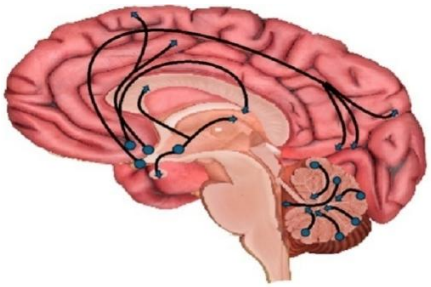
Glutamate is the primary excitatory neurotransmitter, synthesized from α- ketoglutarate. It is involved in the synaptic plasticity and cognitive function. Impaired glutamatergic signaling in the hippocampus, prefrontal cortex and amygdala, particularly in NMDA receptors, is linked to mood disturbance and depression. The sites of action of glutamate are summarized with the help of a diagram.



Glutamatergic pathway

c. GABAergic System

Gamma-Amino Butyric Acid is the primary inhibitory neurotransmitter, synthesized from glutamate. Bipolar depression, mood disorders are associated with reduced GABA levels in prefrontal cortex, amygdala and hippocampus. Depressed patients show approximately 52% lower GABA plasma levels compared to healthy individuals.[23] The sites of action of GABA is summarized with the help of a diagram.



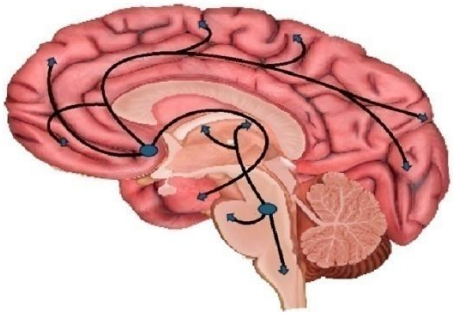
GABAergic pathway

d. Endogenous Opioid System

Endorphins, enkephalins, dynorphins regulate pain perception, mood, social attachment, stress response. Dynorphin, which activates kappa opioid receptors (KORs) may increase the anxiety with depressive symptoms.

e. Cholinergic System

Acetylcholine, synthesized from choline and acetyl-CoA, modulates cognitive function and mood regulation. An increased cholinergic activity (acetylcholinesterase) has been linked to depressive symptoms. The sites of action of cholinergic are summarized with the help of a diagram.



Cholinergic pathway

f. Neuropeptides (NPY & Orexins)

Neuropeptide Y, a hypothalamic peptide, regulates mood, sleep, stress by stimulating Y1 receptors while orexins influence sleep, stress response, arousal and thus both the systems contribute to depressive symptoms and mood disorders**.**[24]

g. Kynurenine Pathway

Tryptophan metabolism via kynurenine pathway leads to production of neurotoxic metabolites like quinolinic acid. The elevated kynurenine to tryptophan (kyn/tryp) ratios are observed in depression. It is suggested that the system "tryptophan-kynurenine" may be one of the main sites of interaction between genetic and environmental factors involved in the pathophysiology of depression.[25]

Responsible Nerves and CNS Causing Depression

The human stress response is primarily mediated by the hypothalamus-pituitary-adrenal (HPA) axis and its dysfunction may contribute to biological vulnerabilities to depression.[26]

Several brain regions such as amygdala, responsible for fear, anxiety, emotional memory processing, mesolimbic dopamine system, associated with reward regulation and the prefrontal cortex, involved in behavioral control exhibit abnormalities in individuals with depression.[27] Resting frontal brain asymmetry has been linked to depressive vulnerability along with decreased left-frontal activity relative to the right. This suggests potential dysfunction in the pre-frontal cortex as a stable neurological marker of depression**.**[27,28]

Postmortem studies reveal that individuals with stress exhibit increased expression of the MKP-1 (mitogen-activated-protein kinase phosphatase-1) gene in the hippocampus, which triggers the depressive behaviors.[29]

Genetic predisposition with including polymorphism in genes such as 5-HTT (5- hydroxytryptamine transporter**),** COMT (catechol-o-methyl transferase), MAO-A (mono amine oxidase A), CRHR1 (corticotropin releasing hormone receptor 1) interact with environmental factors to influence depression susceptibility**.**[30]

The vagus nerve connects directly and indirectly to the cortical-limbic-thalamic-striatal neural circuits, regulating emotional and cognitive functions relevant to depression.[31] Vagus nerve stimulation (VNS) modulates neurotransmitters such as norepinephrine and serotonin, enhances brain-derived neurotrophic factor (BDNF) expression and stimulates hippocampal neurogenesis**.**[32,33] Studies demonstrate VNS patients show significantly higher improvement rates over time (27% response, 16% remission) than those on standard treatment (13% response, 70% remission**).**

Nutritional Influence on Hormonal & Neurotransmitter Effects:

Stress perception activates hypothalamus which releases peptides that stimulate pituitary gland and the hormones are being secreted including cortisol and growth hormone. Growth hormone has been studied as potential biomarker of depression vulnerability[34,35] while cortisol levels in depressed youth show mixed results. Corticotropin-releasing hormone (CRH) and noradrenaline serve as central regulators of the hypothalamic-pituitary-adrenal (HPA) axis.

Nutrition may improve the mental health through various mechanisms including correcting nutrient deficiencies, augmenting the effects of antidepressant medicaments and improving the brain nutritional environment. Certain biological systems, such as brain derived neurotrophic factors (BDNF) and cholecystokinin (CCK) are influenced by diet. The blockade in CCK can be exerted by maintaining diet which reverse the depressive behavior.[36,37,38] BDNF is involved in the vulnerability to depression and the effects of antidepressant treatment.[39-42] Additionally nutritional influences on brain chemistry include the regulation of neurotransmitters, neuroplasticity and stress response systems.

Neurotransmitters such as Serotonin is a key neurotransmitter that plays a crucial role in mood regulation, emotional well-being, and cognitive functions, low levels increase stress, sleep disturbance, suicidal thoughts, regulates neuroplasticity, influence the functions of dopamine, norepinephrine; Aspartate is linked to major depressive disorder by acting on glutamatergic system, influencing HPA axis; Histamine, influencing stress responses, increasing CRH, cause neuroinflammation, sleep dysregulation; Epinephrine, Norepinephrine, Dopamine, regulate mood and alertness, regulate 'fight-or-flight'

response; Glutamate, essential for synaptic plasticity, emotional resilience, cause neural damage, neuroinflammation; GABA, low levels associated with MDD, regulates the HPA axis, increase cortisol production; can be controlled by regulating the consumption of protein rich foods, probiotic foods, vitamin B6, vitamin B12, magnesium, folate, zinc, copper, antioxidants which act as cofactors for various biochemical reactions, support amino acid metabolism, protect the precursor from oxidative degradations, activate the reactions and so on.

Nutrition for Recovery:

A healthy diet is the one that provides all the essential nutrients needed for optimal bodily function including vitamins, minerals, essentials fatty acids, antioxidants etc. which contribute to physical as well as mental well-being.

Traditional approaches to treat depression emphasize pharmaceutical interventions while emerging perspectives highlight the impact of diet and nutrition, recognizing the influence of gut health and the brains chemistry on mood regulation.

There is growing evidence of a connection between gut health and mental health. The gut-brain axis suggests that the health of gut microbiome can influence brain chemistry and mood regulation with probiotics and gut-friendly foods offering potential benefits over pharmaceutical antidepressants.

Key Nutrients on Mental Health:

1. Omega-3- fatty acid

These are essential fats (Linoleic acid (18:2n-6) and -linolenic acid (18:3n-3) are the parent fatty acids of the n-6 and n-3 families of EFAs) found in fish, seeds. Omega-3 fatty acids, particularly EPA (Eicosapentaenoic Acid) and DHA (Docosahexaenoic Acid), play a crucial role in brain health by improving mental health is well documented. An increased omega-3- fatty acid intake especially from fish can reduce depression symptoms and help in maintaining brain structure and function. Eicosapentaenoic acid (EPA 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3) are the n-3 PUFAs that are the most biologically relevant for mental health and are most predominant in the brain. The American Psychiatric Association Practice Guideline for the treatment of patients with Major Depressive Disorder (MDD) states that n-3 fatty acids are generally recommended as an adjunctive therapy for MDD.[43]

2. Vitamin D

A study showing that deficiency in vitamin D is associated with higher risk of depression. A restricted cubic spline analysis revealed that higher serum levels of vitamin D were correlated with lower risk of depressive symptoms. In a completely adjusted analysis it has been shown that an increase by 5ng/ml vitamin D was associated with a 25% reduction in depression.[44]

3. Vitamin B12 and Folate

These are vital for the synthesis of neurotransmitters like serotonin and dopamine.[45,46] Folate helps maintain normal brain concentrations of tetrahydrobiopterin, a cofactor in the synthesis of serotonin and catecholamines. Deficiencies can impair mood regulation.[47] Treatment with vitamin B12 and folic acid supplementation can improve mood in some individuals.

4. Magnesium

Mg is critical for neurotransmitter function. This mineral is involved in over 300 cellular processes, regulate mood and inflammatory responses. Magnesium depletion leads to N-methyl-D-aspartate overactivity and as a consequence to depressive symptoms.[48]

5. Iron

Decreased brain iron stores may impair the activity of iron dependent enzymes that are necessary for the synthesis, function and degradation of dopamine, serotonin and noradrenaline (e.g.- mono amine oxidase and aldehyde oxidase. A study reported a significantly higher depressive symptoms at postpartum day 28 among women who were anaemic on postpartum day 7 compared with non-anemic women.

6. Zinc

Zinc is necessary for optimal activity of 100 of intracellular processes.[49] After iron, zinc has the second highest concentration of all transition metals in the brain. Most zinc is localized within synaptic vesicles of specific neurons. Zinc deficiency include behavioral disturbance such as depression and dysphoria.

7. Antioxidants

Vitamin C is the potent antioxidants required for prevention of oxidative stress. But, interestingly antioxidant concentration of brain is low. High dose of antioxidants supplementation has been shown to slow the progression of neuronal damage and vascular disease.

8. Selenium

The metabolism of selenium in the brain is vastly different than in other organs. Though the mechanism by which selenium affects mood is not certain, it has been observed that individuals with low selenium diets reported more symptoms of depression and hostility than individuals fed higher selenium diets.

9. Heavy metals

Heavy metals like lead, mercury and cadmium can disrupt brain function and contribute to mood disorders including depression. They may induce oxidative stress, neuro inflammation, interfere with neurotransmitters system, exacerbating depressive symptoms.

10. Added sugar

In a meta-analysis of 4 prospective cohort studies, highest vs lowest consumption of sugar-sweetened beverages was associated with an increased risk of depression.[50,51,52] It is also reported[53] that 2 cups/day of sugar-sweetened beverages may increase the depression.

Table 1: The essential nutrients with their sources and dose

Key nutrients	Daily dose			Source	
	Children	Adult	Elder	Animals	Plants
Omega-3 Fatty Acid	1100 – 1400mg	1100 – 1600mg	1100 – 1600mg	fatty fishes- salmon, tuna, trout shellfishes, eggs, dairy and meat etc.	seeds, nuts, plant oils, spinach, kale etc Algae and seaweed
Vitamin B and D	**Vitamin B complex**			Egg, milk, chicken breast, tuna fish, egg, fatty fishes like salmon, cod liver oil etc.	Sunflower seeds, whole grains, sweet potato, oranges, bananas, almond milk, mushrooms etc.
	2 – 10 mcg	10 – 15 mcg	10 – 20 mcg		
	Vitamin D				
	10 – 15 mcg	15 mcg	20 mcg		
Vitamin B12 and Folate	**Vitamin B12**			Beef liver, dairy products such as milk, cheese etc, salmon, tuna fishes, chicken etc.	Soy milk, oat milk, broccoli, spinach, brussels sprouts, papaya, avocado etc
	1.8 – 2.4mcg	2.4 mcg	2.4 mcg		
	Folate				
	200 – 300 mcg	400 mcg	400 mcg		
Magnesium	240 – 360mg	310 – 400mg	320 – 410mg	Mackerel fish, salmon, plain yogurt	Swiss chard, pumpkin seeds, cashew, chia seeds, lentils, brown rice, fig, black beans etc.
Iron	8 – 15mg	18mg	8mg	Beef liver, red meat, sardines, dark meat, egg yolk, mussels, oysters etc.	Tofu, chickpeas, kidney beans, quinoa, spinach, Swiss chard, nuts like cashew, pistachios etc.
Zinc	5 – 8mg	9 – 11mg	8 – 11mg	Oysters, black meat, pork, lamb, beef, dairy products.	Black beans, kidney beans, walnuts, almond, cashew, hemp seeds, sesame seeds, whole grains like oats, whole wheat bread, brown rice mushrooms etc.
Antioxidants	65 - 75mg	75 – 90mg	75 – 90mg	Red meat, shellfish, fatty fishes such as salmon, sardines, eggs etc.	Berries like blueberry, strawberry, blackberry, fruits, spinach, dates, tomatoes, broccoli, beets, carrots, almond, chia seeds, green tea, coffee, turmeric etc.
Selenium	30 – 40mcg	55mcg	55mcg	Brazil nuts, tuna, sardines, pork, beef, shrimp, lobster, turkey, milk, yogurt etc.	White mushroom, brown rice, spinach, white wheat bread, sunflower seeds etc.
Heavy Metals	**Copper**			Arsenic (As) sources: seafood, Mercury (Hg) sources: Contaminated seafood. Cadmium (Cd) sources: cereals, shellfish. Chromium (Cr) sources: Found in dairy products.	Arsenic (As) sources: Contaminated groundwater, rice, vegetables. Mercury (Hg) sources: rice. Cadmium (Cd) sources: Found in leafy greens, Chromium (Cr) sources: Found in vegetables, grains.
	700 – 890mcg	900 mcg	900mcg		
	Chromium				
	21 – 25 mcg	25 – 35 mcg	20 – 30 mcg		
	Arsenic				
	5 – 10 mcg	10 – 15 mcg	10 – 15 mcg		
Added Sugar	25 – 36 g	36g	25 g	Sweetened beverages such as soda- soft drinks, energy drinks, fruit juice. Processed and packed foods such as breakfast cereals, flavoured yogurt, catchup, bottled salad dressings. Baked goods and desserts such as pastries, doughnuts, biscuits, cookies. Candy and chocolates, honey and so on.	

Review of Dietary Patterns & Depression:

The processed foods and sugary products are linked to higher inflammation, oxidative stress, and mood instability, increasing depression risk. It may also contribute to obesity, insulin resistance, and poor gut health, negatively impacting mental well-being. In contrast, the Mediterranean diet, rich in fish, olive oil, vegetables and whole grains supports brain function, reduces inflammation, and promotes emotional stability, offering protective effects.[54-74]

Whole-food-based and anti-inflammatory diets such as fruits, vegetables, lean proteins, omega-3-fatty acid etc. enhance cognitive function, neurotransmitter balance, and stress resilience, while processed diets high in sugar with poor nutritional value can lead to fatigue, anxiety, and depressive symptoms. However, adopting a healthy diet requires accessibility, affordability, and lifestyle adjustments, which may be challenging. Nevertheless, prioritizing balanced nutrition can significantly enhance mental well-being and long-term health. Interestingly, vegetarians experience better mood than omnivores despite their negligible intake of EPA/DHA.[67,68] Consumption of sweetened beverages, refined food, processed meat, refined grains and high intake fat is linked to an associated risk of depression.[54-74] In recapitulation, a recent large study with about 4500 healthy controls, specific dietary patterns predicted 39.8% of the total variance of depression with or without diabetes.[62]

Another study had shown significant relationships between cognitive functioning, measured using the Mini Mental State Examination, and some ten dietary-intake variables. Included among these were intakes of vitamin C, carotene, folate, Fe (positive associations), and intakes of monounsaturated fatty acids, saturated fatty acids, cholesterol (negative associations). Vitamin E status has also been specifically linked with memory function. There is sufficient evidence to suggest that studies of the effects of antioxidant supplementation may well yield positive outcomes for cognitive functioning. This includes the possible involvement of other mechanisms, such as dietary modification of immune function, whereby, for example, vitamin E could be expected to influence the development of arteriosclerosis. Further, there is an association between the apolipoprotein E4 genotype and dementia; which also suggests that potentially protective dietary interventions could be targeted for high-risk groups. In a 12-month, randomized, parallel trial of non-depressed adults with overweight or obesity, differences were observed in depressive symptoms after a moderately energy-restricted, very-low-carbohydrate diet (carbohydrate, 4% kcal; protein, 35% kcal; fat, 61% kcal [saturated fatty acid (SFA), 20%; other fatty acids, not reported]) compared with a moderately energy restricted, low-fat diet (carbohydrate, 46% kcal; protein, 24% kcal; fat, 30% kcal [SFA, <8% kcal].[75] It is seen that depressive symptoms are not affected by diets of differing macronutrient composition but are generally improved by weight-loss diets (regardless of the macronutrient composition).[76]

CONCLUSION

Depression is a multifaceted disorder with profound global health implications, impacting mental and physical health well-being. A try is attempted to find out the relationship between depression and nutrition. The illustration is also made to focus the interplay between depression, neurotransmitters, dietary influences, key nutrients, their roles and the dietary patterns. The data analysis focuses on identifying patterns in nutritional impact on mental health. This article also explores the gut-brain axis, emphasizing probiotics impact on mood regulations. The review incorporates research findings, emphasizing dietary strategies as suitable and conventional treatments for preventing and managing depression through nutritional interventions. Further research is needed to elucidate the mechanisms underlying diet - depression interactions and optimize nutritional psychiatry for mental well-being.

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