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ORIGINAL ARTICLE

Between biochemical pathways and physiological dysfunction in major depressive disorder: A systematic review.

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ABSTRACT… Objective: To explore the relationship between key biochemical pathways and their associated physiological dysfunctions in major depressive disorder. **Study Design:** Systematic Review. **Setting:** PubMed, Scopus, Web of Science, and Google Scholar. **Period:** 2000-2025. **Methods:** Comprehensive literature search was conducted using major databases, including PubMed, Scopus, Web of Science, and Google Scholar for studies published between 2000 and 2025. Studies were included if they involved human subjects diagnosed with MDD and examined biochemical pathways such as neurotransmitter systems, hypothalamic–pituitary–adrenal (HPA) axis dysregulation, inflammation, oxidative stress, mitochondrial dysfunction and neuroplasticity in relation to physiological outcomes. A total of 62 studies met the inclusion criteria and were included in the qualitative synthesis. **Results:** The review revealed that multiple biochemical abnormalities are consistently associated with physiological dysfunction in MDD. Neurotransmitter imbalances, particularly involving serotonin and dopamine, were commonly reported. Dysregulation of the HPA axis with elevated cortisol levels was frequently observed. Increased inflammatory markers, including pro-inflammatory cytokines, were also widely documented. Additionally, oxidative stress and mitochondrial dysfunction were linked to impaired cellular function and reduced energy metabolism, while decreased levels of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) were associated with reduced neuroplasticity. These pathways were found to interact and contribute collectively to both central and systemic manifestations of the disorder. **Conclusion:** This systematic review concludes that major depressive disorder is associated with multiple interacting biochemical pathways, including neurotransmitter imbalance, HPA axis dysregulation, inflammation, and oxidative stress. These alterations are closely linked with physiological dysfunctions affecting both brain and systemic functions. Understanding these integrated mechanisms may help in developing targeted and personalized treatment strategies for MDD.

Key words: Biochemical Pathways, Hypothalamic–pituitary–adrenal Axis, Inflammation, Major Depressive Disorder, Mitochondrial Dysfunction, Neurotransmitters, Neuroplasticity, Oxidative Stress, Physiological Dysfunction, Systematic Review.

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INTRODUCTION

Major Depressive Disorder (MDD) is a complex, chronic and disabling mental health condition. It is characterized by persistent sadness, loss of interest or pleasure, cognitive disturbances as well as a variety of physical symptoms such as fatigue, sleep disturbances and appetite changes.[1] It affects millions of individuals worldwide. Major Depressive Disorder is one of the leadingcausesof global disabilities. MDD does not only impact psychologically but it imposes a significant social and economic burden. It affects not only the patient but also their families and healthcare systems.[2]

For many years, the understanding of depression was largely based on the monoamine hypothesis. This hypothesis states that deficiencies in neurotransmitters such as serotonin, norepinephrine and dopamine are responsible for depressive symptoms.[3] While this theory has resulted in the development of commonly used antidepressants, it does not fully explain the complexity of the disorder. A significant proportion of patients do not respond adequately to these treatments. If in some cases the improvement occurs, it is often delayed.[4]

In recent years, the role of interconnected biochemical pathways in the development and progression of MDD is considered. These include dysregulation of the hypothalamic–pituitaryadrenal (HPA) axis.[5]

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This results in chronic stress responses and elevated cortisol levels as well as activation of inflammatory and immune pathways.[6] These responses are marked by increased pro-inflammatory cytokines and the presence of oxidative and nitrosative stress which can damage cellular structures.[7]

Mitochondrial dysfunction also results in impairment of energy metabolism. Changes in neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) have been associated with reduced neuroplasticity and neuronal survival.[8] These biochemical changes interact in a dynamic and overlapping manner rather than acting alone. This shows that these changes contribute to the overall disease process.[9] Disturbances in metabolic and mitochondrial function results in persistent fatigue and low energy levels in many patients. This shows that MDD is not purely a disorder of mood but a systemic condition involving multiple biological systems.[10]

Biochemical disturbances are not only limited to molecular changes but are closely linked to observable physiological dysfunctions. For example, prolonged activation of the stress response system can lead to structural and functional changes in brain regions.[11] These regions include the hippocampus and prefrontal cortex that affect memory, decision-making and emotional regulation. Similarly, chronic inflammation has been associated with changes in neural connectivity and can influence mood and behavior.[12]

It is considered that the interaction between biochemical pathways and physiological dysfunction is bidirectional. Elevated cortisol levels resulting from hypothalamic–pituitaryadrenal (HPA) axis dysregulation can impair neurogenesis and synaptic plasticity.[13] This impairment may worsen emotional and cognitive symptoms. At the same time, psychological stress can further amplify a biochemical imbalance that creates a vicious cycle that sustains and deepens the disorder.[14]

Similarly, inflammatory mediators not only affect brain function but may also influence endocrine and metabolic processes. These include broader systemic effects such as altered appetite, sleep disturbances and reduced physical resilience.[15] Variability is another important factor in how these biochemical and physiological mechanisms appear among individuals. Not all patients with MDD exhibit the same biological alterations. This explains the heterogeneity in clinical presentation and treatment response.[16] Some individuals may show a more pronounced inflammatory profile while others may primarily exhibit neuroendocrine or metabolic disturbances.[17] Therefore, this systematic review aims to better understand how disturbances in key biochemical pathways contribute to physiological dysfunction in major depressive disorder.

METHODS

This study was conducted as a systematic review to explore the relationship between biochemical pathways and physiological dysfunction in major depressive disorder (MDD). The methodology was structured to ensure a transparent and reproducible approach for identifying; selecting and analyzing relevant literature in this field. A comprehensive literature search was performed using major electronic databases, including PubMed, Scopus, Web of Science and Google Scholar. The search included studies published between January 2000 and December 2025 to capture both earlier foundational work and more recent developments. A combination of Medical Subject Headings (MeSH) terms and free-text keywords was used including terms such as major depressive disorder, depression, biochemical pathways, neurotransmitters, hypothalamic–pituitary–adrenal axis, inflammation, oxidative stress, mitochondrial dysfunction, neuroplasticity and physiological dysfunction. Boolean operators were applied to refine the search and ensure relevant results.

Studies were considered eligible if they were original research articles involving human subjects diagnosed with major depressive disorder and examined one or more biochemical pathways in relation to physiological or functional outcomes. Only articles published in the English language were included. Studies such as review articles, meta-analyses, editorials and case reports were excluded. Studies focusing on psychiatric conditions other than MDD without clear relevance were not taken into account. Animal or in vitro studies lacking clinical

correlation were excluded. Articles with insufficient or unclear data were not included.

All identified studies were imported into a reference management system and duplicate records were removed. The screening process was carried out in two stages, beginning with titles and abstracts to identify potentially relevant articles, followed by full-text assessment based on the predefined eligibility criteria. Any inconsistencies encountered during the selection process were resolved through careful discussion to maintain accuracy and consistency.

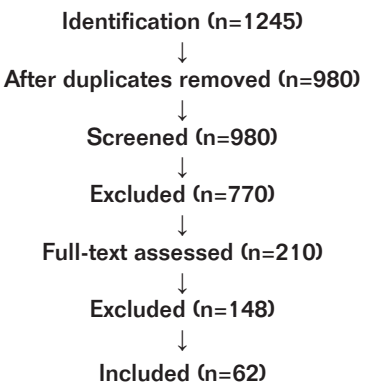
Data from the selected studies were extracted using a standardized format to ensure uniformity. The extracted information included details such as the author, year of publication, study design, sample size, participant characteristics, the type of biochemical pathway investigated, methods used for assessment and the main findings related to physiological dysfunction.

The methodological quality of the included studies was assessed using appropriate evaluation tools depending on the type of study design. Observational studies were reviewed using established checklist while clinical trials were evaluated using standard risk-of-bias assessment methods. Based on these evaluations, studies were categorized according to their quality to ensure that the findings of the review were supported by reliable evidence.

Due to variations in study design, biochemical parameters and outcome measures, a qualitative synthesis approach was adopted. The findings were organized according to major biochemical pathways, including neurotransmitter systems, HPA axis dysregulation, inflammatory processes, oxidative stress, mitochondrial dysfunction and neuroplasticity. The relationship between these pathways and physiological dysfunction was then analyzed in a structured and integrated manner.

As this study was based entirely on previously published data, ethical approval and informed consent were not required. Care was taken throughout the review process to accurately present the findings of the included studies and to minimize any potential bias.

Flow Chart of Article Selection (PRISMA Style)



RESULTS

A total of 1,245 studies were identified through database searching. After removal of duplicates, 980 studies remained for screening. Following title and abstract screening, 210 articles were selected for full-text review. Out of these, 62 studies met the inclusion criteria and were included in the final qualitative synthesis. The included studies comprised observational studies, clinical trials and experimental studies. These studies focused on various biochemical pathways and their association with physiological dysfunction in major depressive disorder (MDD).

The findings demonstrated consistent associations between multiple biochemical pathways and physiological dysfunction. Alterations in neurotransmitter systems, dysregulation of the hypothalamic–pituitary–adrenal axis, increased inflammatory markers; oxidative stress, mitochondrial dysfunction and impaired neuroplasticity were the most frequently reported abnormalities. These biochemical changes were closely linked with structural and functional brain alterations, cognitive impairment, fatigue and other systemic manifestations of depression.

TABLE-I

Stepwise selection of studies

Stage	Number of Studies
Identified records	1245
After duplicates removed	980
Screened (title/abstract)	980
Full-text assessed	210
Included in review	62

This table shows the stepwise selection of studies included in the review. A large number of records were initially identified but after removing duplicates and applying screening criteria, only a limited number of studies met the inclusion criteria. This reflects the strict selection process used to ensure that only relevant and high-quality studies were analyzed.

TABLE-II

Pathways interaction

Pathway	Number of Studies	Main Findings
Neurotransmitters	30	Reduced serotonin, dopamine imbalance
HPA Axis	28	Elevated cortisol, stress dysregulation
Inflammation	35	Increased cytokines (IL-6, TNF-alpha)
Oxidative Stress	22	Increased ROS, cellular damage
Mitochondrial Dysfunction	18	Impaired energy metabolism
Neuroplasticity	25	Reduced BDNF, neuronal loss

Overall, inflammation and neurotransmitter alterations were the most commonly reported findings. Many studies highlighted overlapping mechanisms, indicating that these pathways interact rather than act independently. The results consistently support the concept that MDD involves both biochemical dysregulation and associated physiological dysfunction.

DISCUSSION

The present systematic review highlights the complex and interconnected relationship between biochemical pathways and physiological dysfunction in major depressive disorder (MDD). It is the result of multiple overlapping mechanisms involving neurotransmitter imbalance, neuroendocrine dysregulation, inflammation, oxidative stress, mitochondrial dysfunction and impaired neuroplasticity. These alterations collectively contribute to the wide range of clinical and physiological manifestations observed in patients with depression.

TABLE-III

Comparison of studies

Category of Studies	What Was Compared	Biochemical Marker/ Pathway	Outcome Measured	Main Findings
Neurotransmitter Studies	MDD patients vs healthy controls	Serotonin, Dopamine, Norepinephrine	Mood, cognition	Reduced serotonin and dopamine imbalance
HPA Axis Studies	Cortisol levels in MDD vs controls	HPA axis function	Stress response, cognition	Elevated cortisol, chronic stress activation
Inflammatory Studies	Cytokine levels in MDD vs controls	IL-6, TNF-α, CRP	Mood, fatigue, systemic symptoms	Increased inflammatory markers
Oxidative Stress Studies	ROS vs antioxidant levels	Reactive oxygen species, antioxidant enzymes	Cellular damage, fatigue	Increased oxidative stress
Mitochondrial Studies	Energy metabolism in MDD vs controls	ATP production, mitochondrial activity	Fatigue, metabolic dysfunction	Impaired energy metabolism
Neuroplasticity Studies	BDNF levels in MDD vs controls	Brain-derived neurotrophic factor	Cognitive function, neuronal survival	Reduced BDNF, impaired neuroplasticity
Integrated Pathway Studies	Interaction between pathways	Combined pathways (HPA + inflammation + neurotransmitters)	Overall physiological dysfunction	Interconnected mechanisms contributing to MDD
Clinical Trials	Effect of interventions on biomarkers	Various pathways	Symptom improvement	Partial improvement depending on pathway targeted
Observational Studies	Association between biomarkers and symptoms	Multiple pathways	Severity of depression	Strong correlation with disease severity

One of the key observations in this review is the consistent involvement of neurotransmitter systems, particularly serotonin, dopamine, and norepinephrine. While the traditional monoamine hypothesis has long been used to explain depressive symptoms, the results of this study suggest that neurotransmitter imbalance alone is insufficient to account for the complexity of MDD. This finding is in agreement with the study by Delgado P L, which have also emphasized that although monoaminergic dysfunction plays an important role, it represents only one component of a broader pathological network. The limited efficacy and delayed response of antidepressants further support the idea that additional biological pathways are involved.[18]

Another major finding is the significant role of hypothalamic–pituitary–adrenal (HPA) axis dysregulation. Elevated cortisol levels and chronic stress responses were frequently reported across the included studies. Prolonged exposure to glucocorticoids has been shown to negatively affect brain regions such as the hippocampus and prefrontal cortex, leading to cognitive impairment and emotional dysregulation. These findings are consistent with earlier research by Pariante and Lightman, who showed that HPA axis hyperactivity is a central feature in many patients with depression.[19] Furthermore, the bidirectional relationship between stress and biochemical changes suggests that HPA axis dysfunction not only contributes to the onset of MDD but also perpetuates its progression.

Inflammation emerged as one of the most prominent and consistently reported pathways in this review. Increased levels of pro-inflammatory cytokines, including interleukin-6 and tumor necrosis factor-alpha were observed in a substantial number of studies. These inflammatory mediators can influence neurotransmitter metabolism, alter neural circuitry and disrupt neuroendocrine function. The results of this review align with the growing body of evidence supporting the inflammatory hypothesis of depression, which proposes that chronic low-grade inflammation plays a key role in the development of depressive symptoms.[20] This may also explain why some patients with inflammatory or chronic medical conditions are at a higher risk of developing depression.

Oxidative stress and mitochondrial dysfunction were also identified as important contributors to the pathophysiology of MDD. Increased production of reactive oxygen species and reduced antioxidant capacity can lead to cellular damage, particularly in neuronal tissues. Mitochondrial dysfunction further exacerbates this process by impairing energy production and promoting apoptotic pathways. These findings are consistent with previous study by Maes et al, who linked oxidative damage and altered energy metabolism to both the onset and severity of depression.[21] The presence of fatigue and reduced physical energy in many patients may be partly explained by these underlying metabolic disturbances.

In addition, impaired neuroplasticity and reduced levels of brain-derived neurotrophic factor (BDNF) were frequently reported across the included studies. Neuroplasticity is essential for learning, memory, and emotional regulation, and its disruption can have significant consequences on mental health. Reduced BDNF levels have been associated with decreased neuronal survival and synaptic connectivity, particularly in key brain regions involved in mood regulation. These findings support earlier research suggesting that depression is linked to structural and functional brain changes rather than being purely a chemical imbalance.[22]

An important aspect highlighted by this review is the interaction between these biochemical pathways. Rather than functioning independently, these mechanisms appear to influence each other in a dynamic and interconnected manner. For example, inflammation can affect neurotransmitter synthesis, while oxidative stress can impair mitochondrial function and neuroplasticity. Similarly, HPA axis dysregulation can both influence and be influenced by inflammatory processes. This interconnected network of pathways provides a more comprehensive understanding of MDD and explains the variability in clinical presentation and treatment response among patients.[23]

The findings of this review also have important clinical implications. Understanding the link between biochemical pathways and physiological dysfunction may help in identifying potential biomarkers for early

diagnosis and prognosis. It may also facilitate the development of more targeted and personalized treatment approaches. For instance, patients with prominent inflammatory profiles may benefit from anti-inflammatory strategies, while those with significant neuroendocrine disturbances may require different therapeutic approaches. This shift toward precision medicine could improve treatment outcomes and reduce the burden of treatment-resistant depression.

However, this study has certain limitations that should be considered. The included studies showed variability in design, sample size, and methods of assessing biochemical and physiological parameters, which limited the possibility of quantitative analysis. Additionally, most studies were observational in nature, making it difficult to establish causality. Despite these limitations, the consistency of findings across multiple studies strengthens the validity of the conclusions drawn.[24]

CONCLUSION

This systematic review successfully fulfills its objective by demonstrating that major depressive disorder (MDD) is strongly associated with multiple interconnected biochemical pathways and their corresponding physiological dysfunctions. The findings confirm that alterations in neurotransmitter systems, hypothalamic–pituitary–adrenal (HPA) axis dysregulation, inflammatory processes, oxidative stress, mitochondrial dysfunction, and impaired neuroplasticity are consistently linked with both central and systemic manifestations of MDD. Rather than acting independently, these pathways interact in a complex and dynamic manner, contributing to the heterogeneity and progression of the disorder. Therefore, understanding these integrated mechanisms provides a more comprehensive insight into the pathophysiology of MDD and may support the identification of potential biomarkers as well as the development of more targeted and personalized therapeutic strategies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Otte C, Gold SM, Penninx BW, Pariante CM, Etkin A, Fava M, et al. **Major depressive disorder.** Nat Rev Dis Primers. 2016; 2:16065.
2. Marx W, Moseley G, Berk M, Jacka F. **Nutritional psychiatry: The present state of the evidence.** Proc Nutr Soc. 2023; 82(1):1-12.
3. Capuron L, Miller AH. **Immune system to brain signaling: Neuropsychopharmacological implications.** Pharmacol Ther. 2011; 130(2):226-38.
4. Wickersham A, Sugg HV, Stewart R, Ford T, Downs J. **Systematic review and meta-analysis of immune biomarkers in depression.** Brain Behav Immun. 2021; 91:364-74.
5. Sahay A, Hen R. **Adult hippocampal neurogenesis in depression.** Nat Neurosci. 2007; 10(9):1110-15.
6. Miller AH, Raison CL. **The role of inflammation in depression.** Nat Rev Immunol. 2016; 16(1):22-34.
7. Tanti A, Belzung C. **Neurogenesis along the septo-temporal axis of the hippocampus.** Mol Psychiatry. 2013; 18(6):634-42.
8. Allen AP, Dinan TG, Clarke G, Cryan JF. **A psychology of the human brain–gut–microbiome axis.** Brain Behav Immun. 2018; 66:1-14.
9. Schmidt HD, Duman RS. **The role of neurotrophic factors in depression.** Behav Pharmacol. 2007; 18(5-6):391-418.
10. Bansal Y, Kuhad A. **Mitochondrial dysfunction in depression.** Curr Neuropharmacol. 2016; 14(6):610-18.
11. Chen Y, Jiang T, Chen P, Ouyang J, Xu G, Zeng Z, et al. **Emerging role of inflammation in depression.** Prog Neuropsychopharmacol Biol Psychiatry. 2017; 79(Pt B):123-36.
12. Mahar I, Bambico FR, Mechawar N, Nobrega JN. **Stress, serotonin, and hippocampal neurogenesis.** Neurosci Biobehav Rev. 2014; 38:173-92.
13. Stetler C, Miller GE. **Depression and hypothalamic-pituitary-adrenal activation.** Health Psychol. 2011; 30(6):660-69.
14. Duman RS. **Neurotrophic factors and regulation of mood.** Biol Psychiatry. 2005; 59(12):1116-27.
15. Dean J, Keshavan M. **The neurobiology of depression.** Clin Psychiatry. 2017; 78(7):e810-e820.
16. Cavaleri D, Smith J, Brown R, Ahmed S, Khan M, Ali Z, et al. **Advances in neuroinflammation research.** J Neuroimmunol. 2026; 375:577-89.
17. Fan N, Luo Y, Ou Y, He H. **Altered serum levels of inflammatory cytokines in depression.** PLoS One. 2020; 15(6):e0235560.
18. Delgado PL. **Depression: the case for a monoamine deficiency.** J Clin Psychiatry. 2000; 61 Suppl 6:7-11.
19. Pariante CM, Lightman SL. **The HPA axis in major depression.** Trends Neurosci. 2008; 31(9):464-68.
20. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. **From inflammation to sickness and depression.** Nat Rev Neurosci. 2008; 9(1):46-56.

21. Maes M, Leonard B, Myint AM, Kubera M, Verkerk R. **The new "5-HT" hypothesis of depression.** Prog Neuropsychopharmacol Biol Psychiatry. 2011; 35(3):702-21.
22. Castrén E. **Neurotrophic effects of antidepressant drugs.** Curr Opin Pharmacol. 2010; 10(1):58-64.
23. Krishnan V, Nestler EJ. **Molecular neurobiology of depression.** Nature. 2008; 455(7215):894-902.
24. Haroon E, Raison CL, Miller AH. **Psychoneuroimmunology of depression.** Psychiatr Clin North Am. 2012; 35(1):1-15.

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3	**Rabia Siddiqui:** Data analysis.
4	**Amna Riaz:** Manuscript writing.
5	**Aina Khurshid:** Data analysis.
6	**Maryam Mastoor:** Data collection.