

Review

Tumor associated depression, gut microbiota, and immune checkpoint inhibitor sensitivity

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CITATION

Wang J. Tumor associated depression, gut microbiota, and immune checkpoint inhibitor sensitivity. *Psycho-Oncologie*. 2026; 20(6): 5751.
<https://doi.org/10.18282/po5751>

ARTICLE INFO

Received: 6 March 2026
Revised: 12 May 2026
Accepted: 8 June 2026
Available online: 13 July 2026

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Abstract: The interplay between psychological distress, gut microbiota composition, and immune function represents an emerging frontier in psycho oncology. Tumor associated depression exerts profound biological effects through activation of the hypothalamic pituitary adrenal axis and upregulation of proinflammatory cytokines, which can impair T cell function and reduce the efficacy of immune checkpoint inhibitors. This review specifically distinguishes between major depressive disorder (diagnosed via structured clinical interviews) and subsyndromal depressive symptoms (measured by self-report scales), as their biological correlates may differ. Concurrently, the gut microbiota gut brain axis acts as a critical mediator linking mood, immunity, and cancer progression. Microbial metabolites such as short chain fatty acids and tryptophan derivatives influence neurotransmission and cytokine production, thereby regulating both emotional states and immune competence. Dysbiosis disrupts these mechanisms, leading to systemic inflammation and therapeutic resistance. This narrative review synthesizes current evidence on how tumor associated depression and gut microbial alterations jointly modulate immune checkpoint activity. Unlike prior reviews that focus solely on inflammation, the present work proposes an innovative psycho-microbiological framework that integrates emotional resilience, microbial ecology, and immune regulation within a shared therapeutic continuum. It further explores microbial based sensitization strategies such as probiotics, prebiotics, synbiotics, and fecal microbiota transplantation that may restore microbial balance, reduce inflammation, and enhance immunotherapy response. By integrating psychoneuroimmunology and microbiome science, the review proposes an innovative psycho microbiological framework that unites emotional resilience, microbial ecology, and immune regulation within a shared therapeutic continuum. Understanding this interconnection offers a path toward personalized cancer care in which psychological and microbial interventions complement conventional immunotherapy to achieve durable recovery and improved quality of life.

Keywords: tumor associated depression; gut microbiota gut brain axis; immune checkpoint inhibitors; psychoneuroimmunology; microbiota modulation; psycho oncology; immunotherapy sensitization; probiotics; systemic inflammation

1. Introduction

1.1. Background

The introduction of immune checkpoint inhibitors has significantly transformed cancer treatment through the blockade of inhibitory receptors such as PD-1, PD-L1, and CTLA-4. These therapies reactivate the immune system, leading to durable tumor regression in various malignancies [1,2]. Despite their notable clinical success, only a subset of patients, approximately 25% to 33% had experience persistent benefits, with many others exhibiting limited or no response [3]. This variability in therapeutic

outcomes is influenced not solely by tumor genetics or immune profiles, but by additional biological and psychological factors [2].

Among the emerging modulators that might influence these outcomes is tumor-associated depression, which has garnered increasing attention [4]. Depression is prevalent in roughly one-fourth to one-third of cancer patients undergoing active treatment [5], not only affecting their emotional state but also exerting significant biological effects. Specifically, the activation of the hypothalamic-pituitary-adrenal (HPA) axis, along with the sustained release of inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha, can hinder T cell functionality and potentially impair the efficacy of immune checkpoint inhibitors [6]. This connection underscores the hypothesis that psychological distress may play a pivotal role in shaping the disease's course and therapeutic responses, influencing both outcomes and overall patient well-being [7].

Parallel to this understanding, recent research has revealed the critical role of the gut microbiota and its connection to the brain and immune system, often referred to as the gut microbiota–gut–brain axis [8]. This complex bidirectional network allows intestinal microbes to influence emotional states and immune function through neural, endocrine, and metabolic signaling [9]. The composition and diversity of gut microorganisms affect neurotransmitter synthesis, intestinal permeability, and systemic inflammation [10]. Disruption of this balance, known as dysbiosis, has been associated with depression, immune dysregulation, and poor response to immunotherapy [11]. Preclinical studies demonstrate that alterations in microbial communities can modify mood-related behaviors and the effectiveness of antitumor immune activation [12].

These insights highlight a dynamic interaction among the mind, microbes, and immunity. Depressive symptoms can reshape the gut microbiota, which in turn modulates immune cell activity and treatment sensitivity [9]. This loop establishes a mechanistic bridge linking psychological well-being with therapeutic outcomes in oncology. Understanding and manipulating this interaction may provide new opportunities to enhance immunotherapy effectiveness [13,14].

1.2. Search strategy

To ensure methodological transparency as recommended for narrative reviews, a systematic literature search was conducted. PubMed, PsycINFO, and Web of Science databases were searched from inception to October 2025 using the following keyword combinations: ("tumor associated depression" OR "cancer related depression" OR "major depressive disorder" OR "cancer") AND ("gut microbiota" OR "microbiome" OR "dysbiosis") AND ("immune checkpoint inhibitors" OR "immunotherapy" OR "PD-1/PD-L1"). Additional articles were identified by manual screening of reference lists of included studies and relevant reviews. Only peer-reviewed articles published in English were considered. Given the narrative nature of this review, studies were selected based on their relevance to the mechanistic integration of depression, gut microbiota, and immunotherapy response, with priority given to human clinical studies and well-controlled preclinical experiments.

1.3. Aim of this review

Microbial-based interventions offer a promising approach within this context. Probiotics, prebiotics, synbiotics, and fecal microbiota transplantation (FMT) have shown potential to restore microbial equilibrium, reduce systemic inflammation, and improve antitumor immune responses [15,16]. Recent studies indicate that FMT

can overcome resistance to immunotherapy in melanoma patients whose tumors do not initially respond to treatment, reflecting its potential as an effective strategy in enhancing antitumor immunity [15]. Many of these strategies also exert beneficial effects on mood regulation, suggesting a dual advantage in psycho-oncology care [16].

Therefore, the aim of this narrative review is to synthesize current evidence describing how tumor associated depression, gut microbial alterations, and immune checkpoint regulation interact within a shared biological framework. Specifically, the review will (1) outline the mechanisms linking depression to immune dysfunction, (2) describe how the gut brain axis integrates psychological and immunological pathways, and (3) examine microbial preparations as potential sensitizers to enhance immunotherapy efficacy. Through this perspective, the review proposes an integrative psycho microbiological model that connects emotional health, microbial balance, and cancer immunity as complementary targets for improving patient outcomes.

2. Theoretical foundation: from psycho oncology to psychoneuroimmunology

2.1. Evolution of psycho oncology

Psycho-oncology developed as an interdisciplinary field exploring how emotional states influence cancer development, progression, and patient recovery. The term psycho-oncology was coined in the 1970s to address the unmet psychosocial needs of patients with cancer, focusing on psychosocial issues relevant to cancer prevention, treatment, and survivorship [17]. In its formative stage during the late 20th century, the discipline emphasized psychological adaptation, coping strategies, and the impact of distress on treatment adherence [17]. Later, researchers began to uncover biological mechanisms indicating that persistent psychological stress could influence immune and endocrine pathways that are involved in tumor biology.

This conceptual shift positioned psycho-oncology at the intersection of behavioral science and molecular oncology, acknowledging that the mind and the immune system operate as interconnected entities capable of influencing cancer outcomes [17]. The discipline's maturity paved the way for a new generation of biological models explaining how mental states modulate physiological function and therapeutic response [18].

2.2. The concept of psychoneuroimmunology

Psychoneuroimmunology (PNI) extends the framework of psycho-oncology by focusing on communication among psychological, neural, and immune systems. It posits that stress or depressive states activate the hypothalamic-pituitary-adrenal (HPA) axis, leading to increased cortisol and catecholamine secretion [19]. These neuroendocrine responses can suppress T cell proliferation and natural killer cell activity, thereby potentially diminishing antitumor immunity [19,20].

Conversely, proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha can cross the blood-brain barrier and influence neural circuits involved in emotion regulation [21]. This establishes a feedback loop in which mood and immunity continuously interact [21].

Figure 1 illustrates this process, depicting how psychological stress activates the HPA axis, which triggers cortisol and cytokine release, consequently leading to immune suppression and tumor progression. The feedback loop returning from cytokines to the brain symbolizes the mechanism through which inflammation can alter mood and perpetuate chronic psychological distress. This pathway

emphasizes that emotional dysregulation is not merely a psychological phenomenon but encompasses physiological conditions with measurable effects on immune competence and cancer trajectory [22].

Psychoneuroimmunological Pathway in Cancer

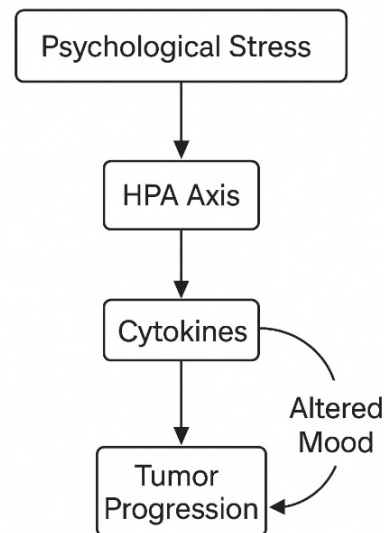


Figure 1. Psychoneuroimmunological pathway in cancer

2.3. Depression as an immunomodulatory disorder

Depression is increasingly recognized as an immune-related disorder characterized by elevated inflammatory activity and altered neurotransmitter metabolism. Patients with depression often exhibit increased concentrations of cytokines such as interleukin-1 beta, interleukin-6, and tumor necrosis factor-alpha, which indicate sustained immune activation [23]. Chronic inflammation is known to disrupt serotonin synthesis, induce oxidative stress, and contribute to neurodegeneration, collectively leading to symptoms such as fatigue and cognitive decline [24].

In patients with cancer, the prevalence of tumor-associated depression can exacerbate this biological imbalance. Overactivation of the hypothalamic-pituitary-adrenal (HPA) axis results in excessive glucocorticoid secretion, which can suppress immune response and interfere with interferon-gamma production [25]. Dysregulation of tryptophan metabolism via the kynurenine pathway results in decreased serotonin levels and the production of neurotoxic metabolites that can further exacerbate mood disorders and impair immune function [26]. **Table 1** summarizes the principal biochemical pathways that connect depressive symptoms with immune dysfunction.

Table 1. Inflammatory and neuroendocrine changes in tumor associated depression

Biological Mechanism	Key Molecules	Functional Outcome
HPA axis activation	Cortisol	Suppression of T cell proliferation
Cytokine elevation	IL 6, TNF α	Chronic inflammation and fatigue
Tryptophan metabolism shift	Kynurenine	Reduced serotonin and neurotoxicity

This integrated framework emphasizes that depression acts as an immunomodulatory disorder that weakens the host's defense system and may directly influence the effectiveness of immune checkpoint inhibitors.

2.4. Relevance of the gut microbiota gut brain axis to psychoneuroimmunology

Recent discoveries regarding the gut microbiota-gut-brain axis (MGBA) have expanded the theoretical scope of psychoneuroimmunology. The intestinal microbiota functions as an active endocrine and immune organ, producing metabolites such as short-chain fatty acids and indole derivatives that influence neurotransmitter synthesis and inflammatory tone [27]. Signals from the gut reach the brain through neural, humoral, and immune routes, including the vagus nerve and circulating cytokines [28]. The brain, in turn, modulates gut motility and barrier permeability through the autonomic nervous system, completing a circular communication loop [28]. Dysbiosis, or imbalance in microbial composition, disrupts this communication, contributing to both mood disorders and immune dysfunction [27].

Figure 2 depicts this multidirectional relationship, demonstrating how gut microbial metabolites affect brain signaling, stress responses, and immune modulation. It also shows that psychological stress can alter gut microbiota composition, creating a feedback loop that reinforces inflammation and emotional instability [29,30]. This model positions the microbiota as a key intermediary that translates psychological states into biological outcomes relevant to cancer immunity. Understanding the MGBA thus enriches psycho-oncology by providing a mechanistic bridge between emotional health and therapeutic efficacy [27].

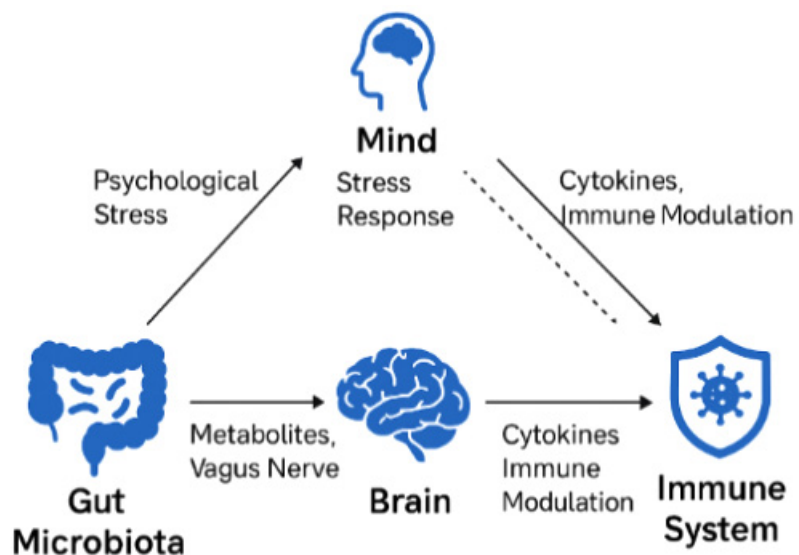


Figure 2. Gut Microbiota Gut Brain immune communication axis

2.5. Integrative perspective

The convergence of psycho-oncology, psychoneuroimmunology, and microbiome science defines a new integrative psycho-microbiological paradigm. Within this framework, mental health, immune activity, and microbial ecology are viewed as interdependent factors influencing cancer prognosis [31]. Emotional stress can reshape the microbiome; alterations in microbiota can affect neurotransmission and immunity, and immune signaling can modulate brain function and mood [32]. This integrative understanding provides a theoretical foundation for developing

interventions that address both psychological and biological targets. Such an approach offers the potential to improve not only emotional resilience but also the clinical effectiveness of immunotherapy through microbiota modulation [33].

3. Tumor associated depression: biological and immunological basis

3.1. Definition and prevalence

Tumor-associated depression refers to the development of depressive symptoms that emerge as a consequence of cancer or its treatment, involving biological, psychological, and immune processes. It extends beyond emotional distress by encompassing measurable alterations in neuroendocrine and inflammatory pathways. A critical distinction must be made between major depressive disorder (MDD), diagnosed via structured clinical interviews such as the Structured Clinical Interview for DSM-5 (SCID-5), and subsyndromal depressive symptoms measured by self-report scales such as the Patient Health Questionnaire-9 (PHQ-9) or Hospital Anxiety and Depression Scale (HADS). This distinction is clinically important because biological correlates—including cytokine levels, HPA axis activity, and microbial composition—may differ significantly between these categories. Clinical evidence suggests that approximately one-quarter to one-third of patients with active malignancy experience clinically significant depression, with higher prevalence in cancers characterized by chronic inflammation, such as pancreatic, lung, and head and neck tumors [34,35].

Depression in cancer patients often remains underdiagnosed because its manifestations, such as fatigue, appetite loss, or cognitive decline, can overlap with treatment side effects [35]. Nevertheless, growing data reveal that depression acts as both a symptom and a biological driver of disease progression. Patients with elevated depressive scores frequently exhibit poorer survival, delayed wound healing, and lower response to systemic therapy [36]. This link underscores the need to view depression not merely as an emotional response but as a physiologically embedded process with immune and metabolic consequences [35,37].

3.2. Neuroendocrine mechanisms and the stress response

The hypothalamic-pituitary-adrenal (HPA) axis is the principal mediator of the body's stress response. In the context of cancer, psychological distress can lead to prolonged HPA activation, resulting in increased secretion of cortisol and catecholamines. Under normal circumstances, this hormonal response aids in adaptation; however, chronic exposure can impair feedback inhibition and maintain a persistent state of immune suppression [38]. Elevated cortisol levels can reduce the proliferation and cytotoxic activity of T lymphocytes, impair antigen presentation, and interfere with interferon-gamma production, thereby diminishing the body's ability to mount an effective antitumor response [38]. This suppression of immune surveillance establishes a biological connection between emotional stress and tumor progression.

Figure 3 visualizes this mechanism through the tryptophan kynurenine pathway, a metabolic process by which inflammatory cytokines contribute to both depressive symptoms and immune suppression, thus highlighting the link between psychological states and immune modulation. This pathway illustrates that inflammatory cytokine such as interleukin-6 and tumor necrosis factor-alpha activate key enzymes that direct tryptophan metabolism toward kynurenine production [39]. The resulting metabolites not only disrupt neurotransmitter balance, leading to depressive symptoms, but also

reduce T cell activity and increase regulatory T cell function, thereby weakening the immune response [40].

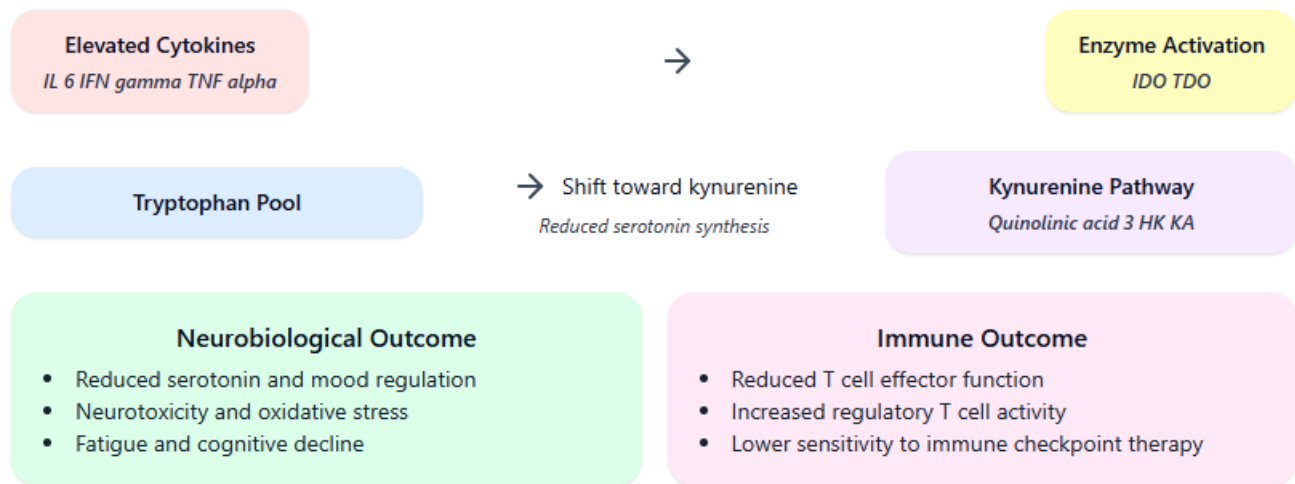


Figure 3. Tryptophan Kynurenine Pathway linking depression and immune modulation in cancer. Abbreviations: IL 6, interleukin 6; IFN γ , interferon gamma; TNF α , tumor necrosis factor alpha; IDO, indoleamine 2,3 dioxygenase; TDO, tryptophan 2,3 dioxygenase; 3 HK, 3 hydroxykynurenine; KA, kynurenic acid.

3.3. Inflammatory cytokines and immune signaling

Depression and inflammation share a mutual reinforcing relationship mediated by cytokines. Elevated circulating levels of interleukin-1 beta, interleukin-6, and tumor necrosis factor alpha are consistently found in patients with major depressive disorder and in those with tumor-associated depression [41,42]. These cytokines can cross the blood-brain barrier and alter neurotransmitter metabolism, particularly serotonin, dopamine, and glutamate, leading to emotional blunting and cognitive impairment [42]. Peripherally, cytokines stimulate angiogenesis, promote tumor cell proliferation, and foster an immunosuppressive tumor microenvironment [43]. The chronic inflammatory state contributes to immune exhaustion by reducing the effectiveness of effector T cells and increasing expression of immune inhibitory molecules such as PD-L1 [44]. This dual effect on the brain and the tumor demonstrates that inflammatory signaling serves as the molecular thread connecting depression and cancer biology. **Table 2** summarizes the major cytokines implicated in tumor-associated depression and their central and peripheral effects. The presence of these cytokines in both the nervous and immune systems confirms that depression is not purely psychological but is deeply intertwined with immunological dysfunction [42,44].

Table 2. Principal cytokines associated with tumor associated depression

Cytokine	Primary Source	Central Effect	Peripheral Effect
IL 6	Macrophages, tumor cells	Reduces serotonin synthesis	Promotes tumor growth and fatigue
TNF α	Monocytes, T cells	Alters neurotransmission	Induces cachexia and systemic inflammation
IL 1 β	Activated macrophages	Increases anxiety and dysphoria	Enhances prostaglandin production and fever

3.4. Neurotransmitter and metabolic pathways

One of the key biochemical mechanisms linking depression and immune modulation is the tryptophan kynurenine pathway. Under inflammatory conditions, enzymes such as indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) are upregulated, diverting tryptophan away from serotonin synthesis toward the kynurenine pathway [45]. This shift results in the accumulation of neuroactive metabolites like quinolinic acid and 3-hydroxykynurenine, which contribute to oxidative stress, neuronal excitotoxicity, and mood decline [46].

Simultaneously, the reduction in serotonin availability weakens mood regulation, while kynurenine metabolites promote immune tolerance by suppressing cytotoxic T cell activity and stimulating regulatory T cells [47]. These processes not only intensify depressive symptoms but also impair antitumor immunity, explaining why patients with a high inflammatory load often respond poorly to immune checkpoint inhibitors [48]. The pathway illustrated in **Figure 3** encapsulates this mechanism, showing the convergence of neurochemical imbalance and immune suppression as dual outcomes of inflammatory activation.

3.5. Interaction with tumor microenvironment and immunotherapy

The tumor microenvironment may serve as a biological amplifier of depression-induced immune dysfunction. Chronic stress can elevate sympathetic activity and norepinephrine release, which may enhance angiogenesis and tumor invasiveness through beta-adrenergic signaling, as highlighted by Won and Kim [39]. Persistent inflammation can contribute to an immunosuppressive environment characterized by regulatory T cell dominance, myeloid-derived suppressor cell recruitment, and elevated PD-L1 expression, although the specific mechanisms linking inflammation and immune modulation in the context of cancer require further elucidation [39].

Clinical data have indicated that psychological distress and elevated inflammatory biomarkers prior to treatment correlate with poorer outcomes during immunotherapy. Patients with tumor-associated depression may exhibit lower response rates and shorter progression-free survival under PD-1 or PD-L1 blockade [49]. These findings suggest that psychological and immunological health jointly influence the therapeutic potential of immune checkpoint inhibition.

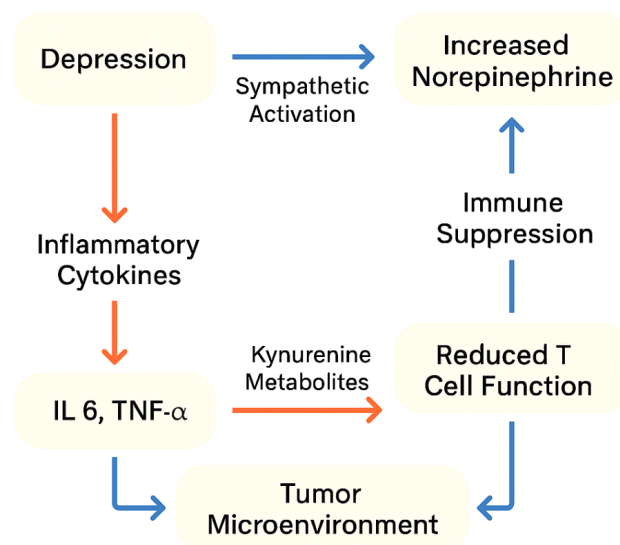


Figure 4. Depression mediated modulation of the tumor microenvironment. Abbreviations: IL 6, interleukin 6; TNF α , tumor necrosis factor alpha.

A model illustrates that chronic stress, inflammatory cytokines, and tryptophan metabolism can converge to modify the tumor microenvironment, reducing cytotoxic T cell response and impairing immune checkpoint efficacy (**Figure 4**). Depression may lead to sympathetic activation and chronic inflammation, resulting in increased norepinephrine release and elevated levels of cytokines such as interleukin-6 and tumor necrosis factor-alpha [49]. These mediators can enhance kynurenine metabolite production, suppress T cell function, and remodel the tumor microenvironment, which can impair immune surveillance and reduce responsiveness to immunotherapy [49].

3.6. Mechanistic convergence and clinical implications

Tumor-associated depression represents a multidimensional syndrome encompassing psychological, endocrine, immune, and metabolic components. It is believed to be influenced by mechanisms such as overactivation of the HPA axis, chronic inflammation, and alterations in neurotransmitter metabolism, particularly through the tryptophan kynurenine pathway. These mechanisms can negatively affect immune function and potentially reduce the effectiveness of immunotherapy in cancer patients [1].

Recognition of depression as an immunomodulatory condition invites a paradigm shift in cancer management—from treating it solely as an emotional byproduct to viewing it as a biological determinant of treatment response [2]. This integrative understanding underscores the importance of exploring the gut microbiota-gut-brain axis, which may act as a connecting network through which mood, immunity, and therapeutic outcomes intersect [3].

4. Gut microbiota gut brain axis (MGBA): the missing link between depression and immunity

4.1. Structure and function of the MGBA

The gut microbiota-gut-brain axis (MGBA) represents a multidirectional communication network linking the central nervous system, the enteric nervous system, and the immune and endocrine systems. This biological interface allows intestinal microorganisms to influence emotional regulation and immune homeostasis through neural, hormonal, and metabolic pathways [50]. The microbiota comprises trillions of microorganisms that collectively shape host physiology. Beneficial bacterial genera such as *Bifidobacterium*, *Lactobacillus*, and *Akkermansia* produce short-chain fatty acids and neuroactive compounds that support intestinal barrier integrity and regulate inflammatory tone [51]. Conversely, dysbiosis or loss of microbial diversity disrupts these functions, leading to intestinal permeability, systemic inflammation, and altered neurotransmitter balance [52].

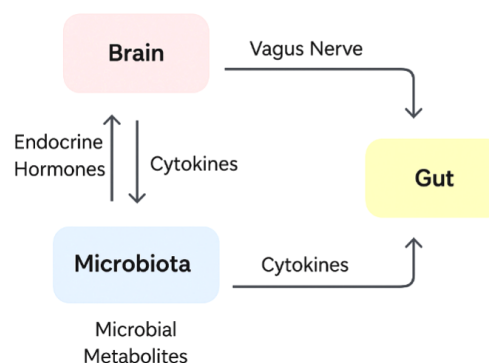


Figure 5. Bidirectional communication within the MGBA

Figure 5 illustrates this multidirectional signaling, showing how microbial metabolites, endocrine hormones, and cytokines connect the gut and brain through neural and immune pathways. The diagram demonstrates that microbial metabolites and short-chain fatty acids signal through the vagus nerve and cytokine cascades, while brain activity modulates gut physiology via stress hormones and neural feedback [53]. This integrated system forms the biological foundation of the gut-brain connection underlying both psychological and immune regulation [52].

4.2. Microbial regulation of neurotransmitters and inflammatory pathways

The gut microbiota influences both neurotransmitter synthesis and inflammatory signaling, thereby bridging emotional and immune processes. Several microbial species produce neuroactive molecules such as gamma-aminobutyric acid (GABA), serotonin precursors, and dopamine intermediates [54]. These metabolites interact with the enteric nervous system and vagus nerve to modulate stress reactivity and emotional stability [55].

Microbiota-derived short-chain fatty acids, particularly butyrate and propionate, are known to regulate the expression of tight junction proteins and reduce the release of proinflammatory cytokines. This process preserves intestinal integrity and limits systemic inflammation [56]. Conversely, dysbiosis leads to elevated interleukin-6 and tumor necrosis factor-alpha, promoting both depression and immune dysfunction [57]. These findings support the view that gut microbial composition and function directly shape emotional and immune homeostasis through the microbiota-gut-brain axis [58].

Table 3. Microbial species and their neuroimmune functions

Microbial Species	Primary Metabolite	Neuroimmune Function
<i>Lactobacillus rhamnosus</i>	GABA	Reduces anxiety like behavior via vagus nerve
<i>Bifidobacterium longum</i>	Short chain fatty acids	Lowers cortisol levels and systemic inflammation
<i>Akkermansia muciniphila</i>	Mucin degradation products	Enhances intestinal barrier and immune signaling
<i>Faecalibacterium prausnitzii</i>	Butyrate	Exerts anti-inflammatory and antidepressant effects

4.3. Dysbiosis and immunotherapy response

Recent studies demonstrate that gut microbial balance significantly influences the clinical efficacy of immune checkpoint inhibitors. Patients with higher microbial diversity and abundance of beneficial genera, such as *Akkermansia* and *Bifidobacterium*, exhibit stronger responses to PD-1 and PD-L1 blockade [59]. In contrast, those with dysbiosis or prior antibiotic exposure tend to experience lower response rates and reduced survival [60]. Mechanistically, beneficial microbes enhance antigen presentation and T cell activation, while pathogenic species promote regulatory T cell dominance and immune suppression [61]. Psychological stress, depression, and antibiotic use can all contribute to dysbiosis, indirectly impairing immune checkpoint sensitivity [60].

This evidence reinforces the concept that microbial and psychological health jointly determine the immunological landscape that supports cancer therapy

outcomes. Integrating microbial restoration strategies into psycho-oncological care could therefore improve both mood regulation and treatment efficacy [59,62].

4.4. Microbiota modulation as a sensitization strategy

Microbiota modulation offers a promising approach to optimize both psychological and therapeutic outcomes (**Table 4**). Interventions include probiotics, prebiotics, synbiotics, and fecal microbiota transplantation (FMT) [63]. Probiotics introduce beneficial microbial strains that can regulate cytokine production and enhance immune responses, but there is limited evidence specifically tying them to serotonin modulation [64]. Prebiotics provide fermentable substrates for beneficial bacteria, enhancing their growth and metabolic activity [65]. Synbiotics, which combine both probiotics and prebiotics, support the gut ecosystem, which can positively affect mental health outcomes [66].

FMT has emerged as a novel immunotherapeutic adjunct. Transferring microbiota from immunotherapy responders to non-responders has been shown to improve immune checkpoint efficacy and restore microbial diversity [67]. Such strategies can influence cytokine production and overall immune balance, although the specific mechanisms and outcomes can vary depending on the context and individual response levels [68].

Table 4. Microbial modulation strategies and psycho immunological outcomes

Intervention	Mechanism	Reported Effect
Probiotics (<i>Lactobacillus</i> , <i>Bifidobacterium</i>)	Regulate cytokine release and serotonin metabolism	Improved mood and immune activation
Prebiotics (inulin, galactooligosaccharides)	Promote beneficial microbial growth	Reduced systemic inflammation
Synbiotics	Combine microbial and metabolic modulation	Enhanced barrier integrity and resilience
Fecal microbiota transplantation	Transfer responder microbiota	Improved immunotherapy efficacy and emotional stability

4.5. Integrative psycho microbiological framework

The integration of psychological, microbial, and immune processes forms the foundation of a psychobiological model of health [54]. In this model, emotional states influence the gut microbiota through neural and endocrine signaling [69], while microbial metabolites regulate inflammation, cytokine release, and brain activity [69]. This continuous loop demonstrates that mood, microbes, and immunity function as a unified system rather than independent domains [71]. **Figure 6** illustrates this concept by showing the reciprocal interactions between the mind, microbiota, and immune system, each influencing the other through metabolites, cytokines, and regulatory pathways [72]. This figure highlights how the mind regulates emotional and stress responses that shape microbial balance [73], how the microbiota produces metabolites influencing the immune system [74], and how immune activity feeds back to affect mood and treatment sensitivity [75]. Together, these dynamic interactions determine the therapeutic outcome and represent the biological essence of psychoneuroimmunology.

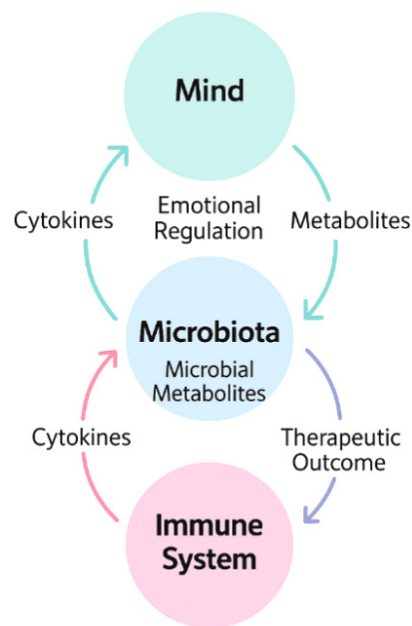


Figure 6. Integrative psycho microbiological framework

4.6. Translational and clinical implications

Understanding the gut microbiota-gut-brain axis (MGBA) has profound implications for psycho-oncology practice [76]. Screening for dysbiosis and inflammatory biomarkers could become an integral part of personalized cancer therapy, although direct evidence connecting microbiome assessment to cancer therapy personalization remains limited [77]. Interventions targeting both psychological health and microbial ecology such as mindfulness, dietary modifications, and probiotics that are being explored for their potential to enhance immunotherapy response and improve quality of life [78]. Future research should emphasize integrating multi-omics analysis, longitudinal microbiome monitoring, and randomized trials evaluating combined psycho-microbial interventions to fully elucidate these relationships [79]. By bridging emotional and biological dimensions, the MGBA framework represents a paradigm shift toward holistic, mechanism-based cancer care that aligns psychological resilience with immune precision [80].

5. Clinical applications and future directions

5.1. Translating the gut brain immune axis into psycho oncological practice

The integration of the gut-brain-immune axis into psycho-oncological care represents a transformative step toward personalized medicine [81]. The recognition that mental health, microbial ecology, and immune regulation form a unified biological system provides an opportunity to design holistic treatment strategies that simultaneously enhance psychological well-being and immunotherapy outcomes [55].

Clinical implementation begins with systematic assessment [82]. Screening tools for depression, anxiety, and stress should be complemented by biomarkers of inflammation and microbial diversity [83]. Such dual evaluation enables early detection of high-risk patients who may experience diminished immune response or treatment adherence [79]. Integrating these measures into multidisciplinary cancer care teams ensures that psychological and biological determinants are addressed in parallel [84]. This integrative screening approach allows clinicians to personalize

interventions that target both emotional distress and immune dysregulation. As shown in **Table 5**, this integrated assessment framework encompasses four domains—psychological status, inflammatory biomarkers, microbiota profiling, and quality of life—providing a systematic tool for identifying at-risk patients and delivering tailored interventions in clinical practice.

Table 5. Integrated assessment framework in psycho oncology

Assessment Domain	Example Measure	Clinical Relevance
Psychological status	HADS, PHQ 9, GAD 7	Identifies depression and anxiety linked to treatment response
Inflammatory biomarkers	IL 6, TNF α , CRP	Reflects systemic inflammation associated with mood and immune dysfunction
Microbiota profiling	16S rRNA sequencing, metagenomics	Evaluates microbial diversity predicting immunotherapy outcome
Quality of life	FACT G, EORTC QLQ C30	Monitors multidimensional well being

5.2. Microbial and psychological co-intervention strategies

The most promising clinical approach involves dual intervention, combining psychological therapy with microbiota modulation [85]. Psychological methods such as cognitive behavioral therapy (CBT), mindfulness, and music therapy have been shown to stabilize mood and reduce stress hormone release [85]. Meanwhile, microbial interventions such as probiotics, prebiotics, and fecal microbiota transplantation (FMT) can help restore gut homeostasis [86]. While **Figure 7** is referenced, the specific physiological pathways mentioned need to be clearly defined based on existing evidence. The intersection of these approaches could potentially reduce inflammation and enhance therapeutic responsiveness, as suggested by recent literature [87]. This framework emphasizes that psychological care and microbial modulation are not parallel domains but complementary components of one therapeutic ecosystem [88]. Their convergence through common neuroimmune pathways may strengthen both mental resilience and the effectiveness of immunotherapy [88].

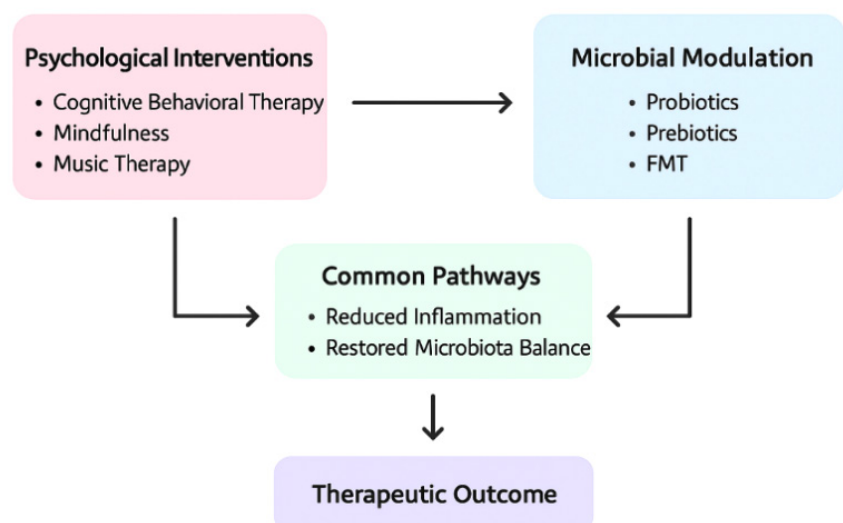


Figure 7. Combined microbial and psychological intervention model

5.3. Personalized nutrition and lifestyle medicine

The main lifestyle factors influencing the gut-brain-immune axis are listed in **Table 6**. Diet and lifestyle profoundly influence the gut-brain-immune network [89]. Diets high in fiber, polyphenols, and fermented foods promote microbial diversity, improve intestinal integrity, and reduce systemic inflammation, whereas refined sugar or high-fat diets impair these mechanisms [90]. Personalized nutritional counseling tailored to the patient's microbiota composition may serve as a beneficial adjunct to immunotherapy [91]. Regular exercise, adequate sleep, and stress management enhance microbial diversity and regulate inflammatory tone [92]. Circadian rhythm stability is particularly important, as disrupted sleep can elevate cortisol levels and impair immune recovery [93]. Lifestyle interventions may act as cost-effective adjuncts to psychomicrobial therapy, but direct studies on this combination of approaches are still emerging [94].

Table 6. Lifestyle factors influencing the gut brain immune axis

Factor	Mechanism	Clinical Benefit
High fiber diet	Increases short chain fatty acid production	Strengthens anti-inflammatory pathways
Fermented foods	Provide beneficial microbes	Enhance serotonin and immune function
Exercise	Improves microbial richness and reduces cortisol	Enhances T cell activity and mood
Sleep optimization	Restores circadian cytokine rhythm	Reduces fatigue and emotional distress

5.4. Technological advances and biomarker development

Emerging multi-omics technologies now permit the integration of microbial, metabolic, and psychological data for precision therapy design [95]. Artificial intelligence tools can analyze patterns linking emotional status, microbiome signatures, and immune responses, enabling predictions of treatment outcomes [96].

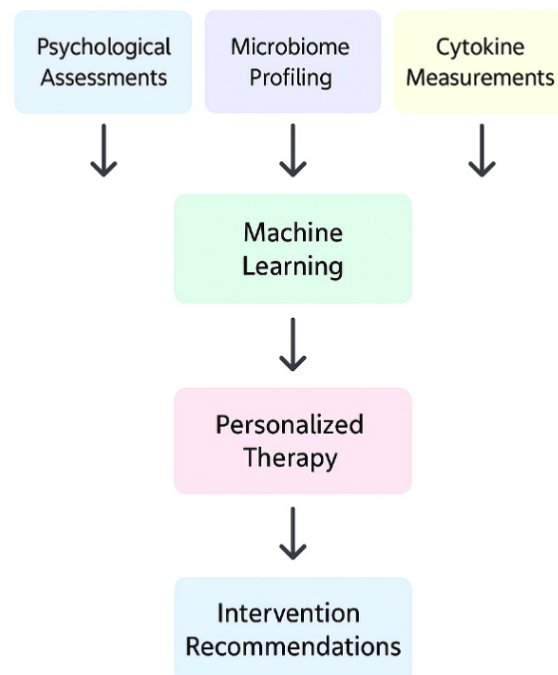


Figure 8. Precision psycho microbiome model

Validated biomarkers such as short-chain fatty acids, kynurenine derivatives, and specific cytokine ratios may guide individualized therapy selection [97]. This approach aligns with precision psycho-oncology, where interventions are tailored to both biological and emotional patient profiles, enhancing treatment effectiveness [98]. A schematic depicting layered data inputs—psychological scores, microbiota sequencing, cytokine profiles—converging into a predictive analytics module that outputs personalized intervention recommendations is essential for this model [99]. As shown in **Figure 8**, the integration of psychological assessments, microbiome profiling, and immune biomarker measurements through artificial intelligence and machine learning algorithms enhances the accuracy and relevance of treatment plans [55]. These data streams converge to generate personalized psychomicrobial therapy plans and predictive intervention recommendations, aligning emotional health and biological regulation to optimize cancer treatment outcomes [100].

5.5. Implementation challenges and ethical considerations

Despite compelling evidence, clinical translation of the microbiome-gut-brain axis (MGBA) model faces practical and ethical challenges [101]. Microbiota composition varies across individuals and populations, making standardization difficult [102]. Safety concerns remain regarding probiotic formulations and fecal microbiota transplantation, especially given the potential for adverse effects and varying responses among patients [103]. Rigorous clinical trials and standardized reporting are required to validate efficacy and ensure reproducibility.

Ethical considerations also arise from the handling of sensitive psychological and microbial data, including the need for informed consent and respect for patient autonomy [104]. Clinicians should maintain transparency while avoiding overinterpretation of preliminary microbiome correlations, as the field is still evolving and preliminary findings may not reflect definitive outcomes [105].

5.6. Future research and clinical translation

Future research should focus on longitudinal studies evaluating the dynamic interaction among mood, microbiota, and immunity during cancer treatment [106]. Randomized controlled trials combining psychological therapy with microbial modulation will clarify synergistic mechanisms and optimal timing of interventions [107].

International collaborations are needed to harmonize protocols for microbiota sequencing, probiotic formulation, and psychometric evaluation [108]. Integration of digital health platforms will further support real time monitoring of stress physiology and microbial diversity, enabling adaptive clinical decision making [106]. As outlined in **Table 7**, future research priorities include longitudinal MGBA tracking, combined psycho-microbial trials, metabolomic and cytokine biomarker validation, and the development of ethical frameworks and standardization—all of which are essential for translating these findings into scalable clinical practice.

Table 7. Future research priorities in psycho microbiome oncology

Research Area	Objective	Expected Impact
Longitudinal MGBA tracking	Monitor microbiota and mood across treatment phases	Identify predictive biomarkers of response
Combined psycho microbial trials	Test synergistic effects on depression and immune activation	Improve survival and quality of life

Continuation Table:

Research Area	Objective	Expected Impact
Metabolomic and cytokine biomarkers	Validate objective indicators of psychoimmunological status	Enable precision patient selection
Ethical frameworks and standardization	Ensure safe data governance and global comparability	Strengthen clinical adoption

5.7. Integrative outlook

The convergence of psychology, microbiology, and immunology marks a paradigm shift in cancer care [109]. By viewing emotional regulation, microbial ecology, and immune activation as mutually reinforcing systems, psycho-oncology evolves from supportive counseling to a mechanistically grounded therapeutic science [110]. Integrative psychomicrobial interventions promise not only to reduce distress but to optimize the biological conditions necessary for immunotherapy success [111]. The gut-brain-immune axis thus becomes both a diagnostic guide and a therapeutic target, uniting mind and biology within one continuum of healing [112].

6. Limitations

While this narrative review provides a comprehensive synthesis of the current literature linking tumor-associated depression, gut microbiota, and immune checkpoint inhibitor sensitivity, several limitations must be acknowledged.

First, the majority of studies reviewed are preclinical or correlational in nature. Direct evidence demonstrating a causal relationship between depression-induced dysbiosis and reduced immunotherapy efficacy in humans remains limited. Most human studies report associations rather than causations, and confounding factors such as diet, medication (e.g., antibiotics, proton pump inhibitors), and lifestyle differences are often inadequately controlled.

Second, the operationalization of depression varies considerably across studies. As noted in Section 3.1, many investigations rely on self-report screening tools rather than structured diagnostic interviews, potentially conflating subsyndromal distress with major depressive disorder. Future studies should standardize depression assessment to enable meaningful cross-study comparisons.

Third, the gut microbiota exhibits high inter-individual and inter-population variability, making it difficult to generalize findings across different geographic, dietary, and treatment contexts. Most microbiome studies are underpowered and lack validation cohorts.

Fourth, the proposed psycho-microbiological framework, while conceptually innovative, has not yet been tested in prospective interventional trials. The clinical efficacy of combined psychological and microbial modulation strategies requires rigorous randomized controlled trials before definitive recommendations can be made.

Finally, publication bias may exist, as studies reporting positive associations between microbial composition and immunotherapy response are more likely to be published than null or negative findings.

7. Conclusions

The synthesis presented in this review underscores that psychological, microbial, and immunological processes are deeply intertwined in determining cancer outcomes.

Despite the limitations outlined above, the convergence of evidence supports a model in which tumor associated depression is not merely an emotional reaction but a biologically active condition that reshapes immune function and alters the gut microbial environment. At the same time, the gut microbiota communicates with the brain and immune system through metabolic, neural, and endocrine pathways, collectively forming the gut brain immune axis. Disruption in this network contributes to chronic inflammation, immune exhaustion, and decreased responsiveness to immunotherapy.

Recognizing this interconnected system transforms psycho oncology from a supportive specialty into a mechanistically grounded field. Integrative interventions that combine psychological therapy with microbiota modulation through probiotics, diet modification, or fecal microbiota transplantation which offer a dual route to improve both mental well-being and immune regulation. Such approaches can reduce inflammatory signaling, enhance cytokine balance, and strengthen the host's capacity to respond to immune checkpoint inhibitors.

The future of psycho oncology lies in this convergence of mind, microbes, and immunity. Routine assessment of psychological distress, inflammatory biomarkers, and microbiota diversity can provide early insight into therapeutic resilience. Ultimately, optimizing emotional health and microbial balance within the same clinical framework represents a new frontier in personalized cancer care, where healing is defined not only by tumor control but by the restoration of systemic harmony across the biological and psychological domains.

Author contributions: Conceptualization, JW; methodology, JW; software, JW; validation, JW; formal analysis, JW; investigation, JW; resources, JW; data curation, JW; writing—original draft preparation, review and editing, JW; visualization, JW ; supervision, JW; project administration, JW. All authors have read and agreed to the published version of the manuscript.

Funding: None.

Ethical approval: Not applicable.

Informed consent statement: Not applicable.

Conflict of interest: The authors declare no conflict of interest.

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