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Review

Biomarkers of Depressive Disorder and Dietary Intervention Strategies

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Abstract: Depressive disorder (DD) is a multifactorial mental illness involving dysregulation across neuroendocrine, immune, metabolic, and microbial systems. Despite substantial research progress, diagnostic and therapeutic approaches remain largely symptom-based, lacking biological precision. This study addresses this gap by systematically reviewing key biomarkers, such as cortisol, IL-6, CRP, BDNF, and the kynurenine/tryptophan ratio, and examining their modulation through dietary interventions. Using an integrative literature analysis spanning psychiatry, molecular biology, and nutritional science, the paper explores how the Mediterranean diet, anti-inflammatory diet, and probiotics/prebiotics regulate inflammatory cytokines, neurotrophic factors, and gut microbiota activity. Results indicate that these nutritional models can attenuate systemic inflammation, enhance neurotrophic signaling, normalize HPA axis function, and restore microbial balance, thereby improving depressive symptoms. The findings underscore the potential of a biomarker-guided, diet-based framework for precision management of depression. Academically, the study contributes to the conceptual integration of biomarker and nutritional psychiatry research; practically, it offers an evidence-based foundation for individualized, non-pharmacological adjunct therapies in mental health care.

Keywords: Depressive disorder; biomarkers; nutritional psychiatry; Mediterranean diet; inflammation; gut-brain axis

1. Introduction

Depressive disorder (DD) is one of the most prevalent and disabling mental illnesses worldwide, characterized by persistent low mood, anhedonia, and cognitive dysfunction. Despite advances in psychopharmacology and psychotherapy, DD remains a major public health challenge due to its high recurrence rate, low treatment adherence, and considerable social and economic burden [1]. Epidemiological data indicate that approximately 15-20% of adults experience depressive symptoms, and the lifetime prevalence in China alone exceeds 6.8%, affecting more than 44 million people [2]. Conventional diagnostic approaches rely heavily on subjective symptom assessments, such as clinical interviews and rating scales, which lack objectivity and reproducibility. Consequently, delayed diagnosis and inconsistent treatment outcomes are common, underscoring the urgent need for objective biomarkers that can facilitate early detection, precise classification, and individualized treatment planning [3].

In recent years, interdisciplinary research integrating psychiatry, neuroscience, and nutrition has gradually revealed the biological foundations of DD [4]. Emerging evidence suggests that multiple systemic abnormalities, such as hypothalamic-pituitary-adrenal (HPA) axis dysregulation, immune-inflammatory activation, neurotrophic factor reduction, and gut microbiota imbalance, jointly contribute to its pathophysiology [5]. Correspondingly, measurable biomarkers, including cortisol, interleukin-6 (IL-6), C-reactive protein (CRP), brain-derived neurotrophic factor (BDNF), and the

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kynurenine/tryptophan ratio, have been identified as potential indicators of disease onset and treatment response. However, most existing studies remain fragmented, focusing on single biological systems or molecular pathways without integrating these findings into a unified framework that links biological mechanisms with modifiable lifestyle factors such as diet [6].

Nutritional psychiatry has recently emerged as a promising field that connects dietary patterns with mental health outcomes through pathways involving inflammation, neuroplasticity, and the gut-brain axis [7]. Interventional and epidemiological studies have indicated that specific diets, such as the Mediterranean diet, anti-inflammatory diet, and probiotic supplementation, can alleviate depressive symptoms and modulate related biological markers [8]. Yet, there remains a substantial research gap: existing literature tends to emphasize either the mechanistic exploration of biomarkers or the symptomatic improvement from dietary changes, seldom integrating both dimensions to elucidate how diet-driven modulation of biomarkers translates into clinical benefit. Moreover, most prior studies have small sample sizes, short intervention periods, and lack longitudinal or multi-factor analyses, limiting their generalizability and practical application.

To address these deficiencies, this study conducts a comprehensive review combining literature analysis and comparative synthesis across psychiatry, molecular biology, and nutritional science. It systematically examines key biomarkers associated with DD and evaluates how distinct dietary patterns influence these biological targets. The paper particularly focuses on the regulatory mechanisms by which the Mediterranean, anti-inflammatory, and probiotic/prebiotic diets affect inflammatory cytokines, neurotrophic factors, and microbial metabolites. By bridging biomarker discovery and dietary intervention research, this work aims to establish an integrative framework that supports the objective diagnosis and precision nutritional management of depressive disorder.

Academically, this study contributes to refining the biological understanding of DD by linking multi-system biomarkers with modifiable nutritional variables, offering new insights for interdisciplinary research in psychiatry and nutrition. Practically, it provides an evidence-based reference for developing non-pharmacological adjunct therapies that are accessible, safe, and personalized, aligning with the growing demand for sustainable mental health interventions. In sum, the present research seeks to transform the current symptom-based paradigm of depression treatment into a biologically informed and nutritionally guided model of precision care.

2. Related Works

2.1 Development of Biomarker Research in Depressive Disorder

Research on DD has evolved substantially over the past decades. Early studies were dominated by the monoamine hypothesis, which attributed depressive symptoms to deficiencies in key neurotransmitters such as serotonin (5-HT), norepinephrine (NE), and dopamine (DA). This framework facilitated the development of pharmacological treatments like selective serotonin reuptake inhibitors (SSRIs), which remain a clinical mainstay [9]. The strength of this early research lies in its clear neurochemical grounding and its success in guiding the first generation of antidepressants, establishing a neurobiological foundation for subsequent inquiry.

However, the monoamine hypothesis alone cannot explain the heterogeneity and treatment resistance observed in many DD cases [10]. As research progressed, scientists identified broader systemic abnormalities beyond neurotransmission. Endocrine markers revealed dysfunction in the HPA axis, such as elevated cortisol levels and impaired feedback regulation. Immune-inflammatory research demonstrated that pro-inflammatory cytokines like IL-6, CRP, and tumor necrosis factor-alpha (TNF-α) are elevated in DD patients and correlate with symptom severity [11]. Moreover, neurotrophic studies uncovered that reduced levels of BDNF are associated with neuronal

atrophy and cognitive decline, while metabolic biomarkers such as the tryptophan ratio highlight the interplay between inflammation and serotonin metabolism [12].

In recent years, multi-omics approaches have advanced the field further by integrating genomic, proteomic, metabolomic, and microbiome data to uncover cross-systemic interactions. The discovery of the gut-brain axis has particularly expanded the biological scope of DD research, showing that intestinal microbiota imbalances can affect neurotransmitter production, immune regulation, and stress response. Collectively, these findings suggest that DD is a multisystem disorder rather than a purely psychological or neurological one. Nonetheless, despite these advances, most studies focus on identifying biomarkers individually rather than mapping their interconnected mechanisms, leaving the field without a unified diagnostic or predictive model.

2.2 Advances in Nutritional Psychiatry

Parallel to biological research, the emerging field of nutritional psychiatry has emphasized diet as a modifiable environmental factor influencing mental health. Numerous observational and interventional studies have demonstrated that nutritional quality strongly correlates with depression risk and treatment outcomes. Mechanistically, dietary components regulate inflammation, oxidative stress, neurotrophic signaling, and the gut microbiota, all of which intersect with known DD biomarkers.

Among various dietary patterns, the Mediterranean diet (MD) has gained significant empirical support. Rich in polyphenols, omega-3 fatty acids, and antioxidants, MD promotes neuroplasticity and reduces systemic inflammation. The SMILES randomized controlled trial (RCT) confirmed that a 12-week MD intervention significantly reduced depressive symptoms compared to social support controls [13]. Similarly, anti-inflammatory diets (AID) emphasizing fruits, vegetables, whole grains, and healthy fats have been shown to lower inflammatory markers such as CRP and IL-6. Furthermore, probiotic and prebiotic interventions have attracted attention for their capacity to restore gut microbial balance, enhance short-chain fatty acid (SCFA) synthesis, and modulate the tryptophan-kynurenine metabolic pathway, leading to improved mood regulation [14].

Nevertheless, while nutritional interventions demonstrate clinical benefits, their mechanistic pathways remain insufficiently characterized. Most existing studies assess symptom outcomes without systematically linking dietary patterns to corresponding biomarker changes [15]. Additionally, heterogeneity in study design, dietary adherence, and population background often results in inconsistent findings, limiting reproducibility and clinical translation.

2.3 Gaps in Existing Studies and This Study's Contribution

Despite significant progress in both biomarker discovery and dietary intervention research, a major conceptual gap persists: the integration of biological and nutritional dimensions. Current research typically examines biomarkers and diet in isolation, biomarker studies focus on mechanistic explanation, while dietary studies prioritize behavioral outcomes. Few works have explicitly connected how specific dietary components influence quantifiable biomarkers to yield antidepressant effects. Moreover, most trials are short-term, lack standardized biomarker panels, and rarely consider patient-specific biological variability, which is crucial for precision-oriented care.

To bridge these gaps, the present study synthesizes cross-disciplinary findings to construct an integrated biomarker-diet interaction framework for DD. Through comprehensive literature analysis and comparative evaluation, it maps the relationships among neuroendocrine, immune, metabolic, and microbial markers, and examines how distinct dietary patterns modulate these biological systems. This approach not only advances theoretical understanding but also supports the clinical transition toward biomarker-guided, nutritionally informed depression management. The study thus contributes both conceptually and practically by proposing a biologically grounded pathway for future precision interventions in mental health.

3. Biomarkers of Depressive Disorder

Biomarkers provide objective insights into the biological mechanisms underlying DD, supplementing traditional symptom-based diagnosis. Current evidence demonstrates that DD arises from interconnected dysfunctions across neuroendocrine, immune, metabolic, and gut microbiota systems. Understanding these indicators enables more precise diagnosis and targeted intervention strategies.

3.1 Neuroendocrine Markers

The HPA axis plays a central role in stress regulation, and its dysfunction is a hallmark of DD. Patients often exhibit hypercortisolism and impaired negative feedback regulation. Meta-analyses reveal that cortisol suppression after dexamethasone testing is reduced, while basal cortisol levels are elevated, confirming chronic HPA axis hyperactivity. This hormonal imbalance damages hippocampal neurons and weakens emotional regulation.

At the genetic and epigenetic levels, variants in the FKBP5 gene affect glucocorticoid receptor (GR) sensitivity, while NR3C1 hypermethylation is linked to early-life stress and greater DD vulnerability. These abnormalities result in persistent overactivation of the stress axis and reinforce the cycle of depressive symptoms, as illustrated in Figure 1, which depicts the dysregulation of the HPA axis and impaired feedback mechanisms in depression.

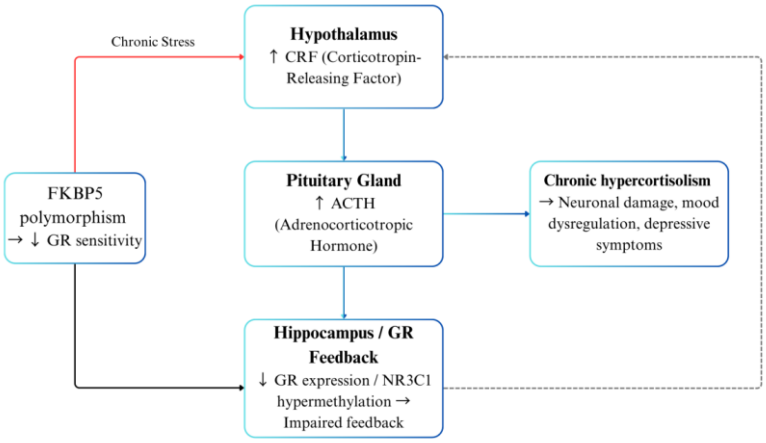

Figure 1. HPA Axis Dysregulation in Depression

3.2 Immune and Inflammatory Markers

The inflammatory hypothesis of depression posits that immune dysregulation contributes to mood disorders. Elevated IL-6, TNF-α, and CRP levels are consistently observed in DD and correlate with symptom severity. Antidepressant treatment often reduces these cytokines, demonstrating their connection to therapeutic response.

Inflammatory mediators can cross the blood-brain barrier, altering neurotransmitter metabolism. Activation of indoleamine 2,3-dioxygenase (IDO) by cytokines diverts tryptophan away from serotonin synthesis toward kynurenine production, decreasing serotonin availability and producing neurotoxic metabolites such as quinolinic acid. These processes explain how systemic inflammation directly contributes to emotional dysregulation.

Table 1 summarizes the key inflammatory biomarkers associated with depressive disorder and their corresponding clinical implications.

Table 1. Major Inflammatory Biomarkers in DD

Marker	Change	Clinical Role
IL-6	↑	Correlates with symptom severity
TNF-α	↑	Promotes neuroinflammation

CRP	↑	Predicts poor treatment response

3.3 Neurotrophic and Metabolic Indicators

The neurotrophic hypothesis highlights brain-derived neurotrophic factor (BDNF) as vital for neuronal survival and synaptic plasticity. Depressed patients show reduced serum and plasma BDNF, while successful antidepressant therapy increases these levels. Thus, BDNF serves as a reliable biomarker for evaluating recovery and treatment efficacy.

Metabolic markers also reveal vital mechanistic links. The tryptophan-kynurenine pathway connects inflammation with serotonin depletion. During inflammation, IDO activation reduces tryptophan and elevates kynurenine, promoting neurotoxicity and emotional instability, as illustrated in Figure 2, which depicts how cytokine-induced activation of the tryptophan-kynurenine pathway redirects tryptophan metabolism away from serotonin synthesis toward neurotoxic by-products.

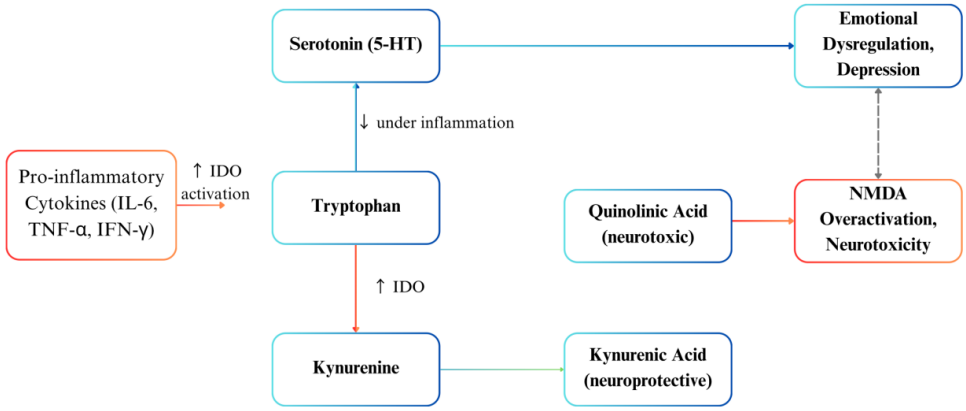

Figure 2. Inflammatory Activation of the Tryptophan-Kynurenine Pathway

3.4 Gut Microbiota and the Gut-Brain Axis

Emerging evidence identifies the gut microbiota as a critical regulator of mental health. Dysbiosis causes increased intestinal permeability ("leaky gut"), allowing lipopolysaccharides (LPS) from Gram-negative bacteria to enter circulation and trigger systemic inflammation. This process amplifies HPA axis activation and immune responses, worsening depressive symptoms.

Patients with DD display reduced microbial diversity and decreased short-chain fatty acids (SCFAs) such as butyrate and acetate, which normally strengthen intestinal barriers and reduce inflammation. Animal and human studies further reveal that gut bacteria influence neurotransmission, microbial metabolites such as GABA and serotonin modulate mood via the vagus nerve.

Table 2 summarizes the main alterations in gut microbiota composition observed in depressive disorder and their biological effects on host physiology.

Table 2. Gut Microbiota Alterations in Depressive Disorder

Component	Observed Change	Effect
Firmicutes/Bacteroidetes ratio	↓	Lower SCFA synthesis
LPS (endotoxin)	↑	Triggers cytokine release and HPA activation
SCFAs (butyrate, acetate)	↓	Weakened barrier, reduced neuroprotection

4. Dietary Intervention Strategies and Biomarker Regulation

Growing evidence demonstrates that diet can influence DD through biochemical and physiological pathways that overlap with known biomarkers. Specific dietary patterns regulate inflammation, neurotransmitter synthesis, neurotrophic signaling, and the gut-brain axis, thereby modulating DD severity and treatment response. Three representative dietary models, the MD, AID, and Probiotic/Prebiotic interventions, illustrate how nutritional modulation can reshape biological mechanisms relevant to DD.

4.1 Mediterranean Diet (MD)

MD, characterized by a high intake of polyphenols, omega-3 fatty acids, tryptophan, and antioxidants, exerts multifaceted protective effects on both brain and systemic health. Substantial epidemiological and interventional evidence indicates that adherence to the MD is associated with a significantly lower risk of depressive symptoms and greater emotional stability.

The antidepressant properties of the MD are mediated through several interconnected biological pathways: First, it modulates the tryptophan-kynurenine pathway by inhibiting the activity of IDO, thereby increasing tryptophan availability for serotonin synthesis and reducing the production of neurotoxic metabolites. Second, it enhances neurotrophic and serotonergic signaling; for instance, tryptophan-rich foods such as fish, legumes, and nuts promote serotonin (5-HT) production, while antioxidants like lycopene and quercetin protect neurons from oxidative stress and support synaptic plasticity. Third, the diet reduces systemic inflammation, polyphenols abundant in olive oil and red wine downregulate pro-inflammatory cytokines such as TNF-α and IL-6, which contributes to improved mood and cognitive resilience.

These mechanisms are supported by clinical trials. The landmark SMILES randomized controlled trial demonstrated that a 12-week MD intervention led to significant reductions in depressive symptoms compared to a social support control. Notably, symptom improvement was not closely correlated with changes in conventional lipid indicators, underscoring that the benefits of the MD are likely mediated through anti-inflammatory, antioxidant, and neuroplasticity-related mechanisms rather than lipid metabolism.

In summary, the Mediterranean Diet represents a biologically grounded, sustainable nutritional strategy for alleviating depressive symptoms via integrated regulation of inflammatory, neurotrophic, and metabolic pathways.

4.2 Anti-Inflammatory Diet (AID)

AID aims to counteract chronic inflammation, which is increasingly recognized as a major biological driver of DD. This dietary model emphasizes nutrient-dense foods such as fruits, vegetables, whole grains, fatty fish, and healthy oils, all of which are rich in polyphenols, vitamins, and omega-3 fatty acids that provide anti-inflammatory and neuroprotective effects. By improving the body's inflammatory profile and oxidative balance, AID supports neural function, mood regulation, and stress adaptation.

Biologically, the antidepressant potential of AID lies in its ability to suppress pro-inflammatory cytokines such as TNF-α and IL-6, thereby reducing systemic and neuroinflammation. It also enhances neurotrophic signaling by increasing brain-derived neurotrophic factor (BDNF) levels, which promotes neuronal survival and synaptic plasticity. Furthermore, it stabilizes the hypothalamic-pituitary-adrenal (HPA) axis, normalizing cortisol rhythms and improving stress resilience. Key nutrients, vitamins C, D, and E, serve as antioxidants that protect neural tissues from oxidative stress, while N-3 polyunsaturated fatty acids (EPA and DHA) inhibit NF-κB activation, reducing microglial overactivation. In addition, tyrosine, a precursor for dopamine and norepinephrine, supports neurotransmitter synthesis and thyroid hormone regulation, an important link given the frequent comorbidity of hypothyroidism and depression.

Table 3 summarizes the principal nutrients in AID, their biomarker targets, and physiological effects, highlighting the diet's multidimensional regulatory capacity.

Table 3. Core Components and Biomarker Effects of the Anti-Inflammatory Diet

Component	Primary Source	Target Biomarker	Physiological Effect
Omega-3 fatty acids	Fish, nuts	↓ TNF-α, ↓ IL-6	Reduced inflammation
Vitamins C/D/E	Fruits, fish, oils	↑ BDNF	Enhanced neuroprotection
Tyrosine	Poultry, soy	↑ Dopamine/NE	Improved neurotransmission

Clinically, adopting an anti-inflammatory dietary pattern has been shown to lower circulating inflammatory markers and alleviate depressive symptoms. Its effectiveness derives from simultaneously modulating oxidative stress, immune balance, and neurotransmitter metabolism, forming a biochemical network that directly addresses the multi-system pathology of DD and provides a sustainable, evidence-based complement to pharmacological therapy.

4.3 Probiotics and Prebiotics

Recent research has increasingly recognized probiotics and prebiotics as key modulators of the gut-brain axis in DD. Specific probiotic strains, such as Bifidobacterium infantis 35624 and Lactobacillus helveticus, have demonstrated antidepressant potential through their influence on both neural and immune signaling pathways. These microorganisms can regulate the tryptophan-kynurenine metabolic pathway by lowering kynurenine levels and restoring serotonin synthesis, thereby improving neurotransmission and emotional stability. They also enhance neurotrophic activity by upregulating BDNF expression, which supports hippocampal neurogenesis and cognitive recovery. Furthermore, probiotics have been shown to reduce cortisol levels and systemic inflammation by suppressing pro-inflammatory cytokines such as IL-6 and TNF-α, while increasing the production of SCFAs such as butyrate. These SCFAs strengthen intestinal barrier integrity, reduce "leaky gut" inflammation, and improve gut-derived neuroimmune communication.

Clinical evidence supports these mechanisms. Randomized controlled trials have reported significant reductions in depressive symptoms, measured by Beck Depression Inventory scores, among participants receiving probiotic supplementation compared to placebo groups. Another study observed that changes in fecal formic acid levels were associated with symptom improvement, suggesting its potential as a metabolite biomarker of probiotic treatment response. Nevertheless, findings remain inconsistent across studies due to variations in bacterial strains, intervention duration, and patient characteristics.

In addition to probiotics, prebiotics such as galacto-oligosaccharides (GOS) enhance the growth of beneficial bacteria including Bifidobacterium and Lactobacillus, indirectly improving mood and reducing stress-related hormone levels. The concept of Microbiota-Directed Foods (MDFs) has emerged from this line of research, precision dietary formulations combining fibers like resistant starch, inulin, and β-glucan to selectively promote beneficial microbial activity. MDFs thus represent a promising approach for individualized, nutrition-based management of depression through targeted modulation of gut microbiota and its metabolites.

5. Discussion

DD represents a multifactorial condition resulting from the interaction of neuroendocrine, immune, metabolic, and microbial systems. An integrated mechanistic understanding highlights that these systems do not operate in isolation; rather, they form a dynamic and reciprocal network where inflammation, neurotransmission, and gut

microbiota collectively influence brain function and emotional regulation. Within this context, dietary factors emerge as powerful modulators capable of acting across multiple biological levels. Nutrients such as omega-3 fatty acids, polyphenols, vitamins, and prebiotics can simultaneously regulate inflammatory cytokines, enhance BDNF expression, normalize HPA axis activity, and reshape gut microbiota composition. This interconnected model suggests that diet-based modulation of biomarkers can produce synergistic antidepressant effects comparable to, or complementary with, pharmacological interventions. The convergence of biomarker discovery and nutritional psychiatry therefore opens a new frontier in precision mental health management, where dietary recommendations are personalized according to biological profiles rather than generalized lifestyle advice.

From a clinical perspective, the findings discussed throughout this study support the feasibility of developing standardized biomarker panels for the biological subtyping of DD. Measuring key indicators such as IL-6, CRP, BDNF, and kynurenine/tryptophan ratios could help differentiate inflammatory, neurotrophic, and metabolic subtypes, enabling tailored interventions. For example, patients exhibiting high inflammatory markers might benefit more from anti-inflammatory or omega-3-rich diets, while those with disrupted gut microbiota could respond better to probiotics and prebiotics. This biomarker-guided personalization not only enhances treatment precision but also validates dietary therapy as a legitimate adjunct to pharmacological and psychotherapeutic approaches. Integrating nutrition into psychiatric care could further reduce medication dosages, minimize side effects, and improve long-term remission rates by targeting the underlying biological dysregulations. The incorporation of such integrative care models into public health strategies would mark a significant shift from reactive treatment to preventive, sustainable mental health management.

Despite these promising perspectives, several limitations remain. Clinical findings on diet-depression relationships are still inconsistent, primarily due to small sample sizes, short intervention durations, and the lack of unified dietary assessment methods. Population heterogeneity, encompassing genetic background, lifestyle habits, and baseline nutritional status, also complicates comparisons across studies. Moreover, the biological mechanisms underlying dietary effects are often inferred rather than directly measured, as many studies rely on self-reported dietary adherence without concurrent biomarker monitoring. Addressing these gaps will require large-scale, longitudinal, and multi-center clinical trials that integrate omics-based profiling, gut microbiome sequencing, and advanced nutritional analytics. Only through such comprehensive approaches can researchers validate causal relationships and establish reliable biomarker-based dietary guidelines for depression management.

6. Conclusion

Depressive disorder continues to pose a major global health challenge, characterized by complex biological underpinnings that span immune, endocrine, metabolic, and microbial domains. Recent advances in biomarker research have identified measurable biological indicators, such as IL-6, CRP, BDNF, the kynurenine/tryptophan ratio, and gut microbiota diversity, that provide objective targets for diagnosis and therapeutic evaluation. These findings represent a critical step toward transforming DD from a symptom-based construct into a biologically stratified disorder with identifiable subtypes and modifiable pathways.

Dietary interventions offer a promising, evidence-based strategy for regulating these biomarkers. The Mediterranean and anti-inflammatory diets, enriched in polyphenols, omega-3 fatty acids, vitamins, and antioxidants, have demonstrated the ability to suppress pro-inflammatory cytokines, enhance neurotrophic signaling, and normalize stress hormone regulation. Similarly, probiotics and prebiotics have shown potential to restore gut microbial balance, increase short-chain fatty acid production, and improve intestinal barrier integrity, thereby indirectly modulating brain function via the gut-brain axis. Collectively, these approaches illustrate that nutritional modulation operates through

anti-inflammatory, neurotrophic, and microbial pathways that converge on mood regulation and cognitive resilience.

The future management of depressive disorder should therefore evolve toward personalized, biomarker-driven, and integrative care models that align psychiatric treatment with individual biological profiles. By combining nutritional psychiatry with continuous biomarker monitoring, clinicians can design adaptive interventions that address each patient's unique biochemical and microbiological characteristics. Such an approach enhances therapeutic efficacy, supports long-term remission, and bridges the gap between medical science and daily health behavior. Through interdisciplinary collaboration among psychiatry, nutrition, and molecular biology, depression care can transform from reactive pharmacological management into a proactive, biologically informed, and nutritionally guided paradigm.

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