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REVIEW ARTICLE

Targeting inflammation: a potential approach for the treatment of depression

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Abstract

Major depressive disorder (MDD) or Depression is one of the serious neuropsychiatric disorders affecting over 280 million people worldwide. It is 4th important cause of disability, poor quality of life, and economic burden. Women are more affected with the depression as compared to men and severe depression can lead to suicide. Most of the antidepressants predominantly work through the modulation on the availability of monoaminergic neurotransmitter (NTs) levels in the synapse. Current antidepressants have limited efficacy and tolerability. Moreover, treatment resistant depression (TRD) is one of the main causes for failure of standard marketed antidepressants. Recently, inflammation has also emerged as a crucial factor in pathological progression of depression. Proinflammatory cytokine levels are increased in depressive patients. Antidepressant treatment may attenuate depression via modulation of pathways of inflammation, transformation in structure of brain, and synaptic plasticity. Hence, targeting inflammation may be emerged as an effective approach for the treatment of depression. The present review article will focus on the preclinical and clinical studies that targets inflammation. In addition, it also concentrates on the therapeutic approaches' that targets depression via influence on the inflammatory signaling pathways.

Keywords Cytokines · Depression · Inflammation · Oxidative stress · TNF-α

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Introduction

MDD is disorder of mood characterized by prolonged sadness, mild to severe emotional symptoms that are present persistently. Some of the symptoms are anhedonia, cognitive instability with low self-esteem and somatic symptoms like vitality loss, insomnia or hypersomnia, weight loss or gain, mental irritancy, fatigability, and suicide. More than 700 000 people die due to suicide every year. Suicide is the fourth leading cause of death in 15-29-year-old teen age and adults. The disorder affects day to day life functions i.e., quality of life and overall health status of the person. Depression may present with many comorbid CNS and metabolic disorders like anxiety, Alzheimer's disease (AD) and schizophrenia and diabetes and obesity. Approximately 05% of adults affected with depression worldwide (https://www.who.int/news-room/fact-sheets/detail/depression). The disorder with comorbid anxiety has marked impact on the worldwide economy and it is estimated that the loss of productivity linked with these disorders may charge almost US$ 1 trillion per year to the global economy (Bhatt et al. 2020). The presented data underline the severity of impact of MDD on the world's health and economy. Several factors like level of NTs and neurotropic factors (NFs), genetics, social and psychological factors, and environmental factors have important role in the progression of depression (Philips 2017). Although effective treatments available for mental disorders but over 75% of the patients are not able to receive any treatment from low- and middle-income countries. Moreover, lacking resource, trained health care workers and social hesitation is also associated with depression treatment to a great extent. Sometimes diagnosis of depression is also not appropriate i.e., it may be misdiagnosed and incorrectly diagnosed in many instances. The major treatment approaches for depression includes correction in the levels of monoaminergic NTs in the synapse. Details of the treatment will be discussed in the later section of this article. Inflammation may have crucial role in the pathogenesis of depression. Levels of inflammatory markers are increased in the brain and plasma of depressed person. Hence targeting depression may be a beneficial therapeutic strategy for the treatment of depression.

Risk factors

Various risk factors have been identified for the development of depression. Some of the important risk factors are: (1) family history and genetics; (2) chronic stress; (3) history of trauma; (4) gender; (5) poor nutrition; (6) grief or loss of near and dear ones; (7) personality traits; 8 medication and substance use. Intensity of some of the risk factor like chronic stress, poor nutrition, personality traits, grief etc. can be reduced by positive thinking and cognitive behavior therapy. Modifications or mutations in gene also identified as crucial factor for the progression of depression. Cognitive behavior therapy or family focussed therapy can be helpful in reducing chronic stress. In today's world long term stress is one of the main causes for the development of depression (https://www.healthline.com/health/depression). Accidents and trauma are one of the important risk factors for development of depression due to degeneration of neurons in the area of brain that is involved in emotions. Females are more prone to affect with depression as they are more emotional (Bremner 2006). Poor nutrition is also considered as main cause for the progression of depression. Balance healthy diet is required for proper development of brain in children. Role of brain-gut-microbiota axis is taking importance in CNS disorders as these microbiomes are helpful in the development of various NTs (Appleton 2018). Personality traits can also be changed after consultation with psychiatrists. Negative thinking and actions can be changed to positive side. Over the counter use of medications causes substance abuse should be restricted.

In addition to above risk factors obesity, hypertension, diabetes, and atherosclerosis could act as "silent contributors" promoting a chronic proinflammatory state (Sandu et al. 2015). The activation of proinflammatory cytokines may be associated with depression. These diseases showed increased levels of various inflammatory markers in plasma (Sandu et al. 2017). Moreover, these disorders are comorbid with depression. This could aggravate the outcome of various pathological entities and can contribute to a number of subsequent post-stroke complications such as dementia, depression and neurodegeneration creating a pathological vicious cycle. In obesity excess of macronutrients in the adipose tissues trigger the release of IL-6 and TNF-α and decrease the adiponectin production predisposing to a proinflammatory state and oxidative stress (Ellulu et al. 2017). Hypertension is important factor for development of cardiovascular disease and associated depression. Inflammation played important role in the development and maintenance of hypertension. Elaboration of cytokines by the inflammasome responsible for end-organ dysfunction and immune activation has been found to play a role in the genesis of hypertension (Solak et al. 2016). In addition, recent studies have suggested a central role of sodium-induced immune cell activation in the progression of hypertension by modifying the gut microbiome and formation of products of lipid oxidation known as isolevuglandins (Patrick et al. 2021). Depression affects 10–20% of patients with type 2 diabetes (T2D) and predicts twofold enhancement in complications and mortality rate (Moulton and Pickup 2018). Recent

research demonstrated that inflammation is associated with type-II diabetes mellitus (T2DM) and elevated depressive symptoms. Study participants with T2DM + MDD exhibited the highest IL-6 levels compared to all other groups. In addition, in this study increased CRP levels were observed in T2M but not elevated symptoms of depression. This suggests the complex association of T2DM, inflammation and depression (Doyle et al. 2013). One other study demonstrated the higher levels of IL-6 and CRP. Lower BDNF levels also observed in depression in T2DM (Nguyen et al. 2021). Atherosclerosis is also significantly associated with inflammation followed by depression. In atherosclerosis the deposition of cholesterol, platelets and hardening of blood vessels stimulate various peripheral inflammatory mediators (Badimon et al. 2012). High concentration of LDL is the major reason for the damage of blood vessels. The LDL is responsible for the activation of various inflammatory mediators and recruitment, adhesion and migration of leukocyte to the arterial wall (Sima et al. 2009).

Comorbid disorders with depression

Depression is a complex disorder that requires immediate attention and treatment. Various comorbid disorders such as anxiety, cognition impairment, post-traumatic stress disorder, schizophrenia, diabetes mellitus, obesity, alcohol dependence and stroke are also may be associated with depression. According to Kessler et al., patients with pure depression, i.e., without comorbidity, accounted for only one-fourth of all patients with that diagnosis (Kessler et al. 1996). According to a worldwide survey 45.7% of individuals with lifetime depression has a life history of one or more anxiety disorder (Kessler et al. 2015). Anxiety is highly comorbid with depression and some of the common preclinical models such as olfactory bulbectomy, traumatic brain injury can be used to evaluate comorbidity of both the disorders. Cognitive dysfunction means deficits in attention, learning abilities, memory, visual and auditory processing, problem solving abilities and speed as well as motor activities (Lam et al. 2014). Cognitive impairment is observed in the patients affected with long term depression. Cognitive deficits in MDD are consistent, replicable, non-specific and clinically significant. The degree of cognitive deficits has been exhibited to be proportionate to the frequency of depressive episodes and duration of illness (Zuckerman et al. 2018). Post-traumatic stress disorder (PTSD) is associated with depression. Areas of brain associated with stress response are amygdala, hippocampus, and prefrontal cortex (McEwen et al. 2016). Traumatic stress may lead to do some changes in the brain areas. It is associated with increased cortisol levels due to long term stress. Approximately 50% of the people with PTSD also suffer from depression. Treatments that are efficacious for PTSD show a promotion of neurogenesis in preclinical studies, as well as promotion of memory and increased hippocampal volume in PTSD. (Flory and Yehuda 2015). There are chances to decrease in the levels of 5-HT and DA in the affected area due to degeneration of neurons (Albert 2015). Patients with schizophrenia are frequently affected by comorbid depression during their total illness duration. Around 25% of people diagnosed with schizophrenia meet the depression criteria. Comorbidity of depression with schizophrenia makes the patient's condition more worsen and disabling course and poor outcome (Ayano et al. 2015). The symptom of depression occurs throughout all the phases of the illness including psychotic episodes and may be linked with hopelessness (Harvey et al. 2017). Metabolic disorders like diabetes mellitus and obesity are highly comorbid with depression. Occurrence of depression is 2–3 times more in the people affected with diabetes mellitus. Most of the cases remaining underdiagnosed (Bădescu et al. 2016). Comorbid patients are associated with poor outcomes (Darwish et al. 2018). Similarly, obesity is very common in the patients affected with depression. The normal activity of the patients with depression is reduced and this leads to increase in body mass index (Ball et al. 2009). A meta-analysis of 19 studies showed a bidirectional relationship between depression and obesity (Mannan et al. 2016). In the above-mentioned study people who were depressed had a 37% increased risk of being obese, and people who were obese had an 18% increased risk of being depressed. Overall, the presence of depression and obesity, along with each other, is associated with more negative health outcomes (Almarhoon et al. 2021). Alcohol dependence is also associated with depression to a great extent. The prevalence of depression among alcohol-dependent persons is high (63.8%) with a significant association between depression and the mean AUDIT score (Kuria et al. 2012). People with depression get into consumption of alcohol to get euphoric effect for time being. On the contrary drinking makes depression worse. People those are depressed with drinking habits have more chances to get severe episodes of depression and enhancement in their suicidal tendency is observed (Pompili et al. 2010). Patients with stroke also affected with co-morbid depression or mood disorders. These disorders have bidirectional association. Patients with depression are at greater risk of developing major metabolic diseases that may in turn lead to stroke. Moreover, depressive symptoms and consumption of antidepressants also associated with the risk of stroke (Li et al. 2012). The mechanism responsible for these underlying late-onset neuropsychiatric and neurocognitive symptoms have received little importance so far in the field of neurobiology. The aged animals fail to recover over younger one after stroke. The development of infract is much faster in old age rats in first 3 days. In the study it was found that

the expression of serotonin receptor type B mRNA was markedly increased in the perilesional area of aged rats as compared to the younger counterparts. In addition, histologically, HTR2B protein expression in degenerated neurons was linked with activated microglia in aged rats as well as human subjects. Treatment with fluoxetine attenuated the expression of Htr2B mRNA, stimulated post-stroke neurogenesis in the subventricular zone and was associated with an improved anhedonic behavior and an increased activity in the forced swim test in aged animals (Buga et al. 2016) Stroke may be involved in progression of depression or vice versa via modulation of inflammatory pathways and increase in the levels of inflammatory mediators. However, further some studies need to be done to confirm the above statement.

Diagnosis and treatment

Diagnosis of depression requires five or more symptoms according to Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) (Tolentino and Schmidt 2018). Depressed mood and anhedonia or loss of pleasure activity is one of the main criteria. However, the secondary symptoms of MDD can be divided into somatic and non-somatic groups, the DSM-5 detect MDD in all or none way. In contrast, severity of depression varies continuously. Therefore, it is commonly assessed with scales such as the Hamilton Depression Rating Scale (HAMD) (Vindbjerg et al. 2019; Hamilton 1967).

Treatment of depression depends on the severity of the disease episodes. Health care professionals may provide psychological treatments like behavioural activation, cognitive behavior therapy, interpersonal psychotherapy and family focussed therapy (Uphoff et al. 2020; Driessen and Hollon 2010). The above treatment approaches are very effective in the treatment of depression without administering the adverse effects of medications. Most of the approaches change the thought process of the patient from negative direction to positive side. Based on the change in thought process action also changes. In addition, some other non-pharmacological approaches like electroconvulsive therapy, transcranial magnetic stimulation, deep brain stimulation, vagal nerve stimulation and light therapy is also used to treat various forms of depression based on the severity (Blumberger et al. 2015; Muller et al. 2018). Pharmacological treatment approach is predominantly based on the modification of NTs levels in the synapse. The medications used widely are selective serotonin reuptake inhibitors (SSRIs), Tricyclic antidepressants (TCAs), Serotonin norepinephrine reuptake inhibitors (SNRIs), Norepinephrine reuptake inhibitors (NRIs), Norepinephrine dopamine reuptake inhibitors (NDRIs) and atypical antidepressants (Kupfer 2005). The major problem with the above-mentioned approaches is treatment resistance in depression. Other drawback is most of the antidepressants takes more time to show its action as the drugs are working through modification of receptors and synthesis of new NTs takes time.

Pathophysiology of depression

Some of the important factors involved in the pathogenesis of depression are;

Genes and psychological stress

Family, twin, and adoption studies provide the strong evidence that depression is a familial disorder and modifications in gene(s) is seen in the pathological progression of depression (Sullivan et al. 2000 reported genetic factor is involved in 30–40% cases of depression. While remaining 60–70% cases have non-genetic influence such as environmental factors, stress, inflammation, sexual abuse in childhood, other lifetime trauma, low social support, marital problems, and divorce etc. (Kendler et al. 2002, 2006). Genes such as SLC6A4 (previously known as SERT), DRDR4, SLC6A4 or 5-HTT and TPH2 are also found to have marked impact on the pathogenesis of depression (Shadrina et al. 2018). Disturbance in the expression of genes is involved in antigen neutralization, autoimmunity, neural plasticity, stress response, signal transduction at the neurovascular unit, dysregulated nuclear RNA processing and translation and epigenetic imprinting signatures is associated with suicide and point to regulatory non-coding RNAs as potential targets of new drugs development. Most of the identified gene expression changes were linked to region-specific dysregulated manifestation of genetic and epigenetic mechanisms underlying neurodevelopmental disorders (Glavan et al. 2021).

Stress is also had predominant role in pathological progression of depression. Depression progression that is associated with stress is linked with gender to some extent. Men have more probability to have MDD episodes following divorce, paternal separation, and difficulties in workplace on the other hand women are more responsive to events in social connections, such as difficulty getting along with an individual, serious illness, or death (Kendler et al. 2001). Two hormones namely norepinephrine (NE) and cortisol are involved in the management of stress. NE is important for management of acute stress and cortisol is involved in the management of chronic stress. In depressed patients, there is high level of cortisol is observed due to dysregulation or improper functioning of hypothalamic-pituitary-adrenal (HPA)-axis and negative feedback mechanism. Corticotropin-releasing hormone (CRH) is released from the hypothalamus part of brain due to stress-like stimulus (Menke 2019). This factor is responsible for release of corticotropin

from anterior pituitary gland, which stimulates the adrenal gland to release cortisol into the plasma. Women are more susceptible to stress as compared to men (Young 1998).

Cytokines in depression

One of the symptoms of depression is sickness like or flu like behavior of patient. The sickness like behavior represents activation of inflammatory pathways. The inflammatory pathways demonstrate many aspects of depression including tiredness, loss of pleasure, retardation in psychomotor activities, and cognitive impairment. Sickness is mediated by the presence pro-inflammatory cytokines such as interleukin-1α, tumor necrosis factor-α, and interleukin-6. These mediators activate the HPA axis and impair the central serotonergic system (Dantzer et al. 2008). Some of the antidepressants like SSRIs additionally increase the levels of serotonin (SER) or 5-hydroxytryptamine (5-HT) in synapse also affect the levels of inflammatory markers. In animals, blocking pro-inflammatory cytokine-mediate signaling produces antidepressant-like effects (Krishnan and Nestler 2008). Bhatt et al. 2017a, b, also presented the lipopolysaccharide (LPS) induced anxiety model. LPS is an endotoxin that induces depression and comorbid anxiety like symptoms in animals. The symptoms are induced through the modification of inflammatory pathways (Bhatt et al. 2017a, b). Clinical data suggest that cytokines may play a role in the pathophysiology of a subgroup of depressed subjects, particularly those with comorbid physical conditions (Dantzer et al. 2008). The antidepressant enhancing effect of acetylsalicylic acid points to the possible clinical relevance of psychoneuroimmunology in clinical depression research (Berk et al. 2020).

Monoamines and other NTs in depression

The most acceptable theory of depression is monoamine theory. Monoamine theory states that decrease in the levels of NE, 5-HT, and dopamine (DA) have been taken place in the different regions of brain i.e., amygdala, hippocampus, hypothalamus in depression (Boku et al. 2018). The above three NTs are involved in various activities such as pleasure, mood, alertness, motivation, reward, obsessions and compulsions, sexual activities, attention, concentration are some of the important one. Mainly the antidepressants used in this category are working through the modification in the levels of monoamine NTs in synapse. Inhibiting the enzyme monoamine oxidase, which induces an increased availability of monoamines in presynaptic neurons, also has antidepressant effects (Belmaker and Agam 2008). In addition, γ-amino butyric acid (GABA) and glutamate also have marked role in the pathogenesis of depression. GABA is inhibitory and Glutamate is excitatory NTs of CNS. GABA is predominantly involved in emotions and Glutamate is involved in synaptic plasticity and long-term potentiation (Lener et al. 2017). A series of magnetic resonance spectroscopy studies consistently demonstrated reductions in total GABA concentrations in the prefrontal and occipital cortex in acute depression (Hasler et al. 2007a, b). Moreover, chronic stress may reduce the function of GABA-A receptor, possibly through the modifications in neuroactive steroid synthesis (Eser et al. 2006).

Few antidepressants are working through modification of these NTs. A single dose administration of the glutamate N-methyl-D-aspartate (NMDA) receptor antagonist ketamine produced fast and predominant antidepressant effects in patients with TRD. Moreover, inhibitors of glutamate release (e.g., lamotrigine, riluzole) also demonstrated antidepressant properties (Zarate et al. 2006; Kendell et al. 2005). However, most of the marketed drugs target these monoaminergic NTs. The main drawback of available treatments is delayed onset of action and treatment resistance. Despite this limitation, the monoamine-deficiency hypothesis has proved to be the most clinically relevant neurobiological theory of depression.

Oxidative stress in depression

Brain is highly vulnerable organ via increased oxidative stress due to its high metabolic demand and oxygen consumption. Excessive formation of ROS and exhaustion of the antioxidative defences stimulate proinflammatory transduction pathways followed by damage to vital macromolecules like protein, fat and DNA and induces apoptosis. In addition, excessive production of inflammatory marker IL-1 and IL-18, formation of cellular pores in cell membrane, leakage of the substances from the cells and leads to cell death (Wooff et al. 2019; Kopschina Feltes et al. 2017). Increase in oxidative stress also leads to alter in brain physiology, neuronal plasticity, and reduction in volume of hippocampal and frontal cortex area. Various preclinical and clinical studies are also suggested that increased generation of reactive oxygen species (ROS) and exhaustion of the antioxidative defences are responsible for the altered brain structure. This is known as oxidative stress hypothesis of MDD (Michel et al. 2004, 2007, 2010). Along with elevation in oxidative stress markers, the stimulation of proinflammatory signalling pathways also contributes to the pathological progression of MDD (Bakunina et al. 2015). Both the process finally leads to activation of apoptotic pathways and cell death. Decrease in the activity of anti-oxidant enzymes like Glutathione Peroxidase (GPX), catalase (CAT) and superoxide dismutase (SOD) is observed in depression (Bhatt et al. 2020). NF-κB regulates the activation, differentiation and effector function of inflammatory T cells and NF-κB activation is also regulated by the ROS production. The importance of NF-κB, HPA axis and stress in activation of neuroinflammation have been shown in Fig. 1.

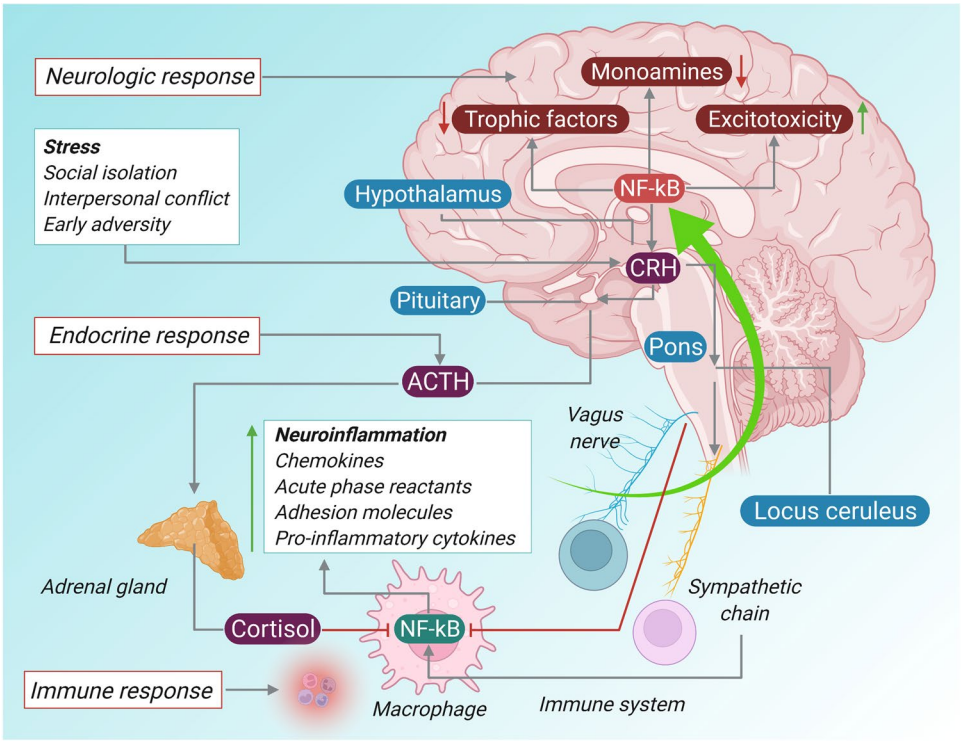

Fig. 1 The importance of NF-κB, HPA axis and stress in activation of neuroinflammation

Neurotrophic factors (NFs) in depression

Consistent evidence is available for the change in volume of hippocampus and other regions of brain is associated with duration of depression. These changes suggested that untreated MDD leads to reduction in hippocampal volume, possibly resulting in enhanced stress sensitivity and increased risk of recurrence (Hasler et al. 2007a, b; 27, Sheline et al. 2003; Frodl et al. 2008). The possible mechanism explains the reduction in brain volume may have combination of endogenous components like glucocorticoid and glutamatergic neurotoxicity, decreased NFs like brain derived neurotrophic factor (BDNF), and decreased neurogenesis. Various preclinical studied have shown decrease in the levels of BDNF in depression and increased expression of BDNF following antidepressant treatment (Gustafsson et al. 2021; Jindal et al. 2015, also reported antidepressant effect of etazolate, a phosphodiesterase-4 enzyme inhibitor in olfactory bulbectomy induced depression model in rats. Treatment with etazolate leads to increase in the cAMP, phosphorylated CREB (pCREB), and BDNF levels. Additionally, they also reported the increased in the levels of anti-oxidant enzymes followed by the treatment of etazolate (Jindal et al. 2015; Bhatt et al. 2017a, b, reported decrease in the levels of BDNF in rats was corrected by the treatment of 6n, a 5-HT_3 receptor antagonist in traumatic brain injury model of depression and comorbid anxiety (Bhatt et al. 2017a, b).

Circadian rhythms in depression

Proper circadian rhythms are important for normal brain functions. Disturbance in light and dark cycle leads to development of untoward stress followed by depression. Disturbances in sleep and fatigue are included in diagnostic criteria of depression (Germain and Kupfer 2008). Our mood changed during different phases of a day and hormones and NTs levels are also varied during a day. In addition, some depressive symptoms may show diurnal variations (mood, psychomotor activity, accessibility of memories of positive and negative experiences), and a subgroup of patients with MDD may have a circadian rhythm disorder. Disturbance in light and dark cycle of the animal also leads to production of excessive stress followed by depression. This is associated with excess of cortisol release followed by disruption of HPA-axis in chronic course (Bhatt et al. 2014). Effectiveness of melatonin receptor (M_1 and M_2) agonist, agomelatine also indicate the importance of circadian rhythm in the treatment of depression.

In recent studies dysregulation in sleep has been observed as an important factor for development of attention deficit hyperactivity disorder (ADHD) (Coogan et al. 2016). The abnormality in circadian rhythmicity may also contribute for the progression of depression. Insomnia and hypersomnia is one of the important symptom of depressed patient and abnormality in sleeping leads to development of abnormality in circadian rhythmicity followed by depression. Depressed patient often show change in circadian rhythms,

sleep dysregulation, and mood variation throughout the day. Antidepressants have marked effects on circadian processes and sleep (Germain and Kupfer 2008). Various melatonin receptors agonists (ramelteon, prolonged-release melatonin, agomelatine and tasimelteon) have recently become available for the treatment of insomnia, depression and circadian rhythms sleep-wake disorders (Laudon and Frydman-Marom 2014). The circadian rhythm regulates various important physiological processes and maintains cellular, tissue, and systemic homeostasis. Disruption of machinery of circadian clock influences key activities involved in immune response and brain function. It also has great influence on normal inflammation and neurodegeneration (Wang and Li 2021). However, further studies are required to associate the relationship of abnormality in circadian rhythmicity with inflammation and followed by depression.

Association of depression and inflammation

Inflammation is having great influence on the progression of depression or MDD. Though, this parameter is not studied well as a point of view of target selection for the treatment of depression. Use of anti-inflammatory drugs may be an important approach for the treatment of depression. Immune response i.e., innate, and adaptive response is associated with the MDD pathophysiology. The immune component hampers the favourable prognosis of MDD (Lee and Giuliani 2019). Presence of anti-inflammatory drugs may also improve the effectiveness of standard antidepressant medications. Major drawbacks of antidepressants are that they are taking more time to show its action and resistance to the treatment develop after chronic use of the drugs. These two drawbacks may be avoided or reduced by using anti-inflammatory drugs. Increased in the level of cytokines for long term produce impairment of NTs signaling and disruption of their synthesis, reuptake, and release process. In brain microglia and other brain cells have critical role in the physiology of CNS such as neuroplasticity (Miller et al. 2013). Excess in the levels of cytokines for long term leads to dysregulation in the synthesis and release and reuptake of NTs. Recent evidence indicated the role of microglial cells in neurogenesis and pruning of synapse. Microglial cells have important role in neuronal inflammation and get charged in various neurodegenerative diseases. However, more detailed research is needed to get proper idea on the impact of microglia in the progression of depression and other functions of brain and disorders. Based on the above facts we can assume that control of inflammation may be a useful therapeutic approach for the treatment of depression (Wang et al. 2015a).

Cytokines in depression

Activation of microglia, inflammation, long-term stress and increased proinflammatory cytokines also activates HPA-axis. The resultant imbalance in serotonergic and noradrenergic pathways facilitates the onset as well as recurrence of depression. Elevated levels of cytokines such as IL-6, TNF-α, and IL-1β enhance indoleamine-2,3-dioxygenase activity, catalysing biotransformation of tryptophan and depleting SER (Kopschina Feltes et al. 2017). It has been hypothesized that increased levels of inflammatory cytokines stimulate different structures in brain like prefrontal cortex, hippocampus, anterior cingulate cortex, and basal ganglia. Activation of these brain structure leads to change in behaviour in depressed individuals (Nerurkar et al. 2019). Patients not responding to antidepressant therapy are more likely to have elevated cortisol and pro-inflammatory markers (Carvalho et al. 2013; Belleau et al. 2019). Hence, targeting inflammation may be considered as useful approach to target TRD cases.

Inflammation is also associated with increased production of reactive oxygen species i.e., oxidative stress (Liguori et al. 2018). Increase in the oxidative stress leads to stimulation of various proinflammatory mediators. Production of inflammatory marker IL-1 and IL-18, formation of cellular pores in membrane, leakage of the substances, stimulation of various apoptotic factors and finally the death of neuronal cells. Degeneration of these neuronal cells results in depression (Kany et al. 2019). The patients affected with depression have exhibit higher levels of IL-1, IL-6, TNF-α, and C-reactive protein (CRP) compared to non-depressed individuals. The major inflammatory mediators like interleukin (IL)-1β, interleukin (IL)-1 receptor antagonist (RA), interleukin (IL)-6, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ, have been recently found to be linked with the brain and influence signaling of nerve cells, physiology of neuroendocrine system, and brain, thereby inducing the changes in the emotional, cognitive, and behavioural setup (Ng et al. 2018; Osimo et al. 2020). One study observed higher CSF levels of IL-1beta, lower IL-6, and no change in TNF-alpha in depressed subjects compared to controls. In addition to above facts, long-term stress is also associated with inflammation followed by depression (Levine et al. 1999). Another study reported no change in cytokines between depressed and normal healthy subjects but did observed relationships between cytokines and depressive symptoms both before and after the treatment of antidepressant (Martinez et al. 2012). In addition, elevated levels of the inflammatory mediator, prostaglandin E2 (PGE2), have been found in the saliva, plasma, and CSF of depressed subjects (Ohishi et al. 1988) (Nishino et al. 1989). Subjects with MDD have shown increased IL-6 production and increased nuclear factor (NF)-kB in peripheral blood mononuclear cells compared to non-depressed controls (Pace et al. 2006). Similarly, depressed subjects demonstrated a decreased ability for glucocorticoids to inhibit inflammatory cytokine production following exposure to a mock interview stressor compared to controls (Miller et al. 2005). Induction of chronic unpredictable mild

stress to mice is responsible for increase in the level of oxidative stress markers and inflammatory markers followed by depression. The administration of long-term stress to animals leads to increase in the levels of nitrates and peroxides and decrease in the levels of catalase, superoxide dismutase and reduced glutathione. Individuals exposed to early life adversity (ELA) exhibit pronounced increased in the levels of proinflammatory cytokines. Targeting stress and inflammation may be emerge as an important strategy for the treatment of depression.

Treatment strategy for depression targeting inflammation

Fortunately, multiple evidence indicated the role of inflammation with the involvement of innate and adaptive immune system in the pathophysiological progression of depression, hence targeting inflammation may be considered as prominent strategy for the treatment of depression as per preclinical and clinical point of view. Various drugs have anti-inflammatory effect can be evaluated for their anti-depressant potential in rodent and human models of depression. The main purpose of this review is to develop a relationship between inflammation and depression and to evaluate current immunotherapies for their antidepressant potential.

Antidepressants on inflammation

There is evidence that antidepressant drugs are also working through the modification of inflammatory mediators' level in the brain and blood. In addition to affect the level of NTS in the brain they act through the modification in the glial cells signaling which are the main origin and targets of cytokines and other mediators of inflammation in the brain (Hashioka et al. 2009). The presence of inflammatory condition in depressed patient affects the outcomes of the antidepressant treatment. In the above situation addition of some anti-inflammatory agent as an add on treatment will be an important approach for the treatment of depression (Hannestad et al. 2011; Arteaga-Henríquez et al. 2019).

Various evidence suggested the role of SSRIs and SNRIs in change in the inflammatory pattern. Some studies reported that modification in the levels of proinflammatory cytokines like TNFα and anti-inflammatory cytokines like IL-10 is takes place in mice (Ohgi et al. 2013). Treatment with standard antidepressants and 5-HT_3 receptor antagonist in LPS induced depression and anxiety model reduces the oxidative stress of the mice and showed their effectiveness in behavioural models (Bhatt et al. 2017a, b). Administration of bacterial endotoxin LPS leads to flu-like symptoms in the animals, which are like that of depression symptoms. LPS mainly acts via enhancing the activity of indoleamine 2,3-dioxygenase (IDO) and kynurenine pathway. IDO is macrophage extrahepatic enzyme that metabolize tryptophan amino acid along with kynurenine pathway. This enzyme is responsible for induction of proinflammatory cytokines like interferon-gamma (IFN-γ) and TNFα. When IDO is activated in conditions of chronic inflammation, its degree of activation is correlated to the intensity of depressive symptoms, as observed in cancer patients (O'Connor et al. 2009). Moreover, *invitro* studies demonstrated the effectiveness of clomipramine and fluoxetine, in reducing the levels of IL-6, IFN-γ, TNF-α on contrary mirtazapine and venlafaxine are linked with increase in their activity (Baumeister et al. 2016). In addition, antidepressant drugs like mianserin a tetracyclic antidepressant also produces anti-inflammatory activity by inhibiting toll-like receptor 8 (TLR-8) signaling (Sacre et al. 2019).

Anti-inflammatory drugs on depression

Aspirin

Some preclinical data indicated the antidepressant potential of Aspirin, an inhibitor of both COX-1 and COX-2). The above results were further supported by limited observational data suggested low rates of depression in the subjects administered with Aspirin. Bhatt et al. 2016, reported that the rats administered with aspirin exhibited increased preference to sucrose, reduction in immobility time in forced swim test (FST), decreased level of serum cortisol, and increased brain SER levels signifying antidepressant action (Bhatt et al. 2016). In an 8-weeks randomized clinical trial study in the patients of depression 160 mg add-on to sertraline (n = 50) showed significant reduction in depression scores as compared to placebo. The combination approach also addressed the issue of TRD (Muller 2019). The response rate is also improved in sertraline + aspirin treated group as compared to sertraline + placebo group. In contrast, outcomes of a placebo controlled, and double-blind clinical trial demonstrated that Aspirin did not show antidepressant potential (Berk et al. 2020).

Celecoxib

Celecoxib, an inhibitor of COX-2 enzyme, is belong to NSAID category, that has potential to treat depression. Acute administration of celecoxib (10 mg/kg) and piroxicam (10 mg/kg) in the modified FST and sucrose preference test in rats to produce antidepressant like effect. In addition, the above drugs also modified the reduced glutathione and SOD levels in the hippocampus of the treated animals.

The results from the above study suggested that the antidepressant-like effects of anti-inflammatory drugs might be involved in antioxidant defense and decrease oxidative stress in the hippocampus (Santiago et al. 2014). In addition, bupropion in combination with celecoxib also shown the antidepressant and anti-inflammatory effect in the mice treated with Complete Freund's Adjuvant (CFA; 50 µl/paw) intraplantar injection (Maciel et al. 2013). The previous trials suggested the use of celecoxib as an additional treatment to benchmark anti-depressants for the treatment of depression (Fourrier et al. 2018). Recent meta-analyses indicated the role of celecoxib in increased efficacy of antidepressant. Augmentation of medications used for depression with celecoxib showed a better efficacy of antidepressants by a standard mean difference (SMD) of 0.82 (95% confidence interval [CI]: 0.46–1.17) and without heterogeneity between the studies (I2 = 0%) (Kohler et al. 2014). Celecoxib has been shown to significantly alleviate depressive symptoms as an augmenting agent. It modifies the clinical symptoms of depression in rheumatoid arthritis patient without significant effect on the pain (Al-Baz and Karim 2020). In addition, long-term treatment with celecoxib attenuated depressive-like behavior and predominantly reversed biochemical parameters associated with obesity in mice (Kurhe et al. 2014; Kohler et al. 2014, demonstrated that addition of celecoxib to reboxetine markedly lower HAM-D (Hamilton Depression Rating Score) scores compared with controls (Kohler et al. 2014). Halaris et al., emphasized the role of celecoxib in the management of depression and anxiety in patients with bipolar TRD. Recent RCT conducted by Halaris et al.'s emphasized the role of celecoxib as safe and efficacious drug in the management of anxiety and depressive symptoms in patients with bipolar TRD (Halaris et al. 2020). Celecoxib has also demonstrated efficacy in alleviating depressive symptoms in brucellosis and patients affected with colorectal cancer (Al-Baz and Karim 2020). The celecoxib produces its antidepressant effect by reducing the levels of inflammatory markers like IL-6 and CRP. The above statements support the role of inflammation in the etiology of depression (Halaris et al. 2020; Abbasi et al. 2012).

Etanercept

Treatment of the rats for 8 weeks with TNF-α inhibitor, etanercept ((0.8 mg/kg/week, subcutaneously) predominantly decreased the duration of immobility in rat model of despair test and produce antidepressant effect. In addition, treatment also showed significant antianxiety effect using elevated plus maze without affecting the locomotion activity significantly (Bayramgürler et al. 2013). Moreover, administration of etanercept to Corticosterone treated rats reduce the duration of immobility in FST as well as improve the memory of the treated animals. Etanercept restore performance, neurogenesis of hippocampus and GABAergic plasticity and indicated that a normalization of expression of reelin in the dentate gyrus could be a critical component that me be responsible for these novel antidepressant effects (Brymer et al. 2018). In human trials, treatment with etanercept in patients affected with inflammatory disorder such as psoriasis was linked with decreased symptoms of depression and improved quality of life of the patients (Tyring et al. 2006). The above finding strengthens the hypothesis that TNF-α has a role in the modulation of emotional process and inhibition strategy may act as a novel strategy for the cure of depression and other CNS disorders.

Infliximab

Treatment with infliximab, a TNF-α inhibitor may be helpful in the reduction of depression in patients having high level of proinflammatory markers. TNF antagonism does not have generalized efficacy in TRD but may reduce symptoms of depression in patients with high baseline levels of biomarkers responsible for inflammation (Raison et al. 2013). Infliximab (Remicade®) is an infusion style drug approved by the FDA for the treatment of conditions linked with inflammation such as like crohn's disease and rheumatoid arthritis. Ersozlu Bozkirli et al. 2014 reported the effects of Infliximab administration on depression, anxiety, and sleep disorders in patients with ankylosing spondylitis (Ersozlu Bozkirli et al. 2014). On contrary a retrospective, observational study conducted by Thillard et al. 2020, confirmed that infliximab treatment is linked with elevated risk of psychiatric adverse events (Thillard et al. 2020).

Ketamine

Ketamine is well known N-methyl-D-aspartate (NMDA) receptor channel blocking drug. Ketamine showed antidepressant effect by repression of proinflammatory cytokines signaling in the hippocampus of rats in CUMS induced depression model. CUMS generated depression like behavior was reversed in the rats by ketamine as observed using FST. In addition, the hippocampal levels of IL-1β, IL-6, TNF-α, IDO, and the KYN/TRP ratio were mitigated by a sub-anaesthetic ketamine dose (Wang et al. 2015b). Another study has shown the antidepressant-like effect of ketamine but same time it worsened working memory but influenced pro-cognitive effects at later (McDonnell et al. 2021). It is approved by FDA for use as anaesthetic in 1970. Nasal spray of ketamine called Esketamine (Spravato) is approved for the treatment of depression out from several available forms. For TRD, patients usually administered with nasal spray twice a week for first 4 weeks; then once a week for weeks 5 to 9; and then once week or 2 after that. Ketamine works by modulation of glutaminergic signaling. Glutamate is the excitatory NTs in the brain that have role in excitotoxicity,

synaptic plasticity, and long-term potentiation. It also activates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors BDNF and mechanistic target of rapamycin (mTOR) signaling pathways to stimulate synaptic plasticity (Aleksandrova et al. 2017). Rapamycin in combination with ketamine may affect inflammation of neurons *via* its immunosuppressant mechanisms or by promoting homeostasis of synaptic density (Matveychuk et al. 2020).

Minocycline

Emerging evidence suggest the antidepressant-like effect of minocycline in animal model like FST and human studies. Minocycline showed effectiveness as neuroprotective and anti-inflammatory agent (Pae et al. 2008). Minocycline may be specifically helpful in patients affected with depression and cognitive impairment. Minocycline can be used as an immunomodulatory therapy for TRD cases. A pilot trial conducted by Husain et al. 2020; of the tetracycline, minocycline as adjunctive therapy in TRD, produced promising outputs, however, a bigger trial is needed to validate the antidepressant potential of this drug (Husain et al. 2020; Schmidtner et al. 2019 reported that effect of minocycline is dependent on sex- and trait are related to a reduced number of microglia in the prefrontal cortex, and with alterations in composition of microbes well as their metabolites. These reports are in support with the microbiome-gut–brain axis as strong target in the treatment of MDD (Schmidtner et al. 2019). Figure 2 in general shows the effect of anti-inflammatory drugs on glutamate, BDNF and monoamines.

Chemistry of some anti-inflammatory drugs having effect in depression

The chemical structures of selected anti-inflammatory agents which displayed antidepressant properties are given in Fig. 3.

Chemistry of aspirin

Aspirin was discovered by hoffman in 1897 (Hoffmann and Förster 1987), it is salicylic acid derivative also known as acetyl salicylic acid and abbreviated as ASA. Chemically, aspirin is named as 2-acetoxybenzoic acid, the molecular formula and molecular weight is $C_9H_8O_4$ and 360.31 gram/mol, respectively. According to the Biopharmaceutics Classification Scheme, aspirin is classified as class I drug. Aspirin is first converted into salicylic acid, which is then metabolised into gentisic acid (GA), salicyluric acid (SUA), salicyl acyl glucuronide (SAAG), salicyl phenolic glucuronide (SAPG), salicyluric acid phenolic glucuronide (SUAPG) and gentisuric acid (GUA) (Li et al. 2017). The salicyluric acid (SUA) is the major metabolite identified in urine, when the patients are treated with daily dose over 600 milligrams (Li et al. 2017).

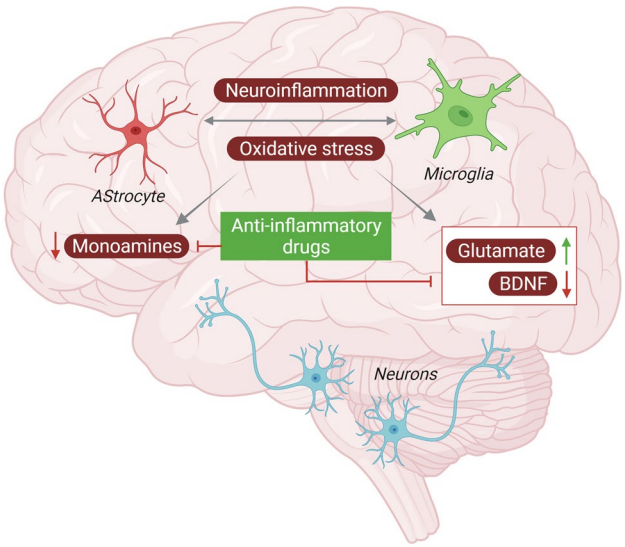

Fig. 2 Demonstrates the effect of anti-inflammatory drugs on glutamate, BDNF and monoamines

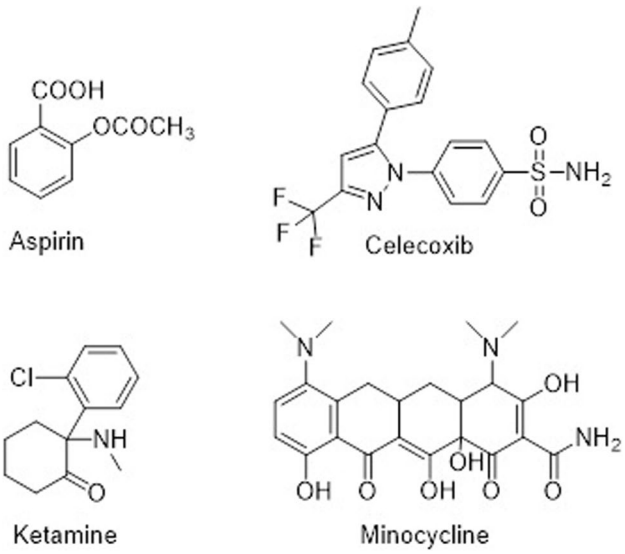

Fig. 3 Chemical Structures of Selected anti-inflammatory agent

Chemistry of celecoxib

Celecoxib is a sulphonamide derivative, chemically it is called 4-[5-(4-methylphenyl)-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide, with the molecular formula $C_{17}H_{14}F_3N_3O_2S$ and molecular weight of 381.373 gram/mol. Celecoxib is hydrophobic, poorly soluble in water and categorized into class II drug as per Biopharmaceutics Classification Scheme (Günaydın and Yılmaz 2015). Celecoxib is oxidized to hydroxycelecoxib by CYP2C9 and CYP3A4. It is further oxidized by alcoholdehydrogenase enzymes (ADH1 and ADH2) to form

carboxycelecoxib. This metabolite on conjugation with glucuronic acid affords 1-*O*-glucuronide; all the metabolites of celecoxib are inactive forms (Li et al. 2012).

Chemistry of etanercept

Etanercept is a protein molecule, obtained by recombinant DNA technology; it is consisting of ^{934} amino acids with molecular weight of 51235.07 gram/mol (Molta, Etanercept (2007). Etanercept is a dimeric fusion protein molecule, composed of extracellular ligand-binding domain of the human 75-kDa TNF-α receptor fused with the Fc portion of human immunoglobulin (Ig) G1. Etanercept is metabolized by either peptide or amino acid degradation pathways. The metabolites (amino acids) of etanercept may be recycled or eliminated through the urine or bile (Molta, Etanercept (2007).

Chemistry of infliximab

Infliximab is a monoclonal antibody produced by the fusion of 25% of murine antibody and 75% of human antibody by genetic engineering. It is composed of 597 amino acids and approximate molecular weight is 149,100 Daltons (Lissy de Ridder et al. 2007; Nahar et al. 2003).

Chemistry of ketamine

The ketamine is a cyclohexanone derivative, chemically it is known as 2-(2-chlorophenyl)-2-(methylamino)cyclohexan-1-one. The molecular formula and molecular weight of ketamine is $C_{13}H_{16}ClNO$ and 237.73 gram/mol, respectively. Keatmine is soluble in both water and lipid and it rapidly penetrates the CNS. It is widely used drug for general anaesthetic and potent analgesic activities (Mion and Villevieille 2013). The ketamine exists in racemic form, the s-enantiomer of ketamine is called esketamine and it is the most active stereoisomers. The norketamine, hydroxynorketamine and 5,6-dehydronorketamine are the active metabolites of ketamine (Dinis-Oliveira 2017).

Chemistry of minocycline

Minocycline is second-generation tetracycline antibiotic, chemically it is called (4 *S*,4*aS*,5*aR*,12*aR*)-4,7-bis(dimethylamino)-1,10,11,12*a*-tetrahydroxy-3,12-dioxo-4*a*,5,5*a*,6-tetrahydro-4 *H*-tetracene-2-carboxamide. The molecular formula and molecular weight of minocylcine is $C_{23}H_{27}N_3O_7$ and 457.48 gram/mol, respectively. The 50% of the minocycline is metabolized into inactive metabolites by liver and eliminated through faeces and urine. The 9-hydroxyminocycline is the principal metabolite of minocycline followed by two other main metabolites, namely mono-*N*-demethylated derivatives (*N*-desmethylminocycline and N_4-desmethylminocycline (Kenneth et al. 2006).

Risk and benefits of Cyclooxygenase-1 (COX-1) and Cyclooxygenase-2 (COX-2) Inhibitor-and their effect on depression via modulation of cytokine activity

COX enzyme is responsible for the synthesis of prostaglandins. COX-1 enzyme is having role in physiological 'housekeeping' functions and COX-2 is inducible enzyme (Zidar et al. 2009). Most of the NSAIDs inhibits COX-1 and COX-2 enzymes non-selectively. The inhibitors are having anti-inflammatory, anti-pyretic, analgesic effects, and anti-depressant-like effect. Though these inhibitors produce certain toxicities like damage of gastric mucosa, bleeding, sodium, and water retention, delay in labour, anaphylactoid reactions are important ones. Suppression of COX-1 also inhibit inflammation, but selective COX-2 inhibitors are more preferred due to less side effects (Zarghi and Arfaei 2011). Recent research has suggested the importance of COX-2 inhibition as a potential approach for the treatment of depression. Excessive ROS production is associated with the expression of COX-2. According to a preclinical study, classical COX-2 inhibitors, and a newly developed substrate-selective COX-2 inhibitor reduce a variety of stress-induced behavioural pathologies in mice (Gamble-George 2016). Inhibition of COX-2 reduces depression-like behaviors via suppressing glial activation, oxidative stress and apoptosis of nerve cells in rats. COX-2 inhibitor celecoxib decreases the levels of pro-inflammatory cytokines such as IL-1β and TNFα and significantly increase IL-10 levels in rodent models (Sethi et al. 2019). In addition to above effects inhibition of COX-2 enzyme is associated with reduction in indoleamine 2,3-dioxygenase (IDO) activity and simultaneously leads to reduction in glutamine-induced excitoxicity. Moreover, the increased expression of COX-2 and IDO1 is linked with excessive production of prostaglandin (PG)E_2 and kynurenines, respectively (lachininoto et al. 2013).

Conclusion

The inflammatory signaling pathways and its mediators may have significant contribution in the pathogenesis of depression. Targeting inflammation can be emerged as a potential approach for the treatment of depression. Anti-inflammatory drugs can be used as a mainstay of treatment or as add-on

treatment with other benchmark antidepressant drugs. Anti-inflammatory drugs also target the increased oxidative stress and reactive oxygen species production and hence have marked contribution in the treatment of depression.

Authors' contributions Shvetank Bhatt: Idea and preparation of manuscript.

Thangaraj Devadoss: Preparation of Chemistry part of the manuscript.

Niraj Kumar Jha: Figure preparation.

Moushumi Baidya: Literature review.

Gaurav Gupta: Literature Review.

Dinesh Kumar Chellappan: Editing and compilation.

Sachin Kumar Singh: Graphical Abstract preparation.

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References

Abbasi SH, Hosseini F, Modabbernia A, Ashrafi M, Akhondzadeh S (2012) Effect of celecoxib add-on treatment on symptoms and serum IL-6 concentrations in patients with major depressive disorder: randomized double-blind placebo-controlled study. J Affect Disord 141(2–3):308–314

Al-Baz N, Karim MA (2020) Rheumatoid Arthritis, Depression, and the Role of Celecoxib. SN Compr Clin Med 2:1848–1852

Albert PR (2015) Why is depression more prevalent in women? J Psychiatry Neurosci 40(4):219-21

Aleksandrova LR, Phillips AG, Wang YT (2017) Antidepressant effects of ketamine and the roles of AMPA glutamate receptors and other mechanisms beyond NMDA receptor antagonism. J Psychiatry Neurosci 42:222–229

Almarhoon FH, Almubarak KA, Alramdhan ZA (2021) The Association Between Depression and Obesity Among Adults in the Eastern Province, Saudi Arabia. Cureus 13(10):e18794

Appleton J (2018) The gut-brain axis: influence of microbiota on mood and mental health. Integr Med (Encinitas) 17(4):28–32

Arteaga-Henríquez G, Simon MS, Burger B, Weidinger E, Wijkhuijs A, Arolt V, Birkenhager TK, Musil R, Müller N, Drexhage HA (2019) Low-grade inflammation as a predictor of antidepressant and anti-inflammatory therapy response in MDD patients: a systematic review of the literature in combination with an analysis of experimental data collected in the EU-MOODINFLAME consortium. Front Psychiatry 10:458

Ayano G, Agidew M, Duko B, Mulat H, Alemayew M (2015) Perception, attitude and associated factors on schizophrenia and depression among residents of Hawassa City, South Ethiopia, cross sectional study. Am J Psychiatry Neurosci 3(6):116–124

Bădescu SV, Tătaru C, Kobylinska L, Georgescu EL, Zahiu DM, Zăgrean AM, Zăgrean L (2016) The association between Diabetes Mellitus and depression. J Med Life 9(2):120–125

Badimon L, Padró T, Vilahur G (2012) Atherosclerosis, platelets and thrombosis in acute ischaemic heart disease. Eur Heart J Acute Cardiovasc Care 1(1):60–74

Bakunina N et al (2015) Immune mechanisms linked to depression via oxidative stress and neuroprogression. Immunology 144(3):365–373

Ball K, Burton NW, Brown WJ (2009) A prospective study of overweight, physical activity, and depressive symptoms in young women. Obes (Silver Spring) 17(1):66–71

Baumeister D, Ciufolini S, Mondelli V (2016) Effects of psychotropic drugs on inflammation: consequence or mediator of therapeutic effects in psychiatric treatment? Psychopharmacology 233(9):1575–1589

Bayramgürler D, Karson A, Ozer C, Utkan T (2013) Effects of long-term etanercept treatment on anxiety- and depression-like neurobehaviors in rats. Physiol Behav 119:145–148

Belleau EL, Treadway MT, Pizzagalli DA (2019) The impact of stress and major depressive disorder on hippocampal and medial prefrontal cortex morphology. Biol Psychiatry Elsevier USA 85:443–453

Belmaker RH, Agam G (2008) Major depressive disorder. N Engl J Med 358:55–68

Berk M, Woods RL, Nelson MR et al (2020) Effect of aspirin vs placebo on the prevention of depression in older people: a randomized clinical trial. JAMA Psychiat 77(10):1012–1020

Bhatt S, Nagappa AN, Patil CR (2020) Role of oxidative stress in depression. Drug Discov Today 25:1270–1276

Bhatt S, Mahesh R, Devadoss T, Jindal A (2017a) Neuropharmacological evaluation of a novel 5-HT3 receptor antagonist (4-benzylpiperazin-1-yl)(3-methoxyquinoxalin-2-yl) methanone (6 g) on lipopolysaccharide-induced anxiety models in mice. J Basic Clin Physiol Pharmacol 28:101–106

Bhatt S, Mahesh R, Jindal A, Devadoss T (2017b) Neuropharmacological and neurochemical evaluation of N-n-propyl-3-ethoxyquinoxaline-2-carboxamide (6n): a novel serotonergic 5-HT3 receptor antagonist for co-morbid antidepressant- and anxiolytic-like potential using traumatic brain injury model in rats. J Basic Clin Physiol Pharmacol 28:93–100

Bhatt S, Mahesh R, Jindal A, Devadoss T (2014) Protective effects of a novel 5-HT3 receptor antagonist, N-n-butyl-3-methoxy quinoxaline-2-carboxamide (6o) against chronic unpredictable mild stress-induced behavioral changes and biochemical alterations. Pharmacol Biochem Behav 122:234–239

Bhatt S, Shukla P, Raval J, Goswami S (2016) Role of aspirin and dexamethasone against experimentally induced depression in rats. Basic Clin Pharmacol Toxicol 119(1):10–18

Blumberger DM, Hsu JH, Daskalakis ZJ (2015) A review of brain stimulation treatments for late-life depression. Curr Treat Options Psych 2:413–421

Boku S, Nakagawa S, Toda H, Hishimoto A (2018) Neural basis of major depressive disorder: Beyond monoamine hypothesis. Psychiatry Clin Neurosci 72:3–12

Bremner JD (2006) Traumatic stress: effects on the brain. Dialogues Clin Neurosci 8(4):445–461

Brymer KJ, Fenton EY, Kalynchuk LE, Caruncho HJ (2018) Peripheral etanercept administration normalizes behavior, hippocampal neurogenesis, and hippocampal reelin and GABAA receptor expression in a preclinical model of depression. Front Pharmacol 9:121

Buga AM, Ciobanu O, Bădescu GM, Bogdan C, Weston R, Slevin M, Di Napoli M, Popa-Wagner A (2016) Up-regulation of serotonin

receptor 2B mRNA and protein in the peri-infarcted area of aged rats and stroke patients. Oncotarget 7(14):17415–17430
Carvalho LA, Torre JP, Papadopoulos AS, Poon L, Juruena MF, Markopoulou K et al (2013) Lack of clinical therapeutic benefit of antidepressants is associated overall activation of the inflammatory system. J Affect Disord 148(1):136–140
Coogan AN, Baird AL, Popa-Wagner A, Thome J (2016) Circadian rhythms and attention deficit hyperactivity disorder: The what, the when and the why. Prog Neuropsychopharmacol Biol Psychiatry 67:74–81
Dantzer R, O'Connor JC, Freund GG (2008) From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 9:46–56
Darwish L, Beroncal E, Sison MV, Swardfager W (2018) Depression in people with type 2 diabetes: current perspectives. Diabetes Metab Syndr Obes 11:333–343. https://doi.org/10.2147/DMSO.S106797
Dinis-Oliveira RJ (2017) Metabolism and metabolomics of ketamine: a toxicological approach. Forensic Sci Res 2(1):2–10
de Ridder L, Benninga MA, Taminiau JAJM, Hommes DW, van Deventer SJH (2007) Infliximab use in children and adolescents with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 45(1):3–14
Doyle TA, de Groot M, Harris T, Schwartz F, Strotmeyer ES, Johnson KC, Kanaya A (2013) Diabetes, depressive symptoms, and inflammation in older adults: results from the Health, Aging, and Body Composition Study. J Psychosom Res 75(5):419–424
Driessen E, Hollon SD (2010) Cognitive behavioral therapy for mood disorders: efficacy, moderators and mediators. Psychiatr Clin North Am 33(3):537–555
Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y (2017) Obesity and inflammation: the linking mechanism and the complications. Arch Med Sci 13(4):851–863
Ersozlu Bozkirli E, Keskek S, Bozkirli E et al (2014) AB0658 The effects of infliximab treatment on depression, anxiety and sleep disorders in patients with ankylosing spondylitis. Ann Rheum Dis 73:1022–1023
Eser D, Schule C, Baghai TC (2006) Neuroactive steroids in depression and anxiety disorders: clinical studies. Neuroendocrinology 84:244–254
Flory JD, Yehuda R (2015) Comorbidity between post-traumatic stress disorder and major depressive disorder: alternative explanations and treatment considerations. Dialogues Clin Neurosci 17(2):141–150
Fourrier C, Sampson E, Mills NT et al (2018) Anti-inflammatory treatment of depression: study protocol for a randomised controlled trial of vortioxetine augmented with celecoxib or placebo. Trials 19:447
Frodl TS, Koutsouleris N, Bottlender R (2008) Depression-related variation in brain morphology over 3 years: effects of stress? Arch Gen Psychiatry 65:1156–1165
Gamble-George JC (2016) Cyclooxygenase-2 inhibition reduces stress-induced affective pathology. Elife 5:e14137
Germain A, Kupfer DJ (2008) Circadian rhythm disturbances in depression. Hum Psychopharmacol 23(7):571–585
Glavan D, Gheorman V, Gresita A (2021) Identification of transcriptome alterations in the prefrontal cortex, hippocampus, amygdala and hippocampus of suicide victims. Sci Rep 11:18853
Günaydın Ş, Yılmaz A (2015) Improvement of solubility of celecoxib by inclusion in MCM-41 mesoporous silica: drug loading and release. Turk J Chem 39(2). https://doi.org/10.3906/kim-1409-56
Gustafsson D, Klang A, Thams S, Rostami E (2021) The role of BDNF in experimental and clinical traumatic brain injury. Int J Mol Sci 22(7):3582
Halaris A, Cantos A, Johnson K, Hakimi M, Sinacore J (2020) Modulation of the inflammatory response benefits treatment-resistant bipolar depression: A randomized clinical trial. J Affect Disord 261:145–152
Hamilton M (1967) Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 6:278–296
Hannestad J, DellaGioia N, Bloch M (2011) The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. Neuropsychopharmacol 36:2452–2459
Harvey PD, Twamley EW, Pinkham AE, Depp CA, Patterson TL (2017) Depression in schizophrenia: associations with cognition, functional capacity, everyday functioning, and self-assessment. Schizophr Bull 43(3):575–582
Hasler G, Fromm S, Alvarez RP (2007a) Cerebral blood flow in immediate and sustained anxiety. J Neurosci 27:6313–6319
Hasler G, van der Veen JW, Tumonis T (2007b) Reduced prefrontal glutamate/glutamine and gamma-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy. Arch Gen Psychiatry 64:193–200
Hashioka S, McGeer PL, Monji A, Kanba S (2009) Anti-inflammatory effects of antidepressants: possibilities for preventives against Alzheimer's disease. Cent Nerv Syst Agents Med Chem 9(1):12–19
Hoffmann W, Förster W (1987) Two years follow-up Cottbus reinfarction study with 30 and 60 mg acetylsalicylic acid. Prog Clin Biol Res 242:393–397
Husain MI, Cullen C, Umer M, Carvalho AF, Kloiber S, Meyer JH, Ortiz A, Knyahnytska Y, Husain MO, Giddens J, Diniz BS, Wang W, Young AH, Mulsant BH, Daskalakis ZJ (2020) Minocycline as adjunctive treatment for treatment-resistant depression: study protocol for a double blind, placebo-controlled, randomized trial (MINDEP2). BMC Psychiatry 20:173
Jindal A, Mahesh R, Bhatt S (2015) Etazolate, a phosphodiesterase-4 enzyme inhibitor produces antidepressant-like effects by blocking the behavioral, biochemical, neurobiological deficits and histological abnormalities in hippocampus region caused by olfactory bulbectomy. Psychopharmacology 232:623–637
Kany S, Vollrath JT, Relja B (2019) Cytokines in inflammatory disease. Int J Mol Sci 20(23):6008
Kendell SF, Krystal JH, Sanacora G (2005) GABA and glutamate systems as therapeutic targets in depression and mood disorders. Expert Opin Ther Targets 9:153–168
Kendler KS, Gardner CO, Prescott CA (2006) Toward a comprehensive developmental model for major depression in men. Am J Psychiatry 163:115–124
Kendler KS, Gardner CO, Prescott CA (2002) Toward a comprehensive developmental model for major depression in women. Am J Psychiatry 159:1133–1145
Kendler KS, Thornton LM, Prescott CA (2001) Gender differences in the rates of exposure to stressful life events and sensitivity to their depressogenic effects. Am J Psychiatry 158:587–593
Kenneth N, Agwuh A, MacGowan (2006) Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. J Antimicrob Chemother 58(2):256–265
Kessler RC, Nelson CB, McGonagle KA (1996) Comorbidity of DSM-III-R major depressive disorder in the general population: results from the US National Comorbidity Survey. Br J Psychiatry 168(30):17–30
Kessler RC, Sampson NA, Berglund P (2015) Anxious and non-anxious major depressive disorder in the World Health Organization World Mental Health Surveys. Epidemiol Psychiatr Sci 24:210–226
Kohler O, Benros ME, Nordentoft M et al (2014) Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects a systematic review and meta-analysis of randomized clinical trials. JAMA Psychiat 71(12):1381–1391

Kopschina Feltes P et al (2017) Anti-inflammatory treatment for major depressive disorder: implications for patients with an elevated immune profile and non-responders to standard antidepressant therapy. J Psychopharmacol (Oxford England) 31(9):1149–1165
Krishnan V, Nestler EJ (2008) The molecular neurobiology of depression. Nature 55:894–902
Kupfer DJ (2005) The pharmacological management of depression. Dialog Clin Neurosci 7(3):191–205
Kurhe Y, Mahesh R, Gupta D (2014) Effect of a selective cyclooxygenase type 2 inhibitor celecoxib on depression associated with obesity in mice: an approach using behavioral tests. Neurochem Res 39(7):1395–1402
Kuria MW, Ndetei DM, Obot IS, Khasakhala LI, Bagaka BM, Mbugua MN, Kamau J (2012) The Association between Alcohol Dependence and Depression before and after Treatment for Alcohol Dependence. ISRN Psychiatry 2012:482802
Lachininoto MG, Nuzzolo ER, Bonanno G, Mariotti A, Procoli A, Locatelli F, De Cristofaro R, Rutella S (2013) Cyclooxygenase-2 (COX-2) inhibition constrains indoleamine 2,3-dioxygenase 1 (IDO1) activity in acute myeloid leukaemia cells. Molecules 18(9):10132–10145
Lam RW, Kennedy SH, Mclntyre RS, Khullar A (2014) Cognitive dysfunction in major depressive disorder: effects on psychosocial functioning and implications for treatment. Can J Psychiatry 59(12):649–654
Laudon M, Frydman-Marom A (2014) Therapeutic effects of melatonin receptor agonists on sleep and comorbid disorders. Int J Mol Sci 15(9):15924–15950
Lee CH, Giuliani F (2019) The role of inflammation in depression and fatigue. Front Immunol 10:1696
Li CT, Bai YM, Tu PC, Lee YC, Huang YL, Chen TJ, Chang WH, Su TP (2012) Major depressive disorder and stroke risks: a 9-year follow-up population-based, matched cohort study. PLoS ONE 7(10):e46818
Li G, Thorn CF, Bertagnolli MM, Grosser T, Altman RB, Klein TE (2012) Celecoxib pathways: pharmacokinetics and pharmacodynamics. Pharmacogenet Genomics 22(4):310–318
Li J-P, Guo J-M, Shang E-X, Zhu Z-H, Liu Y, Zhao B-C, Zhao J, Tang Z-S, Duan J-A (2017) Quantitative determination of five metabolites of aspirin by UHPLC–MS/MS coupled with enzymatic reaction and its application to evaluate the effects of aspirin dosage on the metabolic profile. J Pharm Biomed Anal 138:109–117
Liguori I, Russo G, Curcio F, Bulli G, Aran L, Della-Morte D, Gargiulo G, Testa G, Cacciatore F, Bonaduce D, Abete P (2018) Oxidative stress, aging, and diseases. Clin Interv Aging 13:757–772
Lener MS, Niciu MJ, Ballard ED, Park M, Park LT, Nugent AC, Zarate CA Jr (2017) Glutamate and gamma-aminobutyric acid systems in the pathophysiology of major depression and antidepressant response to ketamine. Biol Psychiatry 81(10):886–897
Levine J, Barak Y, Chengappa KN, Rapoport A, Rebey M, Barak V (1999) Cerebrospinal cytokine levels in patients with acute depression. Neuropsychobiology 40:171–176
Maciel IS, Silva RB, Morrone FB, Calixto JB, Campos MM (2013) Synergistic effects of celecoxib and bupropion in a model of chronic inflammation-related depression in mice. PLoS ONE 8:e77227
Mannan M, Mamun A, Doi S, Clavarino A (2016) Is there a bi-directional relationship between depression and obesity among adult men and women? Systematic review and bias-adjusted meta analysis. Asian J Psychiatr 21:51–66
Martinez JM, Garakani A, Yehuda R, Gorman JM (2012) Proinflammatory and "resiliency" proteins in the CSF of patients with major depression. Depress Anxiety 29:32–38
Matveychuk D, Thomas RK, Swainson J, Khullar A, MacKay MA, Baker GB, Dursun SM (2020) Ketamine as an antidepressant: overview of its mechanisms of action and potential predictive biomarkers. Ther Adv Psychopharmacol 10:2045125320916657
McDonnell CW, Dunphy-Doherty F, Rouine J, Bianchi M, Upton N, Sokolowska E, Prenderville JA (2021) The antidepressant-like effects of a clinically relevant dose of ketamine are accompanied by biphasic alterations in working memory in the wistar kyoto rat model of depression. Front Psychiatry 11:599588
McEwen BS, Nasca C, Gray JD (2016) Stress effects on neuronal structure: hippocampus, amygdala, and prefrontal cortex. Neuropsychopharmacology 41(1):3–23
Menke A (2019) Is the HPA axis as target for depression outdated, or is there a new hope? Front Psychiatry 10:101
Michel TM et al (2004) Cu, Zn- and Mn-superoxide dismutase levels in brains of patients with schizophrenic psychosis. J Neural Transmission 111:1191–1201
Michel TM et al (2007) Evidence for oxidative stress in the frontal cortex in patients with recurrent depressive disorder - a post-mortem study. Psychiatry Res 151:145–150
Michel TM et al (2010) Increased xanthine oxidase in the thalamus and putamen in depression. World J Biol Psychiatry 11:314–320
Miller AH, Haroon E, Raison CL, Felger JC (2013) Cytokine targets in the brain: impact on neurotransmitters and neurocircuits. Depress Anxiety 30:297–306
Miller GE, Rohleder N, Stetler C, Kirschbaum C (2005) Clinical depression and regulation of the inflammatory response during acute stress. Psychosom Med 67:679–687
Mion G, Villevieille T (2013) Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings. CNS Neurosci Ther 19(6):370–380
Molta ChT (2007). In: Boehncke HH, Radeke WH (eds) Biologics in general medicine. Springer-Verlag Berlin, Heidelberg, pp 32–40
Moulton CD, Pickup JC (2018) Innate immunity and inflammation in type 2 diabetes-associated depression. In: Khalida Ismail and others (eds), Depression and Type 2 Diabetes (Oxford, ; online edn, Oxford Academic, 1 Sept. 2018), https://doi.org/10.1093/med/9780198789284.003.0005. Accessed 30 Aug 2022
Muller HHO, Moeller S, Lücke C, Lam AP, Braun N, Philipsen A (2018) Vagus Nerve Stimulation (VNS) and other augmentation strategies for Therapy-Resistant Depression (TRD): review of the evidence and clinical advice for use. Front Neurosci 12:239
Müller N (2019) COX-2 inhibitors, aspirin, and other potential anti-inflammatory treatments for psychiatric disorders. Front Psychiatry 10:375
Nahar IK, Shojania K, Marra CA, Alamgir AH, Anis AH (2003) Infliximab treatment of rheumatoid arthritis and Crohn's disease. Ann Pharmacother 37(9):1256–1265
Nerurkar L, Siebert S, McInnes IB, Cavanagh J (2019) Rheumatoid arthritis and depression: an inflammatory perspective. Lancet Psychiatry, Elsevier Ltd 6:164–173
Ng A, Tam WW, Zhang MW, Ho CS, Husain SF, McIntyre RS, Ho RC (2018) IL-1β, IL-6, TNF- α and CRP in elderly patients with depression or Alzheimer's disease: systematic review and meta-analysis. Sci Rep 8(1):12050
Nguyen MM, Perlman G, Kim N, Wu CY, Daher V, Zhou A, Mathers EH, Anita NZ, Lanctôt KL, Herrmann N, Pakosh M, Swardfager W (2021) Depression in type 2 diabetes: A systematic review and meta-analysis of blood inflammatory markers. Psychoneuroendocrinology 134:105448
Nishino S, Ueno R, Ohishi K, Sakai T, Hayaishi O (1989) Salivary prostaglandin concentrations: possible state indicators for major depression. Am J Psychiatry 146:365–368
O'Connor JC, Lawson MA, André C, Moreau M, Lestage J, Castanon N, Kelley KW, Dantzer R (2009) Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. Mol Psychiatry 14(5):511–522

Ohgi Y, Futamura T, Kikuchi T, Hashimoto K (2013) Effects of antidepressants on alternations in serum cytokines and depressive-like behavior in mice after lipopolysaccharide administration. Pharmacol Biochem Behav 103(4):853–859

Ohishi K, Ueno R, Nishino S, Sakai T, Hayaishi O (1988) Increased level of salivary prostaglandins in patients with major depression. Biol Psychiatry 23:326–334

Osimo EF, Pillinger T, Rodriguez IM, Khandaker GM, Pariante CM, Howes OD (2020) Inflammatory markers in depression: A meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. Brain Behav Immun 87:901–909

Pace TW, Mletzko TC, Alagbe O, Musselman DL, Nemeroff CB, Miller AH, Heim CM (2006) Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. Am J Psychiatry 163:1630–1633

Pae CU, Marks DM, Han C, Patkar AA (2008) Does minocycline have antidepressant effect? Biomed Pharmacother 62(5):308–311

Patrick DM, Van Beusecum JP, Kirabo A (2021) The role of inflammation in hypertension: novel concepts. Curr Opin Physiol 19:92–98

Phillips C (2017) Brain-derived neurotrophic factor, depression, and physical activity: making the neuroplastic connection. Neural Plast 2017:7260130

Pompili M, Serafini G, Innamorati M, Dominici G, Ferracuti S, Kotzalidis GD, Serra G, Girardi P, Janiri L, Tatarelli R, Sher L, Lester D (2010) Suicidal behavior and alcohol abuse. Int J Environ Res Public Health 7(4):1392–1431

Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, Haroon E, Miller AH (2013) A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiat 70(1):31–41

Sacre S, Jaxa-Chamiec A, Low CMR, Chamberlain G, Tralau-Stewart C (2019) Structural modification of the antidepressant mianserin suggests that its anti-inflammatory activity may be independent of 5-hydroxytryptamine receptors. Front Immunol 10:1167

Sandu RE, Buga AM, Uzoni A, Petcu EB, Popa-Wagner A (2015) Neuroinflammation and comorbidities are frequently ignored factors in CNS pathology. Neural Regen Res 10(9):1349–1355

Sandu RE, Dumbrava D, Surugiu R, Glavan DG, Gresita A, Petcu EB (2017) Cellular and molecular mechanisms underlying non-pharmaceutical ischemic stroke therapy in aged subjects. Int J Mol Sci 19(1):99

Santiago RM, Barbiero J, Martynhak BJ, Boschen SL, da Silva LM, Werner MF, Da Cunha C, Andreatini R, Lima MM, Vital MA (2014) Antidepressant-like effect of celecoxib piroxicam in rat models of depression. J Neural Transm (Vienna) 121:671–682

Schmidtner AK, Slattery DA, Gläsner J et al (2019) Minocycline alters behavior, microglia and the gut microbiome in a trait-anxiety-dependent manner. Transl Psychiatry 9:223

Sethi R et al (2019) Neurobiology and therapeutic potential of Cyclooxygenase-2 (COX-2) inhibitors for inflammation in neuropsychiatric disorders. Front Psychiatry 10:605

Shadrina M, Bondarenko EA, Slominsky PA (2018) Genetics factors in major depression disease. Front Psychiatry 9:334

Sheline YI, Gado MH, Kraemer HC (2003) Untreated depression and hippocampal volume loss. Am J Psychiatry 160:1516–1518

Sima AV, Stancu CS, Simionescu M (2009) Vascular endothelium in atherosclerosis. Cell Tissue Res 335:191–203

Solak Y, Afsar B, Vaziri N (2016) Hypertension as an autoimmune and inflammatory disease. Hypertens Res 39:567–573

Sullivan PF, Neale MC, Kendler KS (2000) Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry 157:1552–1562

Thillard EM, Gautier S, Babykina E, Carton L, Amad A, Bouzillé G, Beuscart JB, Ficheur G, Chazard E (2020) Psychiatric adverse events associated with infliximab: a cohort study from the french nationwide discharge abstract database. Front Pharmacol 11:513

Tolentino JC, Schmidt SL (2018) DSM-5 criteria and depression severity: implications for clinical practice. Front Psychiatry 9:450

Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, Lalla D, Woolley M, Jahreis A, Zitnik R, Cella D, Krishnan R (2006) Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet 367(9504):29–35

Uphoff E, Pires M, Barbui C, Barua D, Churchill R, Cristofalo D, Ekers D, Fottrell E, Mazumdar P, Purgato M, Rana R, Wright J, Siddiqi N (2020) Behavioural activation therapy for depression in adults with non-communicable diseases. Cochrane Database Syst Rev 8(8):CD013461

Vindbjerg E, Makransky G, Mortensen EL, Carlsson J (2019) Cross-cultural psychometric properties of the hamilton depression rating scale. Can J Psychiatry 64:39–46

Wang WY, Tan MS, Yu JT, Tan L (2015a) Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. Ann Transl Med 3(10):136

Wang N, Yu HY, Shen XF, Gao ZQ, Yang C, Yang JJ, Zhang GF (2015b) The rapid antidepressant effect of ketamine in rats is associated with down-regulation of pro-inflammatory cytokines in the hippocampus. Ups J Med Sci 120(4):241–248

Wang XL, Li L (2021) Circadian clock regulates inflammation and the development of neurodegeneration. Front Cell Infect Microbiol 11:696554

Wooff Y et al (2019) IL-1 family members mediate cell death, inflammation and angiogenesis in retinal degenerative diseases. Front Immunol 10:1618

Young EA (1998) Sex differences and the HPA axis: implications for psychiatric disease. J Gend Specif Med 1:21–27

Zarghi A, Arfaei S (2011) Selective COX-2 inhibitors: a review of their structure-activity relationships. Iran J Pharm Res 10(4):655–683

Zarate CA Jr, Singh JB, Carlson PJ (2006) A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 63:856–864

Zidar N, Odar K, Glavac D, Jerse M, Zupanc T, Stajer D (2009) Cyclooxygenase in normal human tissues–is COX-1 really a constitutive isoform, and COX-2 an inducible isoform? J Cell Mol Med 13(9B):3753–3763

Zuckerman H, Pan Z, Park C, Brietzke E, Musial N, Shariq AS, Iacobucci M, Yim SJ, Lui LMW, Rong C, McIntyre RS (2018) Recognition and treatment of cognitive dysfunction in major depressive disorder. Front Psychiatry 9:655