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Research Progress on Inflammatory Cytokines in Depressive Disorders

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ABSTRACT

Depressive disorder is a prevalent psychiatric condition characterized by complex and multifactorial pathophysiology, with inflammatory cytokines playing a pivotal role. Previous studies have demonstrated significantly elevated levels of inflammatory cytokines in individuals with depressive disorder. These cytokines contribute to neurotransmitter depletion, impaired neuroplasticity, and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Furthermore, they intensify oxidative stress and disrupt the gut microbiota, collectively exacerbating depressive symptoms. In recent years, novel therapeutic approaches targeting inflammatory pathways have gained increasing attention, encompassing pharmacological, physical, and psychological interventions. These modalities have shown substantial potential in alleviating depressive symptoms by modulating inflammatory responses. This review comprehensively examines the underlying mechanisms of inflammatory cytokines in depressive disorder, outlines clinical research related to cytokine expression in adolescent depression, and systematically summarizes emerging treatment strategies aimed at reducing inflammation. The goal is to provide new theoretical insights and practical guidance for the early identification and precise management of depressive disorders inadolescents.

Keywords: depressive disorder; inflammatory cytokines; mechanisms; treatment

Major depressive disorder (MDD) is one of the most widespread psychiatric conditions, affecting roughly 10% of people across their lifetimes [1]. The World Health Organization reports that depression imposes a significant economic burden, contributing to an estimated annual loss of nearly one trillion US dollars in global productivity [2]. Adolescence is a particularly vulnerable developmental stage, during which up to 34% of young individuals experience depressive symptoms [3]. Growing evidence has underscored the pivotal involvement of inflammatory cytokines in the pathogenesis of depression. Patients diagnosed with MDD frequently present with elevated concentrations of systemic inflammatory markers, such as interleukin (IL)-1β, IL-6, tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) [4]. These immune mediators influence multiple physiological pathways, including but not limited to monoamine neurotransmitter balance, neuroplasticity, regulation of the hypothalamic-pituitary-adrenal (HPA) axis, oxidative stress response, and composition of the gut microbiota [5]. This network of interactions contributes to the intensification of depressive symptoms, reinforcing the disorder's complex and self-perpetuating nature.

Evidence suggests that inflammatory cytokine levels may fluctuate throughout the course of antidepressant treatment. Some studies propose that pharmacological intervention itself may influence peripheral cytokine profiles [6]. However, current antidepressant therapies remain insufficient for a substantial portion of patients, with more than two-thirds failing to achieve stable symptom remission [7]. There is therefore a critical need for innovative therapeutic strategies to address the limitations of conventional pharmacological treatments. Interventions targeting abnormal cytokine expression have become a focal point in contemporary research [8]. This review synthesizes current knowledge on the mechanisms by which inflammatory cytokines contribute to depressive pathology, summarizes clinical investigations examining cytokine expression in adolescent depression, and surveys emerging treatment approaches aimed at reducing inflammation to alleviate depressive symptoms. These findings may provide valuable perspectives for the identification and management of depressive disorders in adolescents.

1 Overview of Inflammatory

Cytokines

Inflammation refers to a set of immune-related biological processes and represents a non-specific response of the body to external stimuli or injury [9]. It is estimated that approximately 16% of individuals with depressive disorders exhibit an inflammatory state, while inflammation accounts for about 7% of the population-attributable risk for depression, implying that inflammation may be etiologically relevant in one out of every fifteen cases [10]. Inflammatory cytokines most closely linked to the onset and progression of depressive disorders include members of the interleukin family, CC chemokines, and tumor necrosis factor-alpha (TNF-α) [11]. These cytokines, a broad class of protein signal molecules, regulate inflammation and various cellular processes [12]. They are involved in a range of biological functions through cell signaling and immune system modulation, and peripheral levels of inflammatory cytokines have shown significant associations with antidepressant treatment outcomes [13].

Evidence indicates that blockade of pro-inflammatory cytokine signaling may exert antidepressant effects. For example, mice deficient in interleukin-6 or TNF-α receptors display phenotypes consistent with resilience to depression-like behaviors [14]. Peripheral cytokines are also able to cross the blood-brain barrier and influence central nervous system inflammation [15]. In depressive disorder, immune function is often characterized by an imbalance between activation and suppression, leading to impaired cellular immunity and abnormal cytokine levels [16]. Complex negative feedback mechanisms exist between pro-inflammatory and anti-inflammatory cytokines; pro-inflammatory cytokines induce compensatory anti-inflammatory responses, which in turn counteract the effects of pro-inflammatory signaling. Persistent dysregulation and interaction of these cytokines may impact multiple biological systems, thereby contributing to both the development and persistence of depressive disorders [17, 18].

2 Inflammatory Mechanisms in Depressive Disorder

The development of depressive disorder arises from intricate interactions among diverse biological systems. Beyond the dysregulation of inflammatory cytokines, other key pathological processes implicated in depression include monoamine neurotransmitter deficits, compr omised neuroplasticity, disruption of hypothalamic-pituitary-adrenal (HPA) axis function, increased oxidative stress, and alterations in the gut microbiome [5]. Inflammatory cytokines can modulate these interconnected pathways through a variety of mechanisms, collectively intensifying the severity of depressive symptoms.

Microglia fulfill vital regulatory functions within the central nervous system (CNS), including the modulation of neuroplasticity, neurogenesis, and synaptic pruning. When activated, microglia modulate neuronal function by altering inflammatory status. Persistent inflammation can disrupt the synthesis, release, and reuptake of neurotransmitters, closely linking long-term neuroinflammation to the onset of depression [19]. Moreover, microglia secrete anti-inflammatory cytokines and engage in direct interactions with neurons to facilitate repair following injuries [20]. The activity of microglia is regulated by inflammatory cytokines, and some antidepressant agents have been shown to affect microglial activation and neuroinflammation [21]. Anti-inflammatory therapies may alleviate depressive symptoms partly by inhibiting microglial activation [22].

Chronic stress engages both the hypothalamic-pituitary-adrenal (HPA) axis and immune system, heightening inflammatory activity. Sustained stress exposure can trigger neuroinflammation, impair dopamine-mediated reward pathways, and ultimately give rise to depressive-like behaviors [23, 24]. Evidence suggests that pro-inflammatory cytokines—such as interferon-gamma (IFN-γ)—can hinder the synthesis of pivotal neurotransmitters, including serotonin (5-HT), dopamine (DA), and norepinephrine (NE) [25]. The release of these cytokines during inflammatory states can initiate abnormal immune activation, thereby disrupting dopaminergic and serotonergic signaling, both vital for mood regulation and cognitive functioning [26]. The HPA axis orchestrates the body's response to stress through a cascade involving corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol. Stressful stimuli elevate the production and activity of these hormones. Hyperactivity of the HPA axis is frequently observed in depression, with approximately 40% of individuals exhibiting increased cortisol concentrations, heightened CRH, or decreased ACTH secretion [27]. Notably, IL-6—a prominent pro-inflammatory cytokine— can sensitize the HPA axis, resulting in exaggerated responses to stress that further drive depressive symptoms [28]. Persistent psychological, physiological, or traumatic stress may lead to chronic HPA axis overactivation and subsequent dysregulation [29].

Inflammatory cytokines also impair tryptophan metabolism, suppressing the synthesis of

serotonin and melatonin, leading to melatonin deficiency. This reduction in melatonin weakens its antioxidant, anti-inflammatory, and mitochondrial regulatory roles, aggravating depressive symptoms [30]. Recent studies reveal that lipopolysaccharide-induced neuroinflammation can elicit depression-like behaviors, autophagy dysfunction, and heightened pro-inflammatory cytokine levels through activation of microglia and astrocytes. Melatonin modulates these effects via the FOXO3a signaling pathway, ameliorating neuroinflammatory and autophagic abnormalities along with behavioral deficits [31].

The gut microbiota, comprising bacteria, fungi, and archaea residing in the gastrointestinal tract, plays a pivotal part in depression's pathogenesis through the gut-brain axis [32]. Dysbiosis may enhance depressive disorder progression by activating inflammatory signaling. Microbiota imbalances compromise the integrity of the intestinal barrier, increasing host susceptibility to exogenous inflammatory stimuli. Once barrier function is breached, bacterial endotoxins and food antigens can translocate, eliciting low-grade systemic and central nervous system inflammation, and subsequently perturbing glial cell function, neurotransmitter metabolism, and neuroinflammation [33]. Furthermore, bidirectional signaling between the gut microbiota and the nervous, endocrine, metabolic, and immune systems can further influence brain function, thus triggering or intensifying depressive symptoms [34].

3 Clinical Studies on Depressive Disorder and Inflammatory Cytokines

Recent research utilizing Mendelian randomization has demonstrated that body mass index (BMI) exerts an independent causal effect on depressive disorder, with the impact of C-reactive protein (CRP) on depression severity being partially mediated by BMI. Moreover, patients with treatment-resistant depression exhibit significantly higher levels of CRP and BMI compared to individuals with less severe depressive disorders [35]. In a 26-week trial, Kofod et al. observed a significant reduction in 17 inflammatory cytokines among patients treated with antidepressants; however, there was no significant association between these cytokine changes and depression scores, nor did cytokine levels predict the risk of relapse at ten years [36].

Elevated concentrations of C-reactive protein (CRP) have been observed to correlate with both depressive symptoms and disturbances in sleep patterns, while increased interleukin-6 (IL-6) levels are strongly linked to clinical features such as anhedonia, hypersomnia, and reduced appetite [37]. Inflammation appears to play a particularly prominent role in comorbid forms of depression; for example, studies in individuals experiencing both asthma and depression have demonstrated that more severe asthma is associated with more pronounced depressive symptoms, which, in turn, are significantly related to heightened levels of IL- 6, monocyte chemoattractant protein-1 (MCP-1), CCL18, and CCL17 [38].

A large-scale national study conducted in China, drawing on health and nutrition survey data collected between 2005 and 2020, identified a significant positive association between the immune-inflammatory index and rates of post-stroke depression [39]. Additional analyses using this dataset confirmed that higher immune-inflammatory index scores are positively correlated with the incidence of depressive disorders [40]. Notably, sex-specific differences have also emerged in the relationship between inflammatory cytokines and depression—for instance, the positive association between IL-6 and depressive symptoms was found exclusively in female patients, indicating potential sex differences in the psychobiological mechanisms underpinning depression [41].

Further investigation has illuminated the link between inflammation and treatment-resistant depression. Patients with depression consistently demonstrate higher levels of inflammatory biomarkers than healthy controls, with individuals exhibiting treatment resistance showing even greater elevations compared to those who respond favorably to antidepressant medications [42]. Synthesizing data from 82 studies, a meta-analysis revealed that individuals with depressive disorder show significantly increased concentrations of IL- 6, TNF-α, IL-10, soluble IL-2 receptor, CCL2, IL-13, IL-18, IL-12, interleukin-1 receptor antagonist (IL-1ra), and TNF receptor 2, while levels of interferon-gamma (IFN-γ) are markedly decreased [43].

4 Novel Therapeutic Approaches Targeting Inflammatory Cytokines in Alleviating Depressive Symptoms

Given the pivotal involvement of inflammation in the pathophysiology of depressive disorders, there has been growing interest in developing therapeutic strategies that target inflammatory cytokines. Accumulating evidence indicates that anti-inflammatory approaches can meaningfully reduce depressive symptomatology [44]. For instance, a meta-analysis has shown that several agents—such as nonsteroidal anti-inflammatory drugs (NSAIDs), omega-3 fatty acids, statins, and minocycline—exhibit significant antidepressant properties,

especially when used as adjuncts to standard antidepressant treatments [45].

Current antidepressant interventions primarily comprise pharmacological, physical, and psychological therapies. This review seeks to summarize research findings on the effects of these three treatment modalities on inflammation-related markers in depression, with the goal of providing both theoretical foundations and practical guidance for developing novel antidepressant strategies.

4.1 Effects of Pharmacological Treatments on Inflammatory Cytokines

Re se arch has de monstrated that ce rtain antidepressants, such as clomipramine and fluoxetine, consistently reduce circulating levels of inflammatory cytokines, including IL-6, IFN-γ, and TNF-α. In contrast, other medications like mirtazapine and venlafaxine may actually elevate these cytokine levels [46]. Mianserin exhibits anti-inflammatory action by inhibiting Toll-like receptor 8 signaling pathways [47]. Additional evidence indicates that antidepressants such as amitriptyline and ketamine suppress inflammatory cytokine production in individuals with MDD by downregulating the expression of the NLRP3 inflammasome and nuclear factor kappa B (NF-κB) in peripheral blood cells [48]. According to a meta-analysis, antidepressant treatment can significantly lower plasma concentrations of IL-4, IL-6, and IL-10 in patients with depressive disorders [49]. Furthermore, systematic reviews have summarized that ketamine reduces pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, a mechanism thought to contribute to its effectiveness in cases of treatment-resistant depression [50].

The roles of cyclooxygenase enzymes (COX- 1 and COX-2) in inflammation have also been investigated in this context. COX-1 is primarily associated with physiological maintenance, whereas COX-2 is induced during inflammation and triggers the production of pro-inflammatory prostaglandins. Non-selective COX-1 inhibition may increase the risk of gastrointestinal side effects, while selective COX-2 inhibition attenuates inflammation with a lower incidence of such adverse effects. Aspirin, which inhibits COX-2, has been found to decrease inflammatory responses. For example, an 8-week randomized controlled trial showed that patients treated with a combination of aspirin and sertraline had significantly improved depressive symptoms, suggesting that aspirin may enhance the efficacy of conventional antidepressants [51]. However, results from a large RCT aimed at prevention in healthy elderly participants indicated that low-dose aspirin did not lower depression incidence or hospitalization rates, which may point to insufficient anti-inflammatory action at that dose [52]. While COX-1 inhibitors also possess anti-inflammatory properties, selective COX-2 inhibitors are generally favored for depressive disorders due to a more favorable side effect profile. These agents have been shown to reduce depressive-like behaviors in animal models by inhibiting glial activation, lowering oxidative stress, and preventing neuronal apoptosis. For instance, celecoxib, a COX-2 selective inhibitor, has been reported to decrease central IL-1β and TNF-α while increasing anti-inflammatory IL-10 in rodents [8].

Omega-3 polyunsaturated fatty acids (n-3 PUFAs) are believed to exert antidepressant effects through modulation of inflammatory pathways. Patients with MDD often exhibit reduced levels of n-3 PUFAs, suggesting their relevance to the disorder's pathophysiology. While most randomized controlled trials indicate only modest efficacy for n-3 PUFAs, beneficial effects are most pronounced in individuals with signs of low-grade inflammation, hinting that the antidepressant potential of n-3 PUFAs may depend on their anti-inflammatory actions [53]. Minocycline can attenuate stress-induced depressive-like behaviors by blocking pro-inflammatory cytokine production and inducible nitric oxide synthase (iNOS) expression. It also inhibits microglial activation, decreases circulating IL-6, and reduces central cytokine secretion, contributing to symptom improvement [53]. An RCT has shown that probiotics, such as CCFM1025, significantly improve depressive mood, reduce gastrointestinal symptoms, and lower serotonin turnover rates in patients with MDD [54].

Vitamin D may influence both inflammation and suicide risk. Studies report that individuals who have attempted suicide have lower serum vitamin D levels compared to non-suicidal depressed patients and healthy controls, with vitamin D concentrations showing a negative correlation with IL-1β and IL-6 [55]. The active form of vitamin D (calcitriol) exerts anti-inflammatory effects by suppressing NF-κB activation and downstream signaling, thus reducing pro-inflammatory cytokine expression [56]. A recent meta-analysis found that vitamin D supplementation is effective in alleviating mild depressive symptoms, with even greater impact in cases of clinically significant depression; efficacy was notably enhanced at daily doses exceeding 2000 IU (50 μg) [57].

4.2 Effects of Physical Therapies on Inflammatory Cytokines

Physical therapies for depression encompass both established and emerging modalities. Traditional approaches include electroconvulsive therapy (ECT), repetitive transcranial magnetic

stimulation (rTMS), and transcranial electrical stimulation (TES), while novel interventions feature photobiomodulation (PBM), low-intensity pulsed ultrasound (LIPUS), and deep brain stimulation (DBS). Comparative analyses have shown that ECT combined with pharmacotherapy produces greater reductions in depressive symptoms compared to pharmacotherapy alone, with notable decreases in IL-6 and increases in TNF-α observed in the combination group [58]. In a study involving elderly patients with treatment-resistant depression, rTMS led to a sustained increase in brain-derived neurotrophic factor (BDNF), which was inversely correlated with depression severity as measured by HAMD scores. Additionally, patients receiving rTMS exhibited lower IL-1β and TNF-α levels than untreated counterparts, with cytokine concentrations positively correlating with depression scores [59].

Investigations by Tian et al. demonstrated that rTMS enhances nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2) in the hippocampus, resulting in decreased TNF-α, inducible nitric oxide synthase (iNOS), IL-1β, and IL-6 levels, thereby mediating both antidepressant and anxiolytic effects. The absence of Nrf2 negated these outcomes, underscoring the importance of Nrf2-driven anti-inflammatory pathways in rTMS efficacy [60]. In animal models, TES and its variant, transcranial direct current stimulation (tDCS), have been shown to attenuate neuroinflammation and microglial activity, as evidenced by diminished expression of IL-1β, IL-6, and TNF-α [61]. Clinical investigations, such as those by Brunoni et al., reported reductions in IL-1β, IL-6, IL-10, and TNF-α after tDCS treatment in depressive patients, though these changes did not achieve statistical significance compared to the sham group [62, 63].

Emerging physical therapies continue to show promise. PBM, particularly at a wavelength of 405 nm, has demonstrated significant potential for reducing IL-6 and IL-8, highlighting its anti-inflammatory capabilities [64]. While clinical applications of LIPUS are still in the early stages, animal studies indicate that LIPUS effectively suppresses TNF-α, IL-1β, and IL-6 via inhibition of the TLR4/NF-κB signaling pathway [65]. DBS targeting the anterior thalamic nucleus has been associated with lowered hippocampal caspase-3 activity and IL-6 levels, indicating anti-inflammatory and anti-apoptotic effects in rodent models [66].

Additionally, acupuncture—a central element in traditional Chinese medicine—has gained international attention for its efficacy and safety profile in depression management. Treatment at acupuncture points such as Baihui (GV20) and Yintang (EX-HN3) modulates IL-1β and IL-6 within the hippocampus and prefrontal cortex, thereby dampening neuroinflammation and alleviating depressive symptoms [67]. Further research by Zhu and colleagues showed that acupuncture decreases central and peripheral immune-inflammatory abnormalities by reducing TNF-α and IL-8, and influencing NF-κB signaling pathways [68]. Electroacupuncture, which integrates electrical stimulation with needle insertion, may further enhance these anti-inflammatory effects. In models of chronic mild stress-induced depression, electroacupuncture inhibits the NF-κB/NLRP3 pathway, diminishes nuclear translocation of NF-κB, decreases p-NF-κB and p-IκBα, and suppresses activation of the NLRP3 inflammasome. These changes culminate in significant reductions of IL- 6, IL-1β, IL-18, and TNF-α in the hippocampus, reversing neuroinflammation and mitigating depressive-like behaviors [69].

4.3 Effects of Psychological Therapies on Inflammatory Cytokines

Research examining the impact of psychological interventions on inflammation in depressive disorders remains relatively limited. Cognitive behavioral therapy (CBT), the most extensively studied and widely adopted form of psychotherapy for depression, has recently attracted growing attention for its potential immunomodulatory effects. A systematic review by Lopresti and colleagues analyzed 23 studies investigating the influence of CBT on inflammatory markers. The results indicated that, in 14 of these studies, at least one inflammatory marker showed a significant reduction following CBT intervention; conversely, three studies reported increased levels of some markers, while six studies observed no substantial change. Notably, three of the included studies assessed whether baseline inflammation influenced therapeutic outcomes, consistently finding that patients with higher initial levels of inflammation experienced poorer outcomes following CBT. These findings suggest a possible bidirectional relationship between CBT and inflammation, with both the anti-inflammatory potential of psychotherapy and the negative predictive value of baseline inflammation for treatment response [70].

5 Conclusion

Inflammatory cytokines are increasingly recognized as central contributors to the onset and progression of depressive disorders. Dysregulated cytokine expression may result in monoamine neurotransmitter imbalances, reduced neuroplasticity, and dysfunction of the

hypothalamic-pituitary-adrenal (HPA) axis, all of which intensify depressive symptomatology. Contemporary studies reveal a strong correlation between the degree of inflammation, the severity of clinical symptoms, and therapeutic response in individuals with depression. Various pharmacological agents—such as ketamine, minocycline, and omega-3 fatty acids—as well as physical treatments including electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and low-intensity pulsed ultrasound (LIPUS), have demonstrated promising antidepressant effects through their ability to modulate inflammatory pathways. Notably, psychological interventions like cognitive behavioral therapy (CBT) are also emerging as modulators of inflammatory markers, although their underlying mechanisms remain to be fully elucidated.

Moving forward, research should aim to further elucidate the pivotal functions of inflammatory cytokines in depression and focus on the development of precise, individualized treatment modalities. Integrative treatment frameworks that combine pharmacological, physical, and psychological approaches warrant exploration to optimize clinical outcomes. Additionally, special attention should be directed toward adolescent populations, utilizing longitudinal research designs and randomized controlled trials to rigorously assess the safety and efficacy of innovative interventions. These efforts are essential to advancing our scientific understanding and guiding the next generation of diagnostic and therapeutic strategies for depressive disorders.

Conflict of Interest Statement

The authors state no conflict of interest.

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