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Review

The role of inflammation and oxidative stress in the pathogenesis of depressive disorders: A review

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ABSTRACT

Introduction: Depressive disorders are among the leading causes of disability worldwide, and a substantial proportion of patients fail to achieve full remission with standard monoaminergic therapies. Consequently, increasing attention has been directed toward alternative pathophysiological mechanisms, particularly chronic inflammation and oxidative stress.

Methods: A narrative review was conducted based on a comprehensive search of PubMed, Scopus, Web of Science, and PsycINFO databases, including studies published between 2000 and 2025. The literature search strategy relied on precise keywords such as "depressive disorders," "chronic inflammation," "oxidative stress," and various "biological biomarkers." The analysis focused on inflammatory markers, oxidative stress parameters, and their association with depressive disorders. To ensure a rigorous study selection process, a two-stage screening strategy was applied, involving an initial evaluation of titles and abstracts followed by a comprehensive full-text review of the shortlisted articles by the authors.

Results: Available evidence indicates that patients with depression frequently exhibit elevated levels of pro-inflammatory markers, including interleukin-6, tumor necrosis factor-alpha, and C-reactive protein. Concurrently, increased production of reactive oxygen species and reduced activity of antioxidant enzymes have been observed. These processes are associated with alterations in neurotransmission, activation of the kynurenine pathway, and impaired neuroplasticity, partly mediated by decreased levels of brain-derived neurotrophic factor.

Conclusions: Inflammation and oxidative stress appear to represent important components of the pathophysiology of depression, particularly in a subset of patients. Their potential role as biomarkers and therapeutic targets remains promising but requires further validation in well-designed prospective studies, taking into account the clinical heterogeneity of depressive disorders.

KEYWORDS

depressive disorders, chronic inflammation, oxidative stress, biological biomarkers, neuroimmunology

INTRODUCTION

Depressive disorders represent one of the most pressing challenges in modern public health, severely undermining patients' quality of life and social functioning. The World Health Organization (WHO) estimates that depression affects over 280 million people worldwide, with

projections suggesting it will become the leading cause of disability globally in the coming decades [1]. Despite a broad range of available interventions, the efficacy of traditional treatments remains limited. A substantial proportion of patients—up to 40% by some estimates—fail to achieve meaningful clinical improvement when treated with classic strategies targeting monoaminergic systems [2]. This high rate of treatment resistance is forcing researchers to rethink established paradigms and look toward broader, systemic biological mechanisms underlying the disorder [3]. In recent years, biological psychiatry and neurophysiology have shifted focus toward the inflammatory hypothesis and the role of oxidative stress. Low-grade chronic inflammation is no longer viewed merely as a localized defense mechanism, but rather as a systemic dysfunction that directly impacts the central nervous system (CNS). Emerging literature consistently shows that individuals with depression exhibit significantly higher levels of pro-inflammatory cytokines—such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP)—compared to healthy controls [4,5]. These molecules cross the blood-brain barrier, triggering microglial activation and disrupting neurotransmitter balance, which ultimately drives mood degradation and cognitive decline [6]. This link is further supported by clinical observations of patients undergoing immunotherapy (e.g., with interferon-alpha) for viral infections, where the sudden surge of pro-inflammatory cytokines frequently triggers full-blown depressive episodes [7]. Parallel to these immunological pathways, oxidative stress plays a key role in the pathogenesis of depression. This state arises from an imbalance between reactive oxygen species (ROS) production and the body's antioxidant defenses, leading to progressive damage to membrane lipids, proteins, and DNA structures [8]. This review aims to critically analyze the current literature regarding the interplay between chronic inflammation and oxidative stress in the development of depression.

METHODS

This narrative review follows methodological guidelines for review articles, with a particular emphasis on maintaining transparency in source selection. To identify relevant literature, a multi-stage search was conducted across international scientific databases: PubMed, Scopus, Web of Science, and PsycINFO. The search window was limited to publications released between 2000 and 2025.

The search strategy relied on precise keywords combining depressive disorders (major depressive disorder, depressive symptoms) with oxidative stress (free radicals, lipid peroxidation) and inflammatory processes (cytokines, CRP, IL-6). Only high-quality sources were included in the analysis: original research papers—both clinical and epidemiological—alongside peer-reviewed meta-analyses and systematic reviews published in English or Polish. Single case reports, editorial commentaries, and studies with ambiguous methodologies (such as those lacking control groups)

were deliberately excluded. Papers focusing on other psychiatric disorders were also omitted unless they directly addressed the pathophysiology of depression. The gathered literature underwent qualitative synthesis to detect recurring trends, highlight inconsistencies across study results, and outline prospects for future interventions focused on stabilizing patients' biological parameters.

RESULTS

Research evidence accumulated in recent years points to a tight, bidirectional relationship between low-grade chronic inflammation and the pathogenesis of mood disorders. Traditional models focusing solely on isolated neurotransmitter deficiencies are giving way to systemic frameworks where overactivation of the immune system is treated as a major pathophysiological driver [9]. Compiled clinical data indicate that individuals struggling with depression exhibit significantly elevated concentrations of circulating pro-inflammatory markers—specifically IL-6, TNF-α, and CRP—when compared to age-matched control groups [10,11]. Importantly, recent meta-analyses confirm that this chronic shift toward a pro-inflammatory state is particularly pronounced in patients whose symptoms fail to remit over time, suggesting that this biological profile can become deeply entrenched [5,12].

The persistence of elevated systemic cytokines triggers a cascade of adverse physiological changes that directly impact brain tissue. Inflammatory molecules compromise the endothelial integrity of the blood-brain barrier, increasing its permeability; this, in turn, amplifies the local immune response and activates microglia. A pivotal event observed in this state is the upregulation of enzymes—primarily indoleamine 2,3-dioxygenase—which reroute the body's metabolic pathways. Under inflammatory conditions, tryptophan, the natural precursor to serotonin, is increasingly shunted into the kynurenine pathway. This shift imposes a dual burden: it potentially restricts neurotransmitter availability while simultaneously promoting the intracellular accumulation of quinolinic acid and other neurotoxic metabolites that damage neurons and impair natural neuroplasticity [6,7].

Parallel to these immunological pathways, oxidative stress serves as a critical driver in the degradation of neural structures. Defined as a persistent imbalance between ROS production and the capacity of endogenous antioxidant defenses, this state acts as a direct destructive force on cellular architecture [13,14]. Enzymatic assays have repeatedly revealed compromised activity in core protective proteins, including superoxide dismutase (SOD) and glutathione peroxidase (GPx) [15,16].

Available data clearly demonstrate that these processes do not occur in isolation but rather form a physiological vicious cycle. Oxidative stress functions as an intracellular messenger that activates

pro-inflammatory pathways—largely through the transcription factor NF-κB—while stimulated immune cells generate additional pools of free radicals as part of their defense mechanisms [17,18]. Understanding this dual biological burden opens entirely new avenues for patient health profiling based on objective biomarkers, such as CRP, IL-6, lipid profiles, or peroxidation indices. This integrated assessment of the body's internal environment has laid the groundwork for precision physiological interventions targeted directly at the root cause [19,20]. Research highlights a substantial potential for therapies aimed at restoring redox homeostasis and dampening inflammation through measures like targeted nutritional support rich in omega-3 fatty acids, polyphenols, and substances that bolster antioxidant pathways, such as glutathione precursors [21,22].

In the search for the primary sources of chronic inflammation in patients with low mood, researchers are increasingly turning their attention toward the gut microbiota and the gut-brain axis. Current analyses indicate that intestinal dysbiosis—the disruption of the microflora's natural balance—compromises the epithelial barrier, a phenomenon commonly referred to as "leaky gut syndrome." Under these conditions, bacterial lipopolysaccharides translocate from the portal circulation into the systemic bloodstream. This process, known as metabolic endotoxemia, acts as an exceptionally potent stimulus that drives the immune system toward continuous, systemic production of pro-inflammatory cytokines, including the previously mentioned IL-6 and TNF-α [23,24,25]. This highlights that the biological roots of mood disorders can reside outside the CNS, suggesting that impaired digestive and absorptive processes may provide the underlying physiological framework for neuroinflammation.

The physiological consequence of sustained oxidative stress and neuroinflammation is a drastic impairment of repair mechanisms within neural tissue. Molecular studies demonstrate that an environment rich in free radicals and pro-inflammatory cytokines suppresses the expression of the gene encoding brain-derived neurotrophic factor (BDNF). This protein serves as a master regulator of neuroplasticity, essential for both the growth of new synapses and the survival of existing neurons [26]. A chronic deficit in BDNF, commonly observed in advanced stages of depression, correlates with macroscopic changes in brain architecture—most notably the atrophy of hippocampal structures and the prefrontal cortex [27]. Understanding this pathway underscores that low mood is not merely a psychological phenomenon, but rather the structural consequence of physical degeneration and stalled cellular renewal. This reality further reinforces the critical need for early implementation of antioxidant and neuroprotective strategies in patient care.

Table I. Inflammatory and oxidative biomarkers in depression (compiled from [4,5,10,15,19,24,26])

Biomarker	Direction of Change in Depression	Strength of Evidence	Clinical Significance	Limitations
CRP	↑	moderate (meta-analyses)	a marker of inflammation; may be associated with a poorer response to treatment	low specificity (obesity, infections, lifestyle)
IL-6	↑	moderate (meta-analyses)	immune system activation indicator	high variability between studies
TNF-α	↑	moderate	participation in neuroinflammatory processes	inconsistent research results
Kynurenine pathway	↑ activity	moderate	associated with tryptophan metabolism and the formation of neuroactive metabolites	no routine clinical use
ROS	↑	moderate	indicates redox imbalance	lack of standardization of measurement methods
SOD, GPx	↓ activity	moderate	reflects weakened antioxidant defense	variability of determination methods
BDNF	↓	relatively strong	associated with neuroplasticity and the course of	intermediate marker, limited

			depression	specificity
Gut microbiota	dysbiosis	emerging	potential impact on the gut-brain axis	limited clinical data, predominance of preclinical studies

CRP – C-reactive protein; IL-6 – interleukin-6; TNF-α – tumor necrosis factor-alpha; ROS – reactive oxygen species; SOD – superoxide dismutase; GPx – glutathione peroxidase; BDNF – brain-derived neurotrophic factor

DISCUSSION

A growing body of scientific evidence demands a thorough reevaluation of how we approach mood disorders. The literature reviewed here demonstrates that the pathogenesis of depression extends far beyond localized neurotransmitter deficits, representing a complex, multifactorial biological dysfunction. Low-grade inflammation, chronic oxidative stress, dysbiosis along the gut-brain axis, and the secondary impairment of neuroplasticity (driven by declining BDNF levels) operate as critical mechanisms that actively fuel and sustain pathology at both the cellular and tissue levels.

Interpreting the compiled research highlights several challenges that have historically limited the ability to draw universal clinical conclusions. A major issue reported in the literature is the pronounced variability in biomarker concentrations across studied populations. These discrepancies largely stem from methodological shortcomings in many studies, which tend to view the body in isolation. Beyond general heterogeneity, significant variations often arise from differences in the analytical sensitivity and methodologies of laboratory assays used across separate clinical trials, complicating direct cross-study comparisons. Furthermore, the well-documented diurnal variation of circulating cytokines introduces substantial measurement noise unless sampling times are strictly standardized. Crucially, underlying or subclinical metabolic comorbidities frequently drive low-grade systemic inflammation independently, thereby confounding the interpretation of whether these peripheral markers reflect the primary pathophysiology of depression or an underlying somatic strain. While variables such as the state of the gut microbiota or daily dietary habits drastically modulate the body's immune response and antioxidant capacity, they remain chronically under-controlled in research protocols evaluating the efficacy of antidepressant interventions [24,25].

A particularly prominent gap in the current understanding of this issue is the underestimation of both circadian rhythms and chronic allostatic load. Chronic psychological stress is not merely an emotional phenomenon, but a measurable biological process that amplifies intracellular free

radical production through the overactivation of the hypothalamic-pituitary-adrenal axis [28]. Furthermore, the sleep deficits that typically accompany mood disorders directly impair the functioning of the brain's glymphatic system—the core mechanism responsible for nocturnally "clearing" neural tissue of neurotoxic metabolites and excess cytokines [29]. Without adequate nocturnal regeneration, quenching neuroinflammation becomes physiologically impossible, trapping the patient in a biological vicious cycle that cannot be broken by interventions targeting a single receptor alone.

From a practical perspective, shifting the focus from classic symptom suppression toward integrated biological support points to promising opportunities. Utilizing comprehensive biomarker profiling—incorporating not only CRP and peroxidation indices but also intestinal barrier integrity—would lay the groundwork for highly individualized interventions [30]. Such an approach, centered on restoring the body's natural homeostasis through targeted nutritional protocols, the correction of antioxidant deficiencies, and the optimization of the sleep environment, may hold the key to helping individuals struggling with chronic mood disorders. Consequently, there is an urgent need for large-scale, prospective studies that account for this broader physiological and environmental context of human bodily function.

Clinical implications

Against the backdrop of growing evidence linking inflammatory processes and oxidative stress to the pathogenesis of depressive disorders, exploring how to apply these findings in daily clinical practice is becoming increasingly relevant. However, it must be emphasized that the current state of knowledge does not yet justify the routine deployment of a broad biomarker panel for all patients; instead, their use should be considered selectively.

The most robust data available concern inflammatory markers such as CRP and IL-6. Clinical studies show that elevated levels of these parameters are more prevalent in patients with treatment-resistant depression, pointing to a distinct patient subgroup with a pronounced inflammatory component [4,5]. Nevertheless, these markers lack the specificity required to serve as standalone diagnostic tools. Their concentrations are influenced by numerous confounding variables—including obesity, co-occurring chronic illnesses, and daily lifestyle habits—which complicates clear clinical interpretation [19].

Consequently, attention is increasingly shifting toward therapies aimed at reducing chronic inflammation and oxidative stress. Available data indicate that specific interventions could serve as valuable adjuncts to standard care, particularly for individuals exhibiting elevated inflammatory markers. One of the most frequently analyzed compounds is N-acetylcysteine, a glutathione precursor. While some clinical trials have reported a reduction in the severity of depressive

symptoms following its administration, the findings remain heterogeneous and require further confirmation [21]. Similar observations apply to omega-3 fatty acids. Their supplementation may support antidepressant treatment as part of a combination therapy, though the resulting effect is typically moderate and does not offer a viable alternative to standard pharmacotherapy [22]. Moving forward, the conceptual framework of "precision psychiatry"—where therapeutic decisions are guided by the patient's unique biological profile—represents a major developmental direction [23]. Although promising, implementing this approach in clinical settings requires further prospective studies and the standardization of biomarker assays.

Limitations

Despite growing evidence linking inflammation and oxidative stress to the pathogenesis of depression, interpreting these data involves navigating several fundamental constraints. A primary limitation is that most available literature relies on observational studies; consequently, these findings make it difficult to definitively determine whether inflammatory disruptions play a causal role in the onset of depressive symptoms [3]. It remains entirely plausible that elevated levels of inflammatory markers represent a consequence of the disorder or co-occurring somatic conditions, rather than functioning as an independent risk factor.

An additional complication stems from the low specificity of biomarkers such as CRP and IL-6. Their values fluctuate in response to numerous variables completely unrelated to psychiatric pathology, including body mass index, physical activity levels, smoking, and chronic systemic diseases. In clinical practice, this confounding reality severely limits the interpretation of these parameters in relation to depressive disorders, demanding a much broader clinical context for any meaningful analysis [19]. Furthermore, depression itself remains a highly heterogeneous clinical entity encompassing distinct biological phenotypes. Emerging evidence suggests that inflammatory mechanisms may drive pathology only within a specific patient subgroup [11]. In the case of oxidative stress, researchers face the added challenge of a widespread lack of standardized measurement methods, which directly restricts the reproducibility of results across different studies [15].

CONCLUSIONS

Mood disorders, such as depression, are increasingly recognized not merely as isolated neurological conditions, but as systemic pathologies affecting the entire body. Within low-grade chronic inflammatory states—which frequently intertwine with oxidative stress—a distinct, reciprocal feedback loop emerges; these processes fuel one another, driving cellular damage and undermining the brain's capacity for adaptation and regeneration. Integrating parameters such as inflammatory or oxidative markers into future personalized diagnostic algorithms would enable a

more precise clinical assessment and, crucially, a highly tailored therapeutic approach. The underlying strategy shifts the focus from superficial symptom management to the root causes of these disorders, aiming ultimately to restore the body's natural homeostasis. Interventions targeting nutrition, patient environments, and the correction of antioxidant deficiencies hold substantial potential for mitigating these complex conditions. Naturally, before such frameworks can be adopted as standard care, extensive rigorous research remains essential to standardize methodologies and facilitate their integration into daily clinical practice.

Based on the available data, an integrated pathophysiological model can be proposed. In this framework, chronic inflammation drives the activation of the kynurenine pathway, disrupting neurotransmission [10]; concurrently, oxidative stress induces structural damage to neuronal architecture [15], while a decline in BDNF levels impairs natural neuroplasticity [26]. Environmental factors—including diet, gut microbiota composition, and chronic stress—actively modulate these interconnected pathways, heavily influencing both their intensity and clinical progression.

Conflict of interest

The authors declare no conflict of interest.

Use of AI tools statement

AI tools as Gemini Google were used to assist in the translation and formulation of the text.

Authors' contribution

Study design – K. Nikel, M. Stojko

Data collection – K. Nikel, M. Stojko, J. Chudy

Manuscript preparation – K. Nikel, M. Stojko, J. Chudy, J. Smolarczyk

Literature research – K. Nikel, M. Stojko, J. Chudy

Final approval of the version to be published – K. Nikel, M. Stojko, J. Chudy, J. Smolarczyk

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