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A review on linking stress, depression, and insulin resistance via low-grade chronic inflammation

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ABSTRACT

Stress is a disturbance in homeostasis caused by psychological, physiological, or environmental factors. Prolonged reactions to chronic stress can be detrimental, resulting in various metabolic abnormalities, referred to as metabolic syndrome (MS). There is a reciprocal increased risk between MS and major depressive disorder. Recent studies established an association between inflammation and insulin signaling in type 2 diabetes mellitus with depression. In the present review, we discuss chronic low-grade inflammation, pathways of insulin resistance, and brain glucose metabolism in the context of neuroinflammation and depression. Specific attention is given to psychotropic drugs such as bupropion, mirtazapine, and nefazodone, anti-inflammatory drugs like Celecoxib (COX-2 inhibitor), Etanercept, adalimumab, IL-4Ra antagonist, Anti-IL- 17A antibody (Ixekizumab) and lifestyle modifications including exercise, dietary changes, and sleep hygiene. These therapeutic solutions offer potential in treating depression by targeting metabolic conditions like insulin resistance and inflammatory pathways. The article further explains the significance of a nutrition and antioxidants-rich diet, emphasizing the role of omega-3 fatty acids, vitamin D, zinc, and polyphenols, to improve immunity and activate anti-inflammatory signaling pathways.

1. Introduction

Depression is a multifaceted mental health disorder that affects millions of people worldwide. While its origins and mechanisms are still being elucidated, there is growing evidence to suggest that depression is not solely a result of disturbances in neurotransmitter function, but rather a complex interplay of various factors. Among these factors, the roles of stress, inflammation, and metabolic processes have emerged as significant contributors to the onset and progression of depression.

Stress is a disturbed state of homeostasis resulting from psychological, physiological, or environmental stimuli. Stress changes the body's hormonal and neurotransmitter environment by activating the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) [1] catecholamines generated as a stress response mechanism affect essential parameters like blood pressure (BP) and heart rate. These responses are necessary for the body to deal with stress [2]. However, prolonged responses to chronic stress can be harmful. Chronic stress has been linked to cardiovascular diseases (CVDs), including atherosclerosis and hypertension. It's also associated with neurodegenerative conditions such as Alzheimer's disease (AD), depression, and Parkinson's disease (PD). Additionally, metabolic diseases like diabetes and non-alcoholic fatty liver disease (NAFLD) can result from extended stress responses [3,4]. Major Depressive Disorder (MDD), often termed depression, exhibits features including anhedonia, guilt, weakness, hallucinations, changes in appetite, mental agitation, sleep difficulties, and suicidal thoughts [5]. This adversely affects the quality of life of the patients and their respective families, leading to numerous comorbid diseases and even suicide episodes. According to the WHO, over 700,000 people die each year due to suicide, and it is the fourth highest cause of mortality among the young generation [6].

Inflammation results from an injury or an infection that activates the immune system and instructs it to heal injured tissue and eliminate substances. When inflammation is persistent, low-grade, and systemic, it is referred to as chronic low-grade inflammation. Chronic low-grade inflammation is observed in various chronic disease states, e.g.,

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Abbreviations

MS	Metabolic Syndrome
MDD	Major Depressive Disorder
T2DM	Type 2 diabetes mellitus
HPA	Hypothalamic-pituitary adrenal axis
SNS	Sympathetic Nervous System
BP	Blood Pressure
CVDs	Cardiovascular Diseases
NAFLD	Non-alcoholic fatty liver diseases
AD	Alzheimer Disease
WHO	World Health Organization
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
PD	Parkinson's disease
NCEP	National Cholesterol Education Program
ACC	Anterior Cingulate Cortex
HDL	High Density Lipoprotein
PPAR-γ	peroxisome proliferator-activated receptor-gamma
TNF-α	Tumor necrosis factor-alpha
IL- 6	interleukin 6
CRP	C-reactive protein
HRV	Heart Rate Variability
CNS	Central Nervous System
O & NS	Oxidative & Nitrosative Stress
PGE2	Prostaglandin E2
Akt	Protein Kinase B
GLUT4	Glucose Transporter 4
MCP-1	Macrophage chemoattractant protein-1
sICAM-1	soluble intracellular adhesion molecule-1
SSRIs	Selective serotonin reuptake inhibitors
SNRIs	Serotonin and noradrenaline reuptake inhibitors
SSNRIs	Selective Serotonin and noradrenaline reuptake inhibitors
NSAID	Non-steroidal anti-inflammatory drugs
NE	Norepinephrine;
5-HT	5-Hydroxytrpytophan
GABA	γ-aminobutyric acid
T1D	Type 1 Diabetes
BMI	Body Mass Index
T3	Triiodothyronine;
T4	Levothyroxine;
TRH	Thyrotropin Releasing Hormone
TSH	Thyrotropin
K3MO	kynurenine monooxygenase
IDO	indoleamine dioxygenase
TDO	tryptophan dioxygenase

metabolic disorders, liver problems, type 2 diabetes mellitus (T2DM), cardiometabolic disorders, and psychiatric disorders [7]. Research has shown that the three conditions, namely stress, depression, and chronic inflammation, are linked to each other and occur due to metabolic disorders. Mental disorders are prevalent among individuals with chronic physical conditions, both in developing and developed countries [8]. With depression becoming globally prevalent, it may overtake CVDs as the second biggest cause of mortality by 2030 [9]. According to The Diagnostic and Statistical Manual of Mental Disorders (DSM-5), MDD is considered an extremely widespread, comorbid, and debilitating condition affecting the adult population in the United States of America [10]. A recent retrospective investigation focusing on the increasing trend of comorbid MDD in patients with T2DM or CVD reflected that extensive use of healthcare facilities and higher expenditure was involved in the patients with either T2DM or CVD and comorbid MDD compared to the patients without MDD. Another recent scientific investigation revealed that one in every five individuals with T2DM had mental health issues associated with increased healthcare utilization [11,12]. According to the Adult Treatment Panel III of the National Cholesterol Education Program (NCEP), at least three of the five risk factors-abdominal obesity, high triglycerides, low HDL-must be present (HDL), hypertension and a rise in glucose levels had been associated with metabolic syndrome (MS) [13,14]. These variables enhance the risk of CVD and non-insulin-dependent diabetes mellitus both separately and in combination [15,16]. MS is considered a new global epidemic of the twenty-first century, posing a threat to greater than half of the world's population by the next two decades [17].

In the present review, we have covered chronic low-grade inflammation, insulin resistance pathways, and brain glucose metabolism as contributors to neuroinflammation and depression.

2. Low-grade chronic inflammation and its links to psychiatric disorders like depression and stress

In recent years, a growing body of research has shed light on the intricate interplay between inflammation, stress, and depression. various psychiatric disorders, particularly depression. Central to this relationship is the concept of low-grade chronic inflammation, which has emerged as a key player in the development and exacerbation of psychiatric conditions. Low-grade chronic inflammation refers to a persistent, low-level activation of the body's immune system, often characterized by elevated levels of pro-inflammatory molecules, such as cytokines and C-reactive protein (CRP) [18]. Studies have shown an association between MDD research investigations observed and low-grade chronic inflammation [19,20]. Additionally, chronic inflammation has been related to various metabolic disorders, such as diabetes and obesity [21,22]. Further, it is well-established that individuals who are obese and have insulin resistance (which is typically regarded as a pre-diabetic stage) are more susceptible to MDD than healthy individuals [23,24]. Thus, these factors are interconnected through underlying physiological processes such as neuroinflammation, hormonal imbalances, and neurotransmitter dysregulation. It is necessary to understand the crucial links between these disorders. The pathophysiology of depression has a strong link. It is associated with chronic low-grade inflammation. Patients with severe depression had higher levels of pro-inflammatory cytokines, particularly tumour necrosis factor-alpha (TNF-alpha) and interleukin 6 (IL-6). Surprisingly, an increase in these cytokines is observed when the body is physically and psychologically stressed, thereby linking inflammation, stress, and depression. Fig. 1 showcases the underlying mechanism of depression that involves the immune system, endocrine system, inflammation, and certain neurotransmitters.

A systematic review and meta-analysis have been carried out related to 17 observational studies which established a connection between depression and MS; the relationship was bidirectional, meaning that MS causes depression and vice versa [25,26]. Depression, interlinked to the MS, upregulates the secretion of hydrocorticotropin, adrenocorticotropic, and cortisol hormones by triggering the HPA axis, resulting in visceral adipose tissue accumulation [27]. Moreover, depression may induce an unhealthy and sedentary lifestyle along with alcoholism, smoking, a junk food diet, insomnia, and poor adherence to treatment [28–30]. Additionally, some people who are depressed show signs of increased hunger, while others show decreased appetite. There are numerous brain areas associated with depression and appetitive responses to food. While hypoactivation of insula, which aids in monitoring the body's physiological status, is linked to depression-related appetite loss, depression-related appetite increases are associated with hyperactivation of putative mesocorticolimbic reward circuitry.

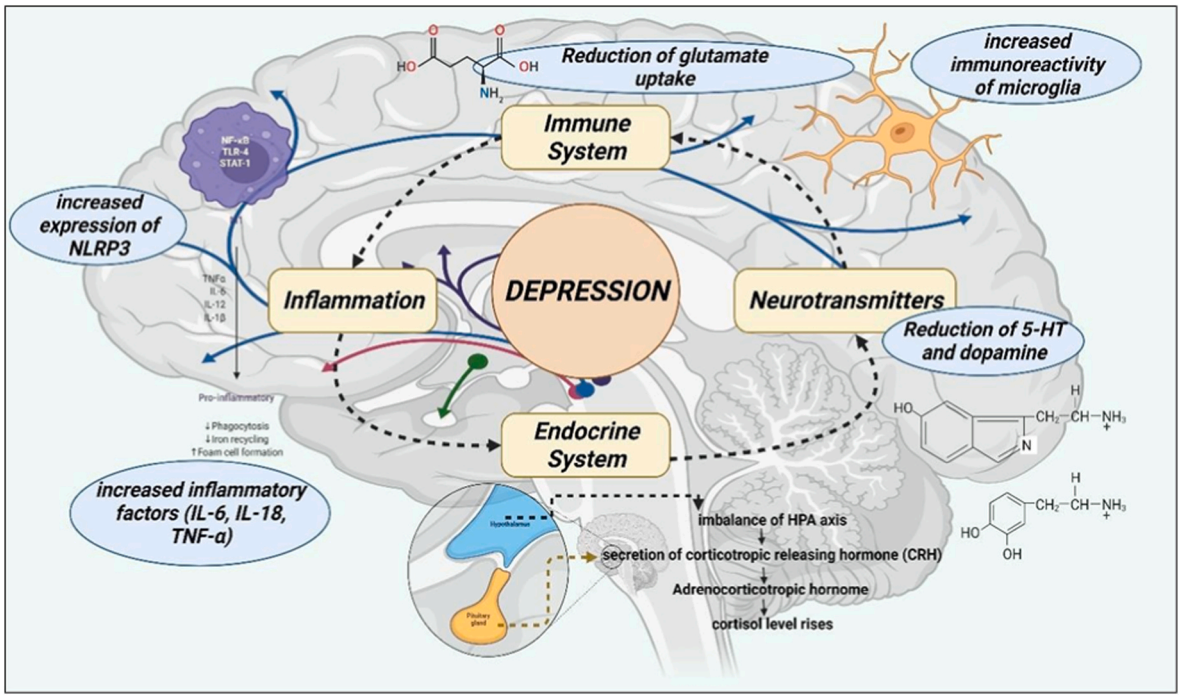

Fig. 1. The underlying mechanism of depression. Brain insulin resistance develops due to the failure of brain cells to respond to insulin activity. The hippocampus, hypothalamus, and cortex regions of the central nervous system regulate insulin levels in the brain. The factors that relate to brain insulin resistance and severe depression include the HPA stress axis, reduced volume of the Anterior Cingulate Cortex (ACC), hippocampal gray matter, and the brain's reward system-C*reated with BioRender.com.*

Notably, the interplay between these areas affects how alterations in hunger caused by depression differ in each person [31].

Similarly, patients with MS suffer from depression linked to their obesity issues, increasing inflammatory cytokines like C-reactive protein (CRP), IL-6, and leptin resistance [32,33]. Increased HPA activity is considered the common pathway linking depression and chronic stress [34]. Chronic activation of the stress system exhibits negative consequences such as higher chances of depression, obesity, and CVDs [35]. The MS and associated insulin resistance, abdominal obesity, and dyslipidemia develop from the altered activity of the HPA axis (Fig. 2) [36].

Depression, insulin resistance, and MS are the most common conditions where abnormalities in the autonomic nervous system's function are seen. Depression is frequently associated with elevated resting heart rates, baroreflex dysfunction, lower heart rate variability (HRV), and higher QT variability. All these factors contribute to an increased risk of cardiac mortality, including sudden death [37]. MS is associated with an

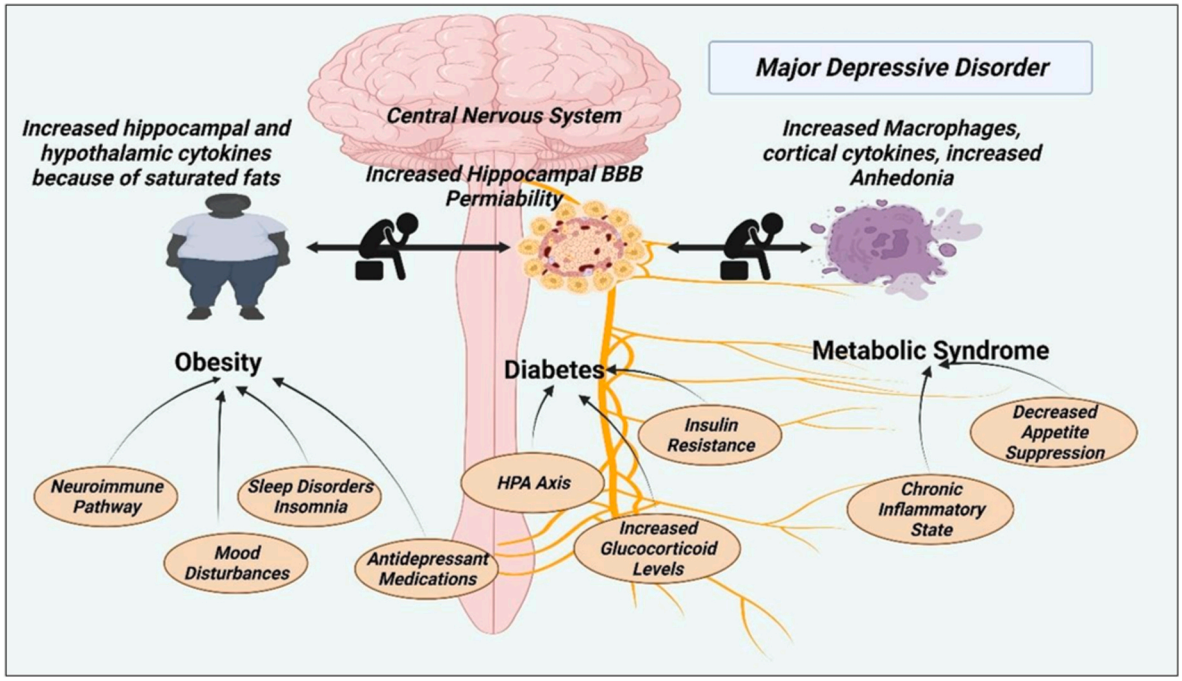

Fig. 2. Obesity, diabetes, and metabolic syndrome are metabolic diseases that coexist with depression-*Created with BioRender.com.*

altered sympathetic/parasympathetic balance, which has been hypothesized to result in elevated serum insulin concentrations and reduced insulin sensitivity [38–40]. The sympathetic branch, which is connected to the heart, large vessels, and skeletal muscles, is stimulated in metabolic syndrome, leading to high blood pressure and insulin resistance [41].

Inflammatory pathways substantially influence the pathogenesis of depression. Both the IL-6 and TNF-α impede resistance to vascular vasodilation through the expression of chemokines in the endothelial cells and adhesion molecules, finally leading to hypertension [42]. Recent research illustrated that depressive men with elevated CRP levels were more likely to develop abdominal obesity and multiple sclerosis than men with normal CRP levels [43]. The higher oxidative metabolic activity, the abundance of polyunsaturated fatty acids, and reduced endogenous antioxidant capacity make the central nervous system (CNS) susceptible to oxidative stress [44]. Pro-inflammatory cytokines exacerbate Oxidative & Nitrosative Stress (O&NS) induced brain damage in depressed patients by reduced neurogenesis and higher neurodegeneration [45]. O&NS disrupts intracellular signaling systems, including the endoplasmic reticulum, mitochondria, uncoupling proteins, and protein kinase B. Protein kinase B plays a critical role in glucose production in the liver, the release of triglycerides, and insulin sensitivity. Increased activation of the protein kinase B impairs the insulin-mediated transport of glucose in the fat cells and muscle. Additionally, protein kinase B acts as a critical regulator in preventing apoptotic cell damage during O&NS [46]. O&NS damages insulin-secreting cells in the pancreas through these methods, leading to insulin resistance.

In individuals suffering from depression, peripheral hormones like leptin and ghrelin can perturb the regulation of the central system of food reward, resulting in “stress-eating” characterized by increased consumption of cholesterol and carbohydrate-rich foods and a lower intake of fresh fish, vegetables, and cereals [47–50]. The high fat and sugar content in food can abrogate homeostatic signals, resulting in overconsumption and obesity. The use of psychotropic drugs is another significant factor that increases the occurrence of MS in psychiatric patients. Weight gain is a common side effect associated with many antipsychotics, mood stabilizers, and antidepressants [51,52]. Moreover, many antipsychotic drugs affect glucose and lipid metabolism [53–56]. Besides the biological factors, psychological aspects also play a significant role in MS and, eventually, depression. Obesity significantly contributes to psychological distress [57,58]. Consequently, obese people develop disturbed eating patterns, eating disorders, and physical pain. Due to sociocultural factors, being overweight makes one feel highly dissatisfied with reduced self-esteem, thereby increasing the risk of depression (Fig. 3) [59,60].

It is established that chronic low-grade inflammation is linked to depression. The relationship between inflammation and insulin resistance related to depression and MS. Major depression is associated with an increase in pro-inflammatory cytokines like TNF-α and IL-6. Prostaglandin E2 (PGE2), reactive oxygen species, and lipid peroxidation—in addition to pro-inflammatory cytokines-also heighten stress-related depression. Hence, there exists a virtual interaction between pro-inflammatory cytokines, and all pathophysiological changes related to major depression, affecting synaptic plasticity, neuronal structure, and neurotransmitter function. Both inflammation and severe depression are characterized by gradual resistance to insulin and glucocorticoid receptors. This is due to insulin insensitivity, which is brought on by pro-inflammatory cytokines and desensitized glucocorticoid receptors. The peripheral and central glucocorticoid receptors become insensitive in depression and chronic stress due to receptor internalization from the cell surface, even though glucocorticoids are anti-inflammatory in the short term [61]. Thus, chronic depression and metabolic syndrome both cause desensitization of the glucocorticoid and insulin receptors [62].

The expression of the glucose transporter 4 (GLUT4), which is mediated by insulin, is downregulated by the reduced activity of the insulin receptor glucocorticoids. Finally, the transport of glucose into the brain is reduced [63]. Therefore, the glucocorticoid and insulin receptors are also desensitized in MS and chronic depression, which causes insulin desensitization.

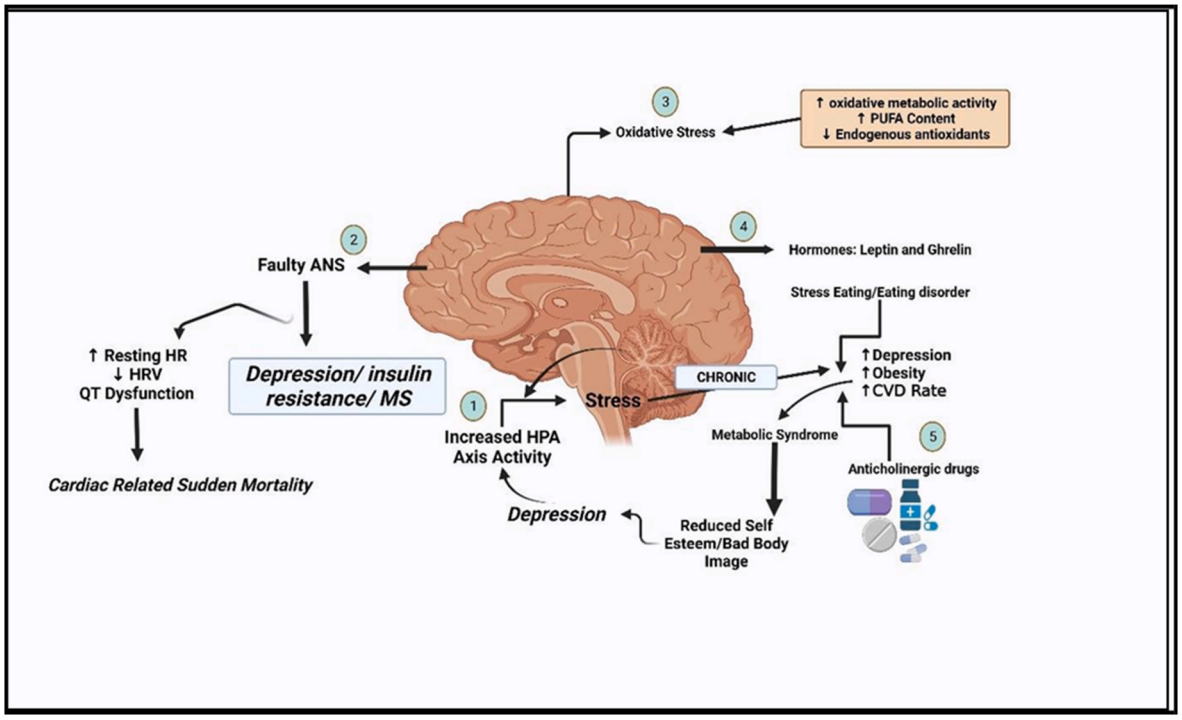

Fig. 3. A schematic representation of various factors leading to metabolic syndrome and depression and their subsequent impact-*Created with BioRender.com.* CVD: Cardiovascular Disorder; HPA: Hippocampal Pituitary Axis; MS: Metabolic Syndrome; HR: Heart Rate; HRV: Heart Rate Variability; PUFA: Polyunsaturated Fatty acids.

In addition, Watson et al. (2021) [64] found that over a 9-year follow-up period, a mild clinical increase in a proxy for insulin resistance (i.e., a one-unit change in triglyceride-HDL ratio) was associated with an 89 % increase in the rate of incident major depressive disorder. According to their research, an insulin resistance surrogate, a common condition that can manifest years before type 2 diabetes develops, may be able to predict the onset of MDD in adults. These findings are broadly in line with research on the relationship between many metabolic disorders and the progression of major depressive disorder. An odds ratio of 1.61 for major depression was associated with insulin resistance values of 1.85, as determined by the homeostasis model assessment of insulin resistance, in a 5-year follow-up study of elderly males in Australia [65].

In elderly and nonelderly adults from Europe, the United States, Australia, and Japan, a meta-analysis of the connection between metabolic syndrome and incident MDD found that metabolic syndrome has been linked to a 49 % increased risk of major depression [66]. Another meta-analysis involving adults from different nations discovered that having type 2 diabetes is linked to a 15 % higher risk of major depression; follow-up in these studies lasted between 2 and 10 years [67]. Given that insulin receptor resistance, age-related pathology associated with dementias, and other major psychiatric disorders, including depression, frequently share this trait, understanding the underlying cause of increased neuronal apoptosis may depend on a chronic decrease in highly energetic substrates brought on by a deficiency in glucose and essential co-factors [68].

3. The correlation of neuroinflammation, depression, and dementia with dysfunctional brain glucose metabolism

Glucose, as the primary energy source for the brain, fuels its intricate neural networks. Disruptions in glucose metabolism, such as insulin resistance or impaired glucose uptake, have been linked to neurodegenerative diseases, including dementia. Under normal physiological conditions, an increase in glucose levels in the blood leads to insulin production in the pancreas. As a result, there is enhanced glucose transport to the tissues and the brain. Insulin promotes the uptake of glucose and glucose transporter-linked mRNA production in the brain [69]. Glucose transporter types 1, 3, and 4 (GLUT 1, 3, and 4) carry the glucose to the functional areas of the brain. Thus, a functional deficit of glucose in the brain results from glucose metabolism and insulin resistance in the elderly and depressed subjects [70]. Reduced glucose levels in the brain are linked to the loss of glycaemic control. Additionally, structural changes in the brain can influence the mental state. Furthermore, it leads to neuronal damage and neurodegeneration and can be linked to the structural basis for dementia [71]. In older Mexican-Americans, a recent study found a substantial correlation between metabolic abnormalities and depressed symptoms, and it was hypothesized that insulin resistance is a key factor in this relationship [72]. Metabolic abnormalities and depression symptoms are linked by a variety of processes. There is a relationship between significant depression in older persons and metabolic abnormalities, which can result in cerebrovascular disease and endothelial dysfunction [73]. Hyperactivation of GSK-3 is caused by insulin resistance and metabolic problems, and it has been independently linked to serious depression in older persons and is also a target for the action of antidepressants [74].

As mentioned earlier, a crucial pathophysiological link between depression and metabolic syndrome is inflammation. Higher concentrations of chemokines, cellular adhesion molecules like human macrophage chemoattractant protein-1 (MCP-1), soluble intracellular adhesion molecule-1 (sICAM-1), and E-selectin, as well as pro-inflammatory cytokines like IL-6, acute phase proteins like CRP, alpha-1-acid glycoprotein, alpha-1-antichymotrypsin, and haptoglobin, have been observed in depressed patients and are considered as risk factors for the progress of MS [75]. By altering the HPA axis, depression increases cortisol and catecholamine, antagonizing insulin's hypoglycaemic effects, resulting in insulin resistance. The prevalence of metabolic diseases such as dyslipidemia, central obesity, insulin resistance, and hypertension can be correlated to increased sensitivity to CRP levels [76,77]. Insulin resistance may be linked to the development of major depression through a variety of biological mechanisms. In neurobiological models of depression, insulin resistance appears to promote neuroinflammation [78,79].

The pro-inflammatory cytokines may cause a decrease in serotonin levels, as well as neurogenesis and synaptic plasticity-physiological states linked to the presence of depression-according to the inflammatory hypothesis of depression [80–82]. Furthermore, the presence of depressive disorders has been repeatedly linked to glucocorticoid dysregulation in the hypothalamic-pituitary-adrenal axis, a condition that is related to insulin resistance [83,84]. In contrast to the findings of the metabolic syndrome, a group of researchers [85,86] and other researchers [87] have previously reported a common pathophysiological platform between insulin resistance and depressive disorders.

Central obesity, an element of MS, contributes to low-grade chronic inflammation [88]. Adipose tissues comprise mature adipocytes, preadipocytes, endothelial cells, and macrophages that generate and secrete pro-inflammatory cytokines and CRP. Recent research indicates that macrophages present in the adipose tissue may be associated with low-grade inflammation in MS [89,90]. Thus, a pro-inflammatory cytokine imbalance increases CRP synthesis by the liver. This excess production may exacerbate insulin resistance and can be related to the development of clinical features of MS and depression [91]. The occurrence and progress of depression can be explained by aberrancies in metabolism, such as alterations in the tryptophan-kynurenine pathway, imbalances in neurotransmitter synthesis, and disruptions in fatty acid metabolism. Detection methods targeting enzymes, proteins, genes, and metabolites are available for understanding the energy metabolism of depression. The expression of endogenous substances, genes, and proteins in the body is dealt with by "omics" technology, as are imaging studies that concentrate on changes in brain energy. Various molecular-level detection techniques are available to monitor the changes in gene expression and cell activity linked to energy metabolism disorders. Various technologies in combination might help in a detailed understanding of the modifications in energy metabolism pathways associated with depression [92].

Studies also confirmed that metabolic pathways, like the tryptophan-kynurenine pathway and fatty acid metabolism related to the peripheral system, are affected in MDD patients [93]. Additionally, depending on the pathophysiology of the psychiatric disorder, the brain regions involved in kynurenine metabolism may change. Steiner and colleagues found that the quinolinic acid concentration in microglia from the anterior cingulate gyrus subregions is elevated in major depression [94]. The increase in plasma 3-hydroxykynurenine provides more proof that depression activates the excitotoxic pathway. Changes in the tryptophan-kynurenine pathway because of immune activation contribute significantly to the dysfunctional neurotransmitter systems in the brain, as well as to the changes in brain structure and function that characterize depression. The main metabolic steps in the tryptophan kynurenine pathway are summarized in (Fig. 4) [95].

The tryptophan-kynurenine pathway is crucial for the synthesis of NAD + because it is thought that 99 % of tryptophan that is not used for protein or serotonin synthesis is converted to NAD + through this pathway [96]. A decrease in the amount of insulin, which is necessary for the transportation of glucose into neurons, would make this situation worse [97]. Therefore, a pathological connection between neurological changes in the elderly depressed patient's brain and the onset of dementia, particularly Alzheimer's disease, may be made thanks to the impact of chronic inflammation, endogenous neurotoxins, and oxidative stress on undesirable changes in brain energy metabolism [98,99].

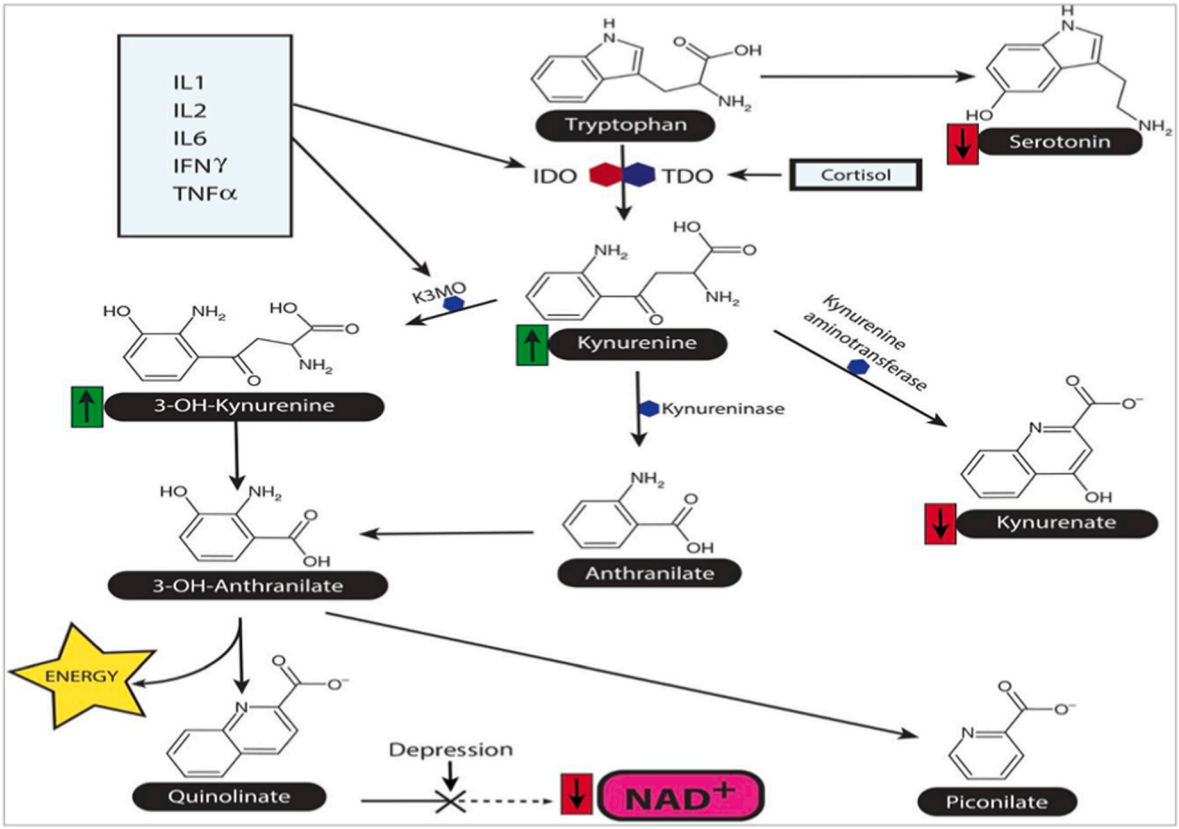

Fig. 4. The tryptophan-kynurenine pathway and how depression affects the HPA axis and inflammation. The main source of nicotinamide adenine dinucleotide (NAD+), a vital co-factor for Kreb's cycle that supports metabolic function, is shown in this diagram. Reproduced with permission from Ref. [62] which was published under the Creative Commons CC BY license.

4. Identifying drug targets in the designing of a new generation of psychotropic drugs

There is a limitation in standard pharmacological treatment related to MDD and related disorders [100]. Approximately 30 % of people with a MDD are unresponsive to antidepressants, like selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) [101].

Moncrieff et al. [102] recently in a systematic review tried to clarify the relationship between serotonin activity and depression. The review found no evidence that people with depression have lower serotonin activity than people without depression. Additionally, the methods used to limit the availability of serotonin by depleting tryptophan did not always make the participants' moods worse. As a result, there is no strong evidence supporting the serotonin hypothesis that depression has a biochemical basis. The authors concluded that a more durable theory may be required because the serotonin theory of depression may not be empirically supported.

Hence, a multimodal approach targeting different biological and clinical aspects of MDD might be valuable. Here, the agents combine multiple molecular mechanisms that target the monoamine and non-monoaminergic systems, such as the glutamatergic system [103]. One such example is Vortioxetine, a multimodal antidepressant that inhibits the reuptake of the transmitter and interrupts the interactions with various 5-HT receptor sites [104]. Combining psychotherapy with psychopharmacology is more effective for treating depression than using either method alone [104,105]. The selective serotonin and norepinephrine reuptake inhibitors (SSNRI), venlafaxine, and paroxetine, the selective serotonin reuptake inhibitors (SSRIs), or some "atypical" antidepressants like bupropion, mirtazapine, and nefazodone have been effective in treating depressed patients with diabetes. This class of antidepressants did not have any quinidine-like effects and exhibited less antidepressants as mentioned earlier and anticholinergic behavior. They are also not fatal.

As inflammation significantly influences the pathogenesis of depression, it can be well anticipated that effective treatment with antidepressants may offset the inflammatory response [106]. A meta-analysis concluded that the symptoms of depression could be well managed with celecoxib, a non-steroidal anti-inflammatory drug (NSAID) with high COX-2 selectivity, without any adverse side effects [107]. In addition, statins possess direct anti-inflammatory properties unrelated to their lipid-lowering effects [108]. The simultaneous application of SSRI and statins reduce the risk of relapse in depression compared to the treatment with SSRI alone [109]. The strategy of using the cytokine blockers like monoclonal antibodies (mAbs) has proven quite effective (Fig. 5).

One such example is infliximab which inhibits the binding of TNF to its receptors at the cell surface. In the beginning, it was used to treat inflammatory joint disorders and psoriasis. Its application also relieved the symptoms associated with depression in psoriasis patients [110]. The application of TNF inhibitors such as etanercept, adalimumab, IL-4Ra antagonists, IL-12/IL-23 antagonists, anti-IL-17A antibody (Ixekizumab), anti-IL-6 antibody (Sirukumab) is more efficacious than placebo and can be considered as a treatment option for the MDD [111–117]. Inhibition of pro-inflammatory cytokine signaling provides an alternative approach to treating depressed patients with increased central or peripheral inflammation. The studies suggest the reversal of cytokine-induced sickness syndrome overlapping symptomatically with depression by applying cytokine antagonists such as IL-1 and anti-inflammatory cytokines like IL-10 directly into the brain [118].

Mesenchymal stem cell therapy targeting central inflammation that exerts antidepressant effects has been proposed to be a probable line of

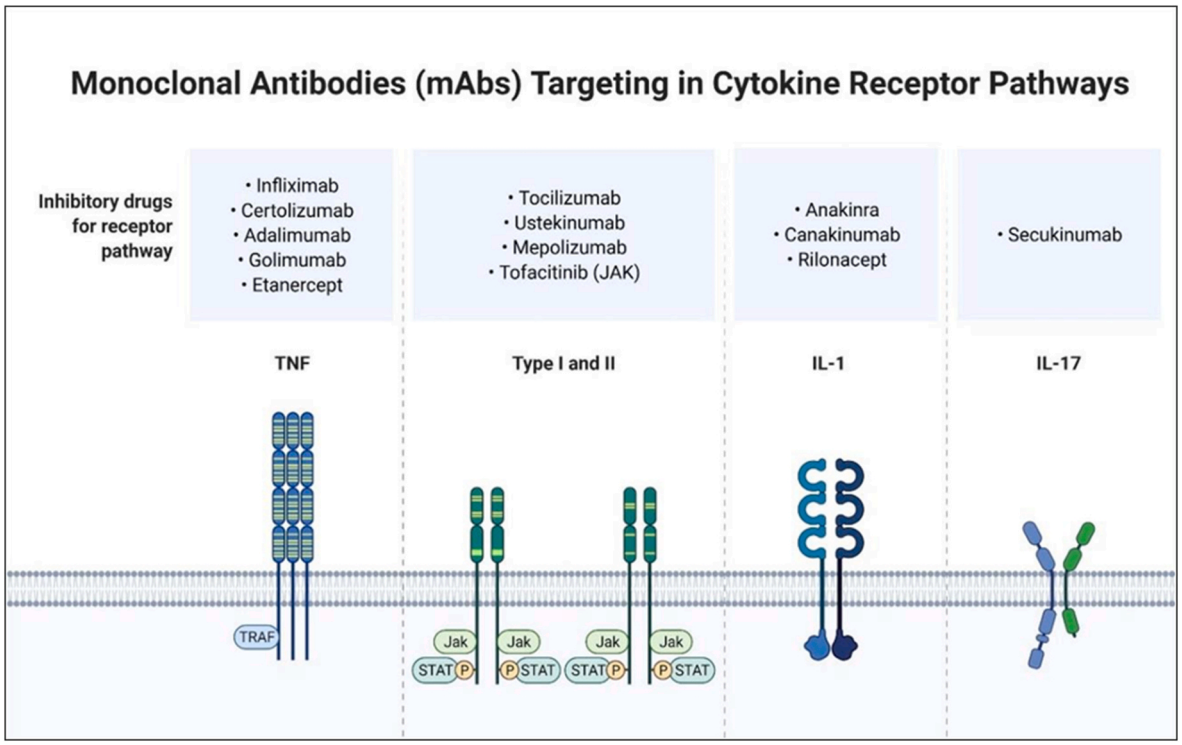

Fig. 5. Treatment option for major depressive disorders-*Created with BioRender.com.*

treatment in the future. Antidepressant therapy by alterations of microbiota is also a promising approach.

Another mechanistically innovative antidepressant, agomelatine, is a melatonergic agonist and a 5-HT2 receptor antagonist, identifying some unmet needs with first-line medications (i.e., SSRIs and SNRIs) (i.e., SSRIs and SNRIs). Also, augmentation, a new medication regimen therapy, is applied where a second agent is introduced to an existing antidepressant to boost clinical response: E.g., TCA medicines with Lithium or SSRIs with pindolol [119]. Study results of ketamine demonstrate that medicines that alter glutamatergic neurotransmission exert immediate and widespread antidepressant benefits in patients who have not responded to SSRIs or SNRIs [120]. The most intriguing breakthroughs in antidepressant pharmacology are N-methyl--D-aspartate receptor antagonists such as ketamine, which seem to operate swiftly (i.e., within 24 h) and robustly [121].

Endocrine dysfunction and depression are interlinked. The malfunctioning of the various endocrine glands has led to various psychiatric symptoms, including depression [122]. Thyroid function and psychiatric disorders, particularly mood disorders, have long been linked [123]. It is now widely accepted that thyroid function problems can have a significant impact on mental health, including emotion and cognition [124]. The disarray of the thyroid axis has been closely associated with psychiatric disorders. Hence the use of Thyrotropin-releasing hormone (TRH) and Thyrotropin (TSH), which activates the thyroid gland, provides effective therapy for depression. Particularly Levothyroxine (T4) and Tri-iodothyronine (T3) are highly efficient in this regard. Elevated T4 levels, low T3, elevated rT3, a blunted TSH response to TRH, positive antithyroid antibodies, and elevated CSF TRH concentrations have traditionally been the most documented abnormalities. Furthermore, thyroid hormone supplements appear to hasten and improve the clinical response to antidepressant drugs. However, the mechanisms underlying the interaction of thyroid function and depression remain unknown [122,125]. There is ample evidence to support testosterone and similar androgens as a potential treatment option for depressed men [126,127]. The functioning of the brain, mood, and cognition are affected by the alterations in estrogen levels [128]. In depressed patients, the circadian rhythms can be restored by using the actual hormones melatonin and agomelatine. These melatonergic agonists act on the melatonin-1 and melatonin- 2 receptors and are considered potential antidepressants [129]. There is a severe elevation of cortisol levels in about half of depressed patients. However, controlling cortisol secretion may show antidepressant effects [130]. Mifepristone, acting as a competitive inhibitor of the glucocorticoid receptor, has exhibited an antidepressant property and has been found to reduce psychotic symptoms in severely depressed subjects [131,132].

Future antidepressants must be created with pharmacology directed at alternative neurotransmitters or neuromodulators other than Norepinephrine (NE) and 5-HT, following novel mechanisms and hypotheses. For instance, it has long been hypothesized that the importance of gamma-aminobutyric acid (GABA) in depression. Corticotropin-releasing factor or melatonin are examples of additional targets for pharmaceuticals, as shown in Table 1 [19,119].

The introduction of new compounds targeting alternative neurotransmitters or neuromodulators may disrupt delicate balances, potentially leading to unforeseen side effects or long-term consequences. The complexity of these pathways and their interactions with other biological systems make it essential to conduct extensive research and clinical trials to ensure the safety and efficacy of these novel treatments. Furthermore, the individual variability in how people respond to different treatments remains a substantial concern.

5. Dietary targets and lifestyle modifications to combat inflammation, depression, and metabolic syndrome

Metabolic syndrome is a multifaceted pathophysiological condition primarily associated with an imbalance in calorie intake. Other factors like an individual's genetic/epigenetic makeup, the prevalence of inactive lifestyles with less physical activity, aging, hormonal imbalance, food quality and composition, and gut microbes also contribute to the development of MS. Recent research connected gastrointestinal and extra-gastrointestinal illnesses to the gut microbiota. Consuming

Table 1
Pharmacological interventions in treating chronic inflammation, metabolic syndrome, and major depressive disorder.

Pharmacological interventions	Clinical Outcomes	Ref
SSRI and SNRI E.g., Venlafaxine and paroxetine Bupropion, mirtazapine, nefazodone	Most patients showed a positive impact after therapy	[26,104]
Monoclonal Antibodies E.g., Infliximab	Successfully reduced depression in psoriasis patients	[100,108]
Celecoxib (COX-2 inhibitor)	Depression was well managed without the incidence of any ADR	[107]
Statins + SSRI	Significantly reduced the risk of relapse of depression	[109]
Vortioxetine	Showed superior clinical effects in patients with MDD	[133]
Inhibitors E.g., Etanercept, adalimumab, IL-4Ra antagonist, Anti-IL- 17A antibody (Ixekizumab)	Exhibited improved clinical outcomes than placebo in MDD patients	[111–117]
Melatonergic antagonist E.g., Agomelatine	Displayed an increase in norepinephrine and dopamine in the prefrontal cortex, with minimal effects on body weight and sexual function	[119]
Levothyroxine and Triiodothyronine	Helpful in treating and activating the thyroid gland; be a potentially promising therapy due to the linkage between endocrine dysfunction and depression	[122]
Mifepristone	Brought a rapid reduction in psychotic symptoms in patients with psychotic depression	[131, 132].

ADR: Adverse Drug Reactions; **MDD:** Major depressive disorder; **SNRI:** serotonin and norepinephrine reuptake inhibitors; **SSRIs:** serotonin reuptake inhibitors.

probiotics may be an option for treating and preventing anxiety and depression as dysbiosis and peripheral inflammation of the gut have been linked to the development of several mental illnesses, including anxiety and depression [62,133].

A healthy gut microbiota transmits brain signals via neuronal transmission, microglial activation, neurogenesis, and behavioral control pathways in both stable and stressful environments, according to another review by Limbana et al. [134]. Changes in the gut microbiome can lead to the production of microbial lipopolysaccharides (LPS), causing inflammatory reactions. These signals are then relayed to the vagus nerve, which can result in behavioral changes. The review concluded that dietary decisions substantially impact the endocrine, immunological, and gastrointestinal systems, among other bodily systems. Whereas high-fat consumption leads to obesity and inflammation of body systems, a healthy diet and probiotics reduce anxiety and sadness by improving the gut flora.

Insulin resistance is a common symptom of most people with T2DM and one of the hallmark clinical aspects of MS [135]. Studies have established that hereditary abnormalities in mitochondrial activity lower its capacity to oxidize fatty acids. As a result, patients with type 2 diabetes suffer insulin desensitization [136]. Furthermore, obesity contributes significantly to insulin resistance in T2DM. It is well known that chronic, low-grade peripheral inflammation linked to obesity is a critical etiologic mechanism for suppressing insulin signaling (Fig. 6) [137].

Lifestyle modifications are the first line of defense against the constellation of interconnected metabolic risk factors that contribute to MS, such as atherogenic dyslipidemia, increased blood pressure, and raised plasma glucose. Fundamental lifestyle changes such as weight loss, increased physical activity, and changes in diet plan can help control MS. Primarily, emphasis should be given to weight reduction and maintenance through a good combination of physical exercise, proper food habits, and behavioral interventions such as maintaining a waist circumference (higher than 40 inches in men and higher than 35 inches in women) [138]. Moreover, patients must be advised to limit trans fats and simple carbohydrates and increase their consumption of

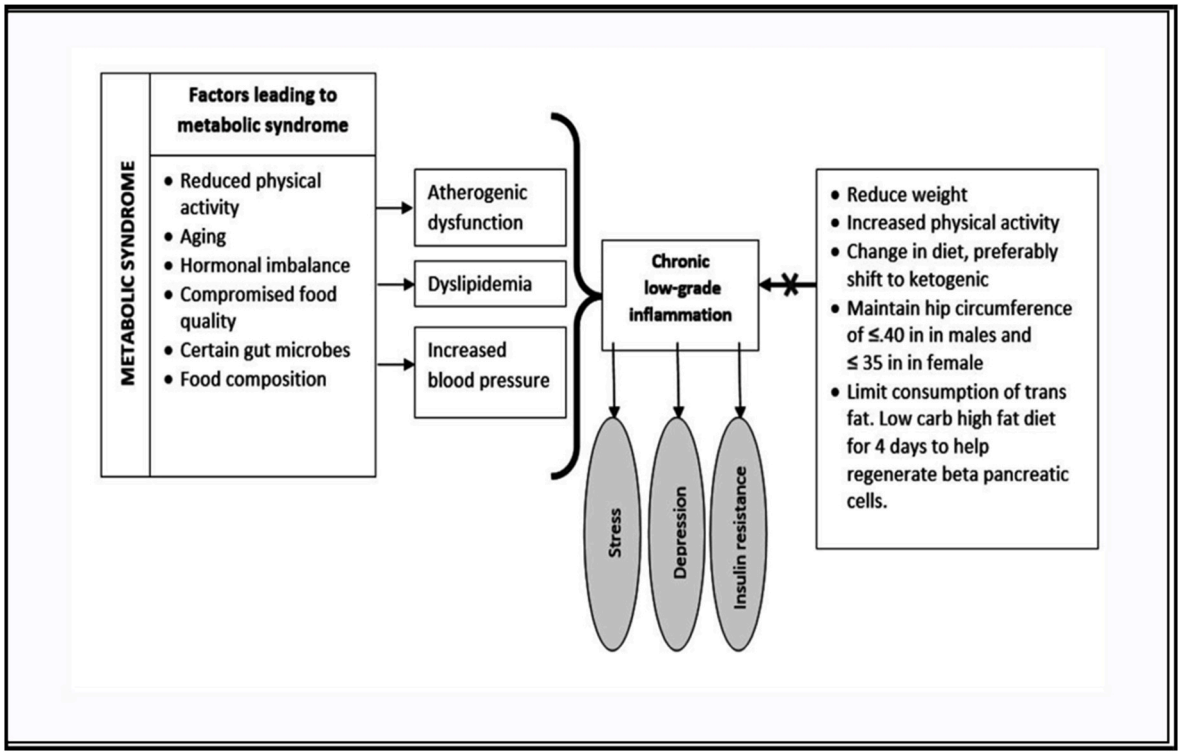

Fig. 6. A schematic representation of the factors affecting metabolic syndrome and the corresponding dietary and lifestyle changes for the alleviating the same.

unsaturated edible fats [139].

Several studies demonstrated that the Mediterranean diet effectively prevents diabetes and MS. Numerous dietary components, including capsaicin, luteolin, curcumin, cinnamon, and rosemary, have prevented MS [140,141]. Similarly, soy isoflavone, citrus products, hesperidin, and quercetin help in the metabolism of lipids, while cocoa supplements benefit hypertensive and diabetic individuals. Green tea has been found to considerably decrease body mass index (BMI) and waist circumference and improve lipid metabolism. Studies demonstrated that a low-calorie, fasting-mimicking ketogenic diet with less protein and less carbohydrate but high-fat content for 4 days elevated the production of pancreatic beta cells with simultaneous reversal of the type 1 diabetes and type 2 diabetes phenotypes in mouse models (Cheng et al. 2017) [142]. Ketone bodies provide energy for oxidative phosphorylation and the high-energy substrates to maintain the activity of the neurons. Hence, a ketogenic diet rich in fat improves the brain's energy state overall. Ketones increase the biochemical performance of mitochondria despite the loss in mitochondrial activity due to pro-inflammatory cytokines and reactive oxygen species (ROS damage) at the onset of severe depression. The inclusion of ketones, mainly in the diet of older depressive individuals, might be beneficial for increasing brain energy metabolism [143].

Regular exercise provides anti-inflammatory and other beneficial effects that may boost healthy food habits and antidepressant properties in individuals with major depressive disorder. Immunotherapy can successfully relieve MDD symptoms without excess immunosuppression [144]. Conclusively, there is compelling evidence that several lifestyle variables contribute to the etiology of depression. While many of these characteristics can be changed, little attention is paid to them in the current management of depression, which relies mainly on medicine and psychological therapy. Additionally, improving lifestyle-related wellness can present chances to improve overall health and possibly ward against depression [145–147].

While many therapeutic interventions are under exploration for managing depression and its associated metabolic disturbances, the significance of nutritional strategies cannot be understated. A balanced diet, rich in specific nutrients and antioxidants, has shown promise in improving mental health outcomes. Some noteworthy components include: Studies have indicated that omega-3 fatty acids, commonly found in fish like salmon, mackerel, and sardines, can have anti-inflammatory effects and play a role in brain health and mood regulation [148]. Vitamin D deficiency has been correlated with depressive symptoms in certain populations. Sun exposure and foods like fortified dairy products and oily fish can help maintain optimal levels [149]. Zinc, present in foods like beans, nuts, and whole grains, is crucial for numerous biochemical pathways. Its deficiency has been linked to mood disturbances in various research [150]. These antioxidants, abundant in fruits like berries, vegetables, and beverages like tea, have anti-inflammatory properties and can protect against oxidative stress, which has been associated with depressive disorders [151].

6. Conclusion

While inflammation is a necessary component of host defense, chronically unresolved inflammation may result in dysfunctional metabolism and neurodegeneration. The relationship between MS and MDD is bilateral. The major factors leading to these conditions include increased HPA activity, altered ANS activity, stimulation of inflammatory pathways and peripheral hormones, side effects of psychotropic drugs, and a chronic feeling of low esteem and dissatisfaction.

Other factors include an inactive lifestyle combined with unhealthy food habits, which result in obesity and insulin resistance.

The efficacy of standard pharmacological therapy in treating depression and associated diseases is limited. Synergically targeting monoamine and non-monoaminergic systems is found to be beneficial.

Further, the anti-inflammatory approach, which uses NSAIDs, statins, mAbs, or inhibiting pro-inflammatory cytokine signaling, has shown promising results in treating depression. Moreover, melatonergic agonists and 5-HT2 receptor antagonists have improved results over SSRIs or SNRIs.

Moreover, certain hormones such as T3 and T4, androgens in men, and estrogen in women have also illustrated antidepressant effects. Hence, to offer a more holistic approach in terms of treatment for depression and related disorders, pharmacological treatment may be combined with lifestyle modifications, a balanced diet, and psychotherapy.

7. Future perspectives

According to recent research, psychological stress and overeating can cause chronic low-grade inflammation that can disrupt insulin signalling and glutamate metabolism in MDD, especially in the atypical subtype. Additionally, compared to other disorders, depression receives considerably fewer consultations, and more than 90 % of patients are unable to receive a proper diagnosis and course of therapy. Given the circumstances, understanding the etiology of depression will be crucial for both diagnosing and treating depression.

To develop a novel approach to treating depression in the future, further study is required. Depression research is still extensive because of the negative effects it has on people and society, which is useful for developing cutting-edge treatment approaches.

Therefore, in addition to participant-reported measures, it is recommended that pertinent future investigations additionally include standardized diagnostic approaches for the accurate assessment of mental health comorbidity.

Author contributions

S.M., and **T.F.R:** conceptualized and proposed the literature. **S.U.D. W., S.M.:** Figure preparations, manuscript editing, and established the conditions for the literature. **S.M.,** and **K.L.K.:** Supervision. **N.K.:** Scientific Consultation.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author(s) did not use any AI Tool Service.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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