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From gums to moods: Exploring the impact of the oral microbiota on depression

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ABSTRACT

Depression is a complex and heterogeneous disorder that results from a combination of genetic vulnerability, environmental stressors, and dysregulated biological processes. While systemic inflammation and gut dysbiosis have been extensively investigated in the context of depression, the role of the oral microbiome has only recently begun to emerge. The oral microbiome is a highly diverse and dynamic ecosystem, comprising bacteria, fungi, viruses, and archaea, which coexist in a delicate balance with the host's immune system. This microbial community plays a fundamental role in maintaining not only oral health, but also systemic homeostasis. Emerging evidence suggests that disruptions in this balance, or oral dysbiosis, may contribute to a range of systemic inflammatory conditions, including psychiatric disorders such as depression. Factors comprising periodontal disease, dental infections, and poor oral hygiene can lead to an imbalance in oral microbial composition, promoting immune system activation, chronic inflammation and microbial translocation, which are increasingly recognised mechanisms involved in the pathophysiology of depression. This review delves into the emerging evidence linking oral dysbiosis to depression, elucidating the underlying biological mechanisms and their clinical implications. By bridging the gap between oral health and mental well-being, it underscores the importance of a multidisciplinary approach in addressing depression—one that extends beyond conventional psychiatric treatments to include oral health interventions as a viable component of comprehensive care strategies.

1. Introduction

Depression is a pervasive and multifaceted mental health disorder that affects over 264 million people worldwide, posing significant social and economic challenges (World Health Organization, 2017). It is characterised by persistent sadness, loss of interest in daily activities, cognitive impairment, and physical symptoms, such as fatigue and sleep disturbances. The disorder is a leading cause of disability globally, contributing to diminished quality of life and increased morbidity and mortality due to its associations with chronic illnesses, including cardiovascular disease, diabetes, and neurodegenerative disorders (Otte et al., 2016). The aetiology of depression is complex, involving a dynamic interplay of genetic predisposition, environmental stressors, and biological processes. Despite advancements in pharmacological and psychotherapeutic treatments, the prevalence of depression continues to rise, indicating the need for novel perspectives on its pathophysiology.

Recent scientific advances have highlighted the pivotal role of the microbiota in overall health, with a specific focus on its influence on the gut-brain axis (Hou et al., 2022). The microbiota plays a crucial role in various physiological processes, such as regulating the hypothalamic-pituitary-adrenal (HPA) axis, modulation of immune responses, and synthesising neurotransmitters (Cryan et al., 2019). In the context of mental health, a growing body of research has underscored the importance of inflammation, with dysregulated immune responses, including elevated levels of proinflammatory cytokines such as interleukin-6 (IL-6) and Tumour Necrosis Factor-alpha (TNF-α), frequently observed in individuals with depression (Dantzer et al., 2008). Within this framework, the gut microbiota has emerged as a key mediator of neuroinflammation, influencing the brain's neurochemical and immune pathways (Margolis et al., 2021). Despite this recognition, most studies have primarily focused on the gut microbiome, leaving other microbial ecosystems within the body relatively unexplored.

The oral microbiome, a diverse and dynamic microbial community that occupies various niches within the oral cavity, plays a fundamental

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role in maintaining not only oral health but also systemic well-being (Dewhirst et al., 2010; Wade, 2013; (Baker et al., 2024)). In fact, it performs essential functions, such as preventing pathogenic colonisation, modulating local inflammation, and maintaining mucosal homeostasis (Krishnan et al., 2017). However, dysbiosis of the oral microbiome can contribute to a cascade of detrimental effects, ranging from periodontal disease to systemic inflammatory responses (Hajishengallis and Chavakis, 2021). Notably, oral dysbiosis has been linked to chronic illnesses such as cardiovascular and gastrointestinal diseases, diabetes, and adverse pregnancy outcomes, underscoring its systemic implications (Han and Wang, 2013; Kunath et al., 2024).

Evidence has begun to emerge linking the oral microbiome to mental health disorders, particularly depression (Scassellati et al., 2021; (Martínez et al., 2022a). Moreover, oral pathogens may indirectly influence brain function by translocating to the gut, altering the gut microbiota's composition and function, further contributing to depression through disruption of gut permeability (i.e., leaky gut) and altered neurochemical signalling (Atarashi et al., 2017). For instance, one potential pathway linking the gut microbiota to neuroinflammation involves the systemic circulation of endotoxins—such as lipopolysaccharides (LPS), a component of the external wall of Gram-negative bacteria—and other microbial-associated molecular patterns (MAMPs/PAMPs). When mucosal barriers like the gut or oral epithelium are compromised, these proinflammatory molecules can enter the bloodstream, triggering immune responses that may extend to the central nervous system. This mechanism has been implicated in conditions like depression, anxiety, and schizophrenia ((Martínez et al., 2022a) ; (Wingfield et al., 2021a); (Maes et al., 2008); Zheng et al., 2025; (Simpson et al., 2020)).

Despite these emerging insights, the role of the oral microbiome in depression remains underexplored. This knowledge gap presents a significant opportunity for advancing our understanding of depression's pathophysiology and developing holistic, integrative therapeutic strategies. Maintaining oral health could potentially serve as an accessible and cost-effective approach to mitigating the inflammatory and neurochemical disruptions associated with depression. Furthermore, identifying specific microbial signatures or biomarkers within the oral cavity could pave the way for novel diagnostic tools and personalised interventions.

This narrative review aims to delve into the intricate relationship between the oral microbiome and depression, focusing on the underlying the potential different mechanisms that bridge oral health and mental health. By summarising current research, this work seeks to illuminate the systemic impact of oral dysbiosis, highlight the importance of interdisciplinary approaches to managing depression, and inspire future studies to address this overlooked aspect of mental health. Ultimately, understanding the connection between the oral microbiome and depression has the potential to revolutionise preventive and therapeutic strategies, fostering improved mental and physical well-being.

2. Composition of the oral microbiome

The oral microbiome is among the most diverse and complex microbial communities in the human body, hosting over 700 microbial species, including bacteria, fungi, viruses, archaea, and protozoa (Dewhirst et al., 2010). These microorganisms are distributed across distinct niches within the oral cavity, such as the tongue, gingival crevices, tooth surfaces, palatal mucosa, and saliva, each providing unique environmental conditions that shape the microbial composition (Proctor and Relman, 2017). For instance, the supragingival biofilm—the layer of microorganisms adhering to tooth surfaces above the gumline—is typically dominated by aerobic and facultative anaerobic bacteria, such as species from the genera Streptococcus and Actinomyces, due to the availability of oxygen (Lamont et al., 2018). In contrast, the subgingival region, located below the gumline, is an anaerobic environment where obligate anaerobic species like *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Fusobacterium nucleatum* thrive (Zambon and Haraszthy, 2021).

The oral cavity also harbours diverse fungi, especially *Candida albicans*, which resides as a commensal organism in healthy individuals but can act as an opportunistic pathogen under conditions of immune suppression or dysbiosis (Mukherjee et al., 2018). Viruses, including bacteriophages, are another integral part of the oral microbiome, influencing bacterial populations through predation or gene transfer, thereby shaping the community's overall functionality and stability (Pride et al., 2012). Saliva serves as a critical medium in the oral ecosystem, acting as both a reservoir and transport mechanism for microbes while providing nutrients, buffering capacity, and antimicrobial compounds such as lysozyme, lactoferrin, and immunoglobulin A (IgA) (Marsh and Devine, 2011). This intricate microbial ecosystem is dynamic and self-regulating, relying on microbial interactions, environmental stability, and host factors to maintain oral health (Krishnan et al., 2017).

3. Oral microbial functional roles in health

Commensal bacteria contribute to oral health by occupying ecological niches and preventing colonisation by pathogens through competitive exclusion and producing bacteriocins, antimicrobial peptides that inhibit the growth of harmful microbes (Rosier et al., 2018). The oral microbiota initiates digestion by interacting with food components and triggering key biochemical processes. Some oral bacteria convert dietary nitrates into nitrites, precursors of nitric oxide, which aids gut function and blood flow. Others break down carbohydrates and proteins, shaping the nutrients that reach the gut and influencing overall nutrient absorption and metabolism—linking oral health to digestive and systemic efficiency (Sedghi et al., 2021). Oral microbiota is also crucial for maintaining oral pH balance, preventing the growth of pathogenic bacteria and the trigger of local and systemic inflammation, and, therefore, preventing or worsening the detrimental effects on oral health, cardiovascular, metabolic, and neurological conditions (Huang et al., 2024; Wade, 2021). For instance, certain beneficial bacteria, such as *Streptococcus salivarius*, metabolise urea and arginine to produce ammonia, which buffers acid levels generated by other bacteria that ferment dietary sugars (Wade, 2013). Additionally, the microbiome modulates local and systemic immune responses by stimulating the production of anti-inflammatory cytokines, antimicrobial peptides such as defensins, and immunoglobulins, thereby fortifying the oral epithelial barrier against pathogenic invasion (Krishnan et al., 2017). However, this balanced ecosystem is highly susceptible to disruption. Poor oral hygiene, an unhealthy diet (particularly excessive sugar intake), smoking, alcohol consumption, and systemic conditions like diabetes or immunosuppression can disrupt the microbiota's equilibrium. Such disruptions can lead to dysbiosis, where pathogenic species outcompete commensal microbes, creating an imbalanced microbial community that contributes to oral and systemic diseases (Mira et al., 2017). For instance, understanding the factors that influence the composition and stability of the oral microbiome is critical for developing preventive strategies and interventions aimed at preserving oral and systemic health.

4. Oral dysbiosis and its consequences

Oral dysbiosis is marked by a significant shift in the composition and functionality of the microbial community, favouring pathogenic organisms at the expense of commensal species. An overgrowth of key oral pathogens such as *Porphyromonas gingivalis*, *Treponema denticola*, *Fusobacterium nucleatum*, and *Aggregatibacter actinomycetemcomitans* often accompanies this imbalance. These bacteria produce an array of virulence factors, including proteases, toxins, and immunostimulatory components, such as LPS, that disrupt host tissues and provoke chronic inflammation (Hajishengallis, 2015). For instance, *Porphyromonas*

gingivalis, a keystone pathogen in periodontitis, produces gingipains—proteolytic enzymes that degrade host proteins, impair immune signalling, and exacerbate tissue destruction (Van Dyke et al., 2020). Similarly, *Fusobacterium nucleatum* facilitates biofilm formation by bridging interactions between early and late colonisers, enhancing the complexity and pathogenic potential of the oral microbiome (Han and Wang, 2013).

The consequences of dysbiosis are not limited to the oral cavity. Periodontal pathogens and their metabolic byproducts can enter the bloodstream through compromised oral epithelial barriers, leading to systemic dissemination and widespread inflammation. For example, bacterial antigens and inflammatory mediators released by Porphyromonas gingivalis have been implicated in the development of atherosclerosis, contributing to endothelial dysfunction, plaque formation, and cardiovascular complications (Pussinen et al., 2007).

Emerging evidence also suggests that oral dysbiosis may contribute to mental health disorders, including depression. Chronic low-grade inflammation originating from the oral cavity can elevate systemic levels of proinflammatory cytokines, such as IL-6 and TNF-α, which have been consistently associated with depressive symptoms (Miller and Raison, 2016). Furthermore, inflammatory mediators and bacterial components such as LPS can cross the blood-brain barrier, promoting neuroinflammation, disrupting synaptic plasticity, and altering neurotransmitter systems involved in mood regulation (Chung et al., 2019). For instance, increased levels of peripheral LPS have been linked to reduced brain-derived neurotrophic factor (BDNF) expression, a critical neurotrophin involved in neurogenesis and mood stabilisation (Yirmiya and Goshen, 2011).

5. Mechanisms linking the oral microbiome to depression

Fig. 1 illustrates the primary pathways through which the oral microbiome may be directly or indirectly associated with depressive symptomatology. Oral microbiota dysbiosis can have systemic consequences, influencing gut health, immune responses, and mental health (Malan-Müller et al., 2024).

5.1. Oral-brain axis

Growing evidence supports direct neuroanatomical routes by which the oral microbiota may influence brain function (Kristensson, 2011). Unlike gut-derived microorganisms, which typically undergo hepatic filtration before reaching systemic circulation, oral microbes can bypass this pathway via microbial translocation (Burgos-Larraín et al., 2022). Specifically, the trigeminal nerve and olfactory system provide direct anatomical connections between the oral/nasal cavity and the central nervous system, including the brainstem and olfactory bulb, respectively (Dando et al., 2014; Kristensson, 2011; Tao et al., 2024). These findings highlight a neuroinvasive route through which oral pathogens can impact central nervous system function.

Studies have demonstrated that the composition of the oral microbiome in individuals with depression is different from that of healthy individuals. For example, individuals with depression often show overgrowth of pathogenic bacteria (e.g., gram-negative bacteria), both of

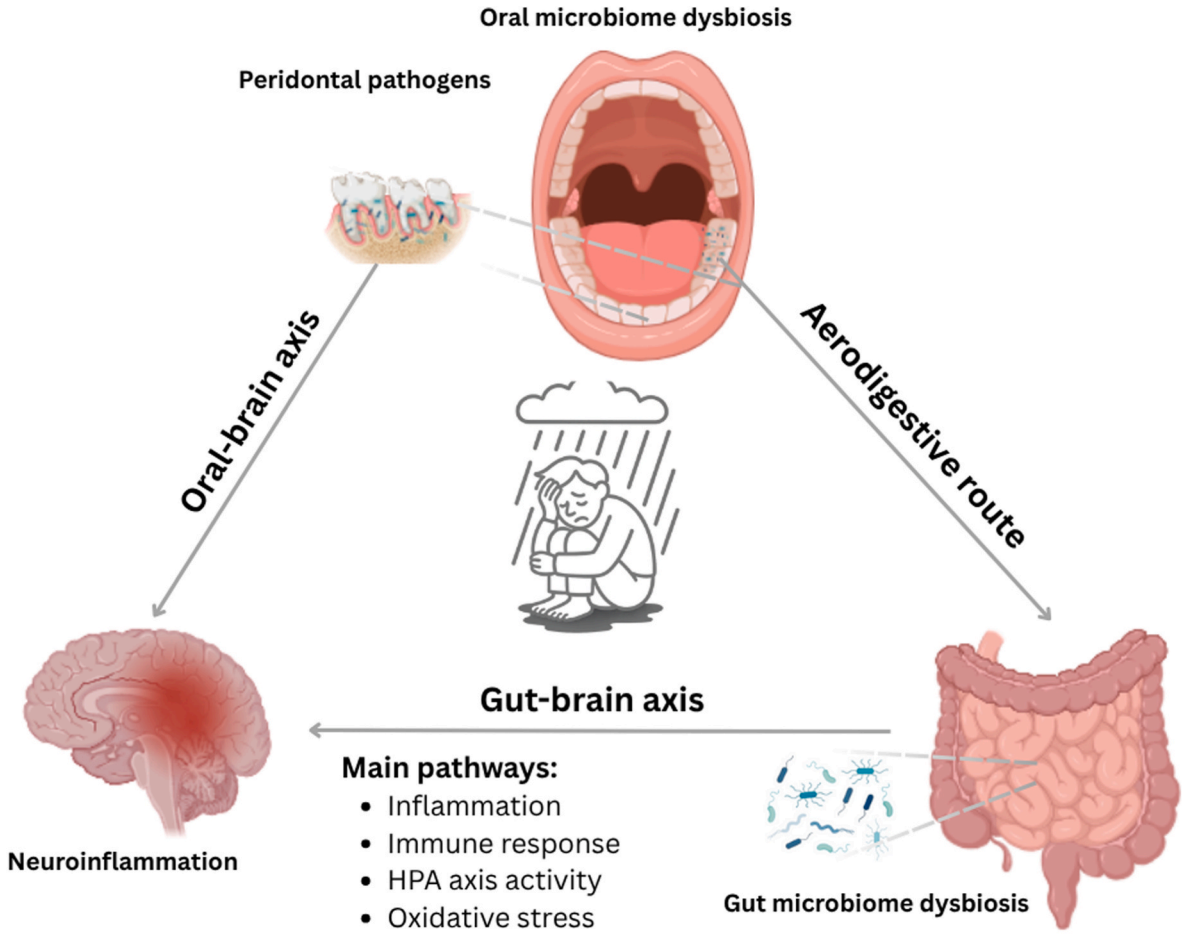

Fig. 1. Conceptual representation of the main pathways linking oral microbiome dysbiosis and depressive symptoms. Periodontal pathogens and oral dysbiosis may affect brain function directly via the oral–brain axis (e.g., promoting neuroinflammation) or indirectly through the aerodigestive route, leading to gut microbiome dysbiosis. This gut disturbance can further impact the brain via the gut–brain axis, involving multiple pathways such as systemic inflammation, immune activation, hypothalamic–pituitary–adrenal (HPA) axis dysregulation, and oxidative stress.

which are implicated in neuroinflammation (Martínez et al., 2022a). The neuroinvasive capacity becomes particularly relevant under conditions of oral dysbiosis, where pathogenic Gram-negative bacteria (e.g., *Fusobacterium nucleatum*, *Porphyromonas gingivalis*) dominate the microbiota, leading to systemic inflammation, a known contributor to depression (Maes et al., 2008). Recent studies have demonstrated that microbial components - such as LPS - can translocate along these nerves and accumulate in brain regions involved in cognition and emotional regulation. For example, small LPS fragments bound to apolipoproteins have been detected in the perfused prefrontal cortex of alcohol-exposed animal models, suggesting microbial access to cortical structures (Leclercq et al., 2019). In this case of oral dysbiosis, changes in the salivary microbiome can precede or coincide with the onset of depressive symptoms (Wingfield et al., 2021a; Zheng et al., 2025), making it a potential early marker for psychological as well as physical health issues.

Moreover, chronic oral diseases such as periodontitis can compromise the oral mucosal barrier, facilitating microbial entry into both peripheral nerves and the bloodstream (Sedghi et al., 2021). Once in systemic circulation or neural pathways, bacterial components may induce neuroinflammation and promote blood-brain barrier (BBB) dysfunction, mechanisms increasingly implicated in the pathophysiology of neurodegenerative and neuropsychiatric disorders (Tao et al., 2024).

5.2. Oral-gut-brain axis: from aerodigestive route to neuroinflammation

In addition to direct neuroanatomical communication, an important potential mechanism involves the interaction between the oral microbiome and those in other gastrointestinal tract regions. The oral gut-brain axis is a crucial conceptual framework that helps to elucidate how the oral microbiome can influence depressive symptoms (Scassellati et al., 2021). This axis represents the complex, bi-directional communication network linking the mouth, gastrointestinal (GI) tract, and the brain. The gut microbiota plays a crucial role in metabolic processes, immune modulation, and the synthesis of neuroactive metabolites. These functions have profound effects on brain health, influencing mood, behaviour, and cognitive function (Margolis et al., 2021; McGuinness et al., 2024). Various biological systems, including the vagus nerve, endocrine signalling, and immune pathways, facilitate this communication, making it a powerful network for regulating physical and mental health.

Oral disturbances may trigger systemic changes that affect the gut microbiota, leading to gut dysbiosis, which in turn can influence brain function. The transfer of oral microbes to the gut is common, as demonstrated by Segata et al. (2011) who found that in nearly 45 % of individuals in the Human Microbiome Project, oral and gut microbiota overlapped. The saliva contains an enormous number of oral bacteria, that in general, are poor colonisers of the healthy intestine. However increased levels of bacteria of oral origin have been reported in the gut microbiota of patients with severe periodontitis (Bao et al., 2022). These might suggest that, under certain conditions, a subset of oral microbiota may ectopically colonise and persist in the intestine, potentially leading to aberrant activation of the intestinal immune system and contributing to chronic inflammatory diseases (Read et al., 2021).

The ectopic colonisation of the gut by oral bacteria – such as *Porphyromonas gingivalis* – has been observed in both animal models and humans and is considered a hallmark of systemic and neuroinflammatory disease (Martínez et al., 2022b; Nakajima et al., 2015). These inflammatory responses, together with increased leaky gut, can facilitate the systemic dissemination of microbial products such as LPS, contributing to blood–brain barrier (BBB) disruption and neuroinflammation—mechanisms strongly implicated in neurodegenerative and psychiatric conditions.

The colonisation of the gut by oral bacteria, especially opportunistic species affect the gut microbiome, leading dysbiosis can impair the gut's ability to produce beneficial metabolites like short-chain fatty acids (SCFAs). SCFAs serve a variety of vital functions that can significantly affect both gut and brain health (Paudel et al., 2022). They help maintain the integrity of the BBB, an essential structure that protects the brain from harmful pathogens and toxins (Parker et al., 2020). A compromised BBB is often associated with increased neuroinflammation and altered brain function, which are both key contributors to the pathophysiology of depression. SCFAs also regulate neuroinflammation by influencing immune signalling pathways. They promote the production of anti-inflammatory cytokines and reduce the expression of proinflammatory molecules, which helps to maintain a balance in the immune system and prevent chronic inflammation (He et al., 2020; Yao et al., 2022).

Furthermore, SCFAs promote the release of serotonin, a neurotransmitter that plays a central role in regulating mood, sleep, and cognition (Bruun et al., 2024; Magzal et al., 2021; Margoob et al., 2024). The gut microbiota has been shown to directly influence serotonin synthesis in the intestines, where approximately 90 % of serotonin is produced. SCFAs support the functioning of enterochromaffin cells, which are responsible for releasing serotonin into the bloodstream (L. Jiang et al., 2024; Luo et al., 2021). The production of adequate serotonin is essential for maintaining emotional well-being, and deficiencies in serotonin are commonly associated with depression. In addition to SCFAs, the gut microbiome also impacts the levels and activity of other neurotransmitters, including dopamine, GABA, and glutamate. These neurotransmitters are critical for regulating mood, stress response, and cognitive function. A disruption in the production or regulation of these neurotransmitters—due to gut dysbiosis resulting from oral microbiome imbalances—can lead to mood disorders, including depression. For example, dopamine, which plays a key role in the brain's reward system and is involved in motivation and pleasure, can be influenced by the gut microbiota's ability to synthesise or metabolise specific precursors (Hamamah et al., 2022). Changes in dopamine production can contribute to symptoms of anhedonia (the inability to feel pleasure), a hallmark feature of depression.

Similarly, GABA, the brain's primary inhibitory neurotransmitter, plays a critical role in maintaining emotional stability and reducing anxiety. Gut dysbiosis has been shown to influence GABAergic signaling pathways, potentially leading to an imbalance between excitatory and inhibitory neurotransmission (Hamamah et al., 2022). In addition, certain gut bacteria—such as *Lactobacillus* and *Bifidobacterium* species—are known to produce GABA, and their depletion in dysbiosis states may reduce its availability (Strandwitz et al., 2018). Dysbiosis may also impair vagus nerve-mediated signaling between the gut and brain, which is crucial for emotional regulation (Bonaz et al., 2018). Furthermore, increased intestinal permeability associated with dysbiosis can lead to systemic inflammation and neuroinflammatory responses, both of which have been implicated in mood disorders (Kelly et al., 2015). In contrast, glutamate, the brain's major excitatory neurotransmitter, can also be influenced by the gut microbiota. Several microbial species modulate glutamatergic pathways directly by producing or degrading glutamate (Strandwitz et al., 2018), or indirectly through metabolites such as short-chain fatty acids (Dalile et al., 2019), and inflammatory cytokines that cross the blood–brain barrier (Kelly et al., 2015). Alterations in these pathways can disrupt the delicate balance between excitation and inhibition in the central nervous system, leading to various psychiatric disorders, including depression and anxiety (Sanacora et al., 2012).

In the next sections, the review explores some important pathways triggered in the oral-gut-brain axis.

5.2.1. Chronic inflammation and immune dysregulation

Chronic inflammation is a well-established contributor to depression, and the oral microbiome plays a significant role in driving systemic inflammatory processes. Oral dysbiosis, especially in the form of periodontal disease, reflects microbial imbalance and is a major driver of

systemic inflammation. Bacteria, such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, play a pivotal role in periodontitis development have been shown to produce LPS and other virulence factors capable of triggering systemic immune activation (Hajishengallis, 2015). These inflammatory mediators can cross the blood-brain barrier, promoting neuroinflammation and affecting critical neurotransmitter systems involved in mood regulation, such as serotonin, dopamine, and gamma-aminobutyric acid (GABA) pathways (Miller and Raison, 2016). Other pathogens such as *Porphyromonas gingivalis* and *Tannerella forsythia* indeed release virulence factors like gingipains and LPS, which activate toll-like receptors (TLRs) on immune cells, triggering a cascade of proinflammatory cytokine production (Hajishengallis, 2015; Zhao et al., 2024), that can enter systemic circulation and cross the BBB, where they promote neuroinflammation, a hallmark of depression (Morris et al., 2018). Microglial cells, the brain's resident immune cells, are activated in response to inflammatory signals, leading to the release of neurotoxic mediators, such as nitric oxide and reactive oxygen species, which impair neuronal function and plasticity (Miller and Raison, 2016). Chronic neuroinflammation has been implicated in structural and functional brain changes observed in depression, including reduced hippocampal volume and disrupted synaptic connectivity (Furtado and Katzman, 2015). Furthermore, inflammation-induced alterations in the HPA axis exacerbate depressive symptoms. Elevated cytokine levels disrupt glucocorticoid receptor signalling, leading to increased cortisol secretion and prolonged stress responses, both of which are strongly associated with depression (Slavich and Irwin, 2014) In addition to these systemic effects, specific oral pathogens may exert more direct influences on the brain. For example, Porphyromonas gingivalis has been detected in the brains of individuals with Alzheimer's disease and has been shown to produce gingipains capable of directly degrading neural proteins and contributing to neurodegeneration (Dominy et al., 2019). While much of this research has focused on neurodegenerative diseases, similar mechanisms may play a role in depression, particularly given the shared involvement of neuroinflammation and disrupted brain plasticity. This evidence highlights the critical role of oral inflammation in systemic and neural health and underscores the need to address oral dysbiosis as part of a broader strategy to mitigate depression. Gingivitis and periodontitis increase production of proinflammatory cytokines in the oral cavity, which can spill over into the systemic circulation, contributing to systemic inflammation. Periodontal disease is associated with the production of inflammatory biomarkers such as IL-6, interleukin-1 beta (IL-1β), and C-reactive protein (CRP) (D'Aiuto et al., 2013). These biomarkers are elevated not only in oral diseases but also in various conditions related to chronic inflammation, including depression. Research has shown that elevated IL-6 and IL-1β levels are associated with depressive symptoms, and systemic inflammation is considered a key driver of the pathophysiology of depression (Maes, 2011). Both IL-6 and IL-1β contribute to neuroinflammation, which can interfere with neurotransmitter metabolism and brain regions' functioning in mood regulation (Pace et al., 2007). Additionally, CRP, a marker of acute systemic inflammation, has been found to be elevated in individuals with depression, and it correlates with the severity of depressive symptoms (Haapakoski et al., 2015). Salivary analysis of these inflammatory proteins could, therefore, provide valuable insights into the inflammatory status in individuals with depression, especially those with concurrent oral diseases like periodontal disease. Elevated IL-6, IL-1β, and CRP levels in saliva can reflect the oral-systemic inflammation connection, indicating poor oral health and the potential for mental health disturbances.

5.2.2. The kynurenine pathway

The tryptophan–kynurenine pathway (KP) is responsible for approximately 95 % of dietary tryptophan catabolism and plays a crucial immunometabolic role in the pathophysiology of major depressive disorder (MDD) (Ogyu et al., 2018). Under pro-inflammatory conditions – commonly elicited by microbial dysbiosis – indoleamine 2, 3-dioxygenase 1 (IDO1), and to a lesser extent tryptophan 2,3-dioxygenase (TDO), are induced. This metabolic shift diverts tryptophan away from serotonin synthesis toward the production of kynurenine and its neuroactive downstream metabolites, including quinolinic acid (QUIN), kynurenic acid (KYNA), and 3-hydroxykynurenine (3-HK) (Savitz, 2020). QUIN acts as an NMDA receptor agonist and contributes to excitotoxicity, while 3-HK promotes oxidative stress and neuroinflammation—mechanisms that are increasingly recognised as central to MDD pathogenesis (Ogyu et al., 2018; Schwarcz and Stone, 2017).

While gut microbiota involvement in KP activation is well established, recent evidence points to the oral microbiome as a potential upstream contributor (Kis-György et al., 2024). Chronic oral inflammation, such as that observed in periodontitis, is associated with elevated systemic cytokines (e.g., IL-6, TNF-α), which are potent inducers of IDO1 (Hajishengallis, 2015; Hajishengallis and Chavakis, 2021). Notably, pathogens like *Porphyromonas gingivalis* and *Fusobacterium nucleatum* can trigger TLR-mediated activation of NF-κB signaling, thereby stimulating IDO1 expression and promoting systemic kynurenine production (Kis-György et al., 2024).

Experimental models support this hypothesis: a recent study using germ-free mice demonstrated that oral dysbiosis alone—induced by chronic stress—was sufficient to elevate peripheral kynurenine levels via increased IDO1 activity, independent of gut microbial alterations (Lou et al., 2025). Moreover, clinical studies have identified associations between salivary microbial composition and altered kynurenine-to-tryptophan ratios in individuals with depressive and anxiety symptoms (C. Li et al., 2022; Qiu et al., 2025; Wingfield et al., 2021a,b). Functional metagenomic analyses suggest that oral microbial communities in MDD may have an enhanced metabolic capacity to influence tryptophan catabolism through the KP.

Together, these findings support a mechanistic model wherein oral microbiota dysbiosis promotes systemic inflammation, leading to IDO1-mediated activation of the kynurenine pathway. The resulting accumulation of neurotoxic metabolites and depletion of tryptophan for serotonin biosynthesis may constitute a key biological link between oral health and mood disorders. Future longitudinal and interventional studies are warranted to assess whether modulation of the oral microbiota could mitigate KP-related neuroinflammatory processes in depression.

5.2.3. Microbial metabolites and toxins

Beyond the inflammatory and tryptophan-dependent mechanisms discussed above, dysbiosis of the oral microbiota generates a spectrum of virulence factors—lipopolysaccharides (LPS), cysteine proteases (gingipains), short-chain fatty acids (SCFAs) and reactive oxygen species (ROS)—that can relay signals from periodontal niches to the central nervous system. LPS produced by keystone pathogens such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum* traverses ulcerated gingival epithelium, enters the bloodstream and elevates systemic TNF-α and IL-6; these cytokines, together with LPS itself, disrupt tight-junction integrity at the blood–brain barrier and prime microglia, thereby amplifying neuroinflammation (Jiang et al., 2025).

Gingipains secreted or vesicle-packaged by *Porphyromonas gingivalis* do more than disrupt local tissues: they degrade complement proteins, dismantle synaptic scaffolds, promote tau hyper-phosphorylation and, crucially, set off neurobiological changes characteristic of depression. In vivo and ex vivo work shows that chronic exposure to gingipains elevates hippocampal IL-1β and TNF-α, lowers brain-derived neurotrophic factor (BDNF) and precipitates anhedonia- and despair-like behaviours in rodents (Mamunur et al., 2023; Wang et al., 2019). Complement-dependent microglial pruning of dendritic spines—heightened in the presence of gingipains—has likewise been linked to stress-induced synaptic loss and mood dysregulation (Dominy et al., 2019). Human data echo these findings: patients with periodontitis and high salivary gingipain activity display elevated C-reactive protein and IL-6 levels that track with depressive symptom severity, while

hippocampal proBDNF/p75NTR signalling alterations have been observed in murine models of periodontitis-induced low mood (Y. Li et al., 2023). Gingipains also increase blood–brain-barrier permeability via caveolin-1-dependent transcytosis, providing a route for peripheral inflammatory mediators to enter the brain (Lei et al., 2023).

Oral biofilms also generate millimolar concentrations of propionate and butyrate; once absorbed or swallowed, these SCFAs modulate hypothalamic–pituitary–adrenal activity, alter amino-acid pools for monoamine synthesis and sustain low-grade systemic inflammation (Magrin et al., 2020). Consistent with these actions, individuals with depression display a distinctive salivary metabolomic profile—higher propionate-to-acetate ratios and lower circulating butyrate—which correlates with symptom severity and inflammatory markers (Aleti et al., 2022).

Finally, periodontal spirochetes (*Treponema denticola*) and bridging bacteria such as *Fusobacterium nucleatum* liberate high levels of ROS and volatile sulphur metabolites; this redox burst disrupts mitochondrial respiration and triggers oxidative DNA lesions. A growing body of pre-clinical and clinical evidence shows that such bacterially driven oxidative stress is associated with cortical thinning, psychomotor slowing and other neurocognitive sequelae that characterise major depressive disorder (Bhatt et al., 2020a; Kang et al., 2019; McIlvanna et al., 2021; Wu et al., 2022).

Collectively, these microbial products outline a plausible—though still largely pre-clinical—route by which oral dysbiosis may perpetuate systemic inflammation, compromise the blood–brain barrier and deliver neuroactive signals to the brain, underscoring periodontal health as a potentially modifiable factor in major depressive disorder.

5.2.4. Neurotransmitter-mediated pathways

In addition to the toxic-metabolic route described above, the oral microbiome may influence brain function by shaping neurotransmitter availability. Several resident taxa—*Streptococcus*, *Lactobacillus* and *Actinomyces* spp. in particular—possess enzymes that synthesise or degrade γ-aminobutyric acid (GABA), an inhibitory transmitter central to stress regulation (Barrett et al., 2012; Strandwitz, 2018). Peripherally produced GABA can signal to the brain via trigeminal afferents or by modulating systemic stress hormones. Oral bacteria also metabolise glutamate, tryptophan and tyrosine, thereby adjusting the precursor pool for serotonin, dopamine and norepinephrine (Allaband et al., 2019).

Dysbiosis-associated inflammation may further compromise neurotransmission by down-regulating rate-limiting enzymes such as tryptophan hydroxylase and tyrosine hydroxylase (Capuron and Miller, 2011). Elevated IL-6 and TNF-α released in response to periodontal pathogens interfere with receptor signalling and synaptic plasticity in the prefrontal cortex and hippocampus—regions repeatedly implicated in major depressive disorder. Clinically, individuals with chronic periodontitis show altered salivary tryptophan metabolites and reduced central monoamines, paralleling higher depressive-symptom scores (Kurgan et al., 2022; Neupane et al., 2022a).

Although human evidence is still preliminary, these findings outline a credible pathway through which oral microbial composition may modulate mood via neurotransmitter systems. Integrative studies that pair oral metagenomics with neurochemical imaging and longitudinal mood assessments will be critical for clarifying causality and therapeutic potential.

5.2.5. Oral microbiome and stress response via the hypothalamic-pituitary-adrenal (HPA) axis

The HPA axis plays a pivotal role in the body's response to stress by regulating cortisol release. While this mechanism is essential for acute adaptation, its chronic activation has been consistently implicated in the development of depression and anxiety. Increasing evidence suggests that the oral microbiome may influence this neuroendocrine pathway. Inflammatory oral conditions and microbial dysbiosis, particularly involving pathogens such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, have been shown to affect HPA axis activity. In rodent models, experimental periodontitis induced by these bacteria resulted in elevated plasma corticosterone levels and increased glucocorticoid receptor expression in the frontal cortex, along with enhanced neuroinflammatory signaling marked by TNF-α, IL-1β, and NF-κB (Martínez et al., 2022c). These neurobiological changes mirror those observed in chronic stress and depressive states, where sustained cortisol elevation contributes to structural and functional alterations in stress-sensitive brain regions such as the hippocampus and prefrontal cortex (O'Brien, 2004; Veer et al., 2012).

In human, measuring salivary cortisol, especially in combination with other oral health markers, offers a non-invasive approach to assess the stress-induced biological changes and HPA axis activity linked to depression. Salivary cortisol levels are widely recognised as indicators of the body's stress response and are frequently measured to assess the function of the HPA axis (Saxbe, 2008). However, chronic or sustained elevations in cortisol can contribute to neuroendocrine dysregulation, which is a key factor in the pathophysiology of depression (Maes et al., 2008). In individuals with depression, salivary cortisol levels are often found to be elevated, reflecting hyperactivity of the HPA axis (Gunnar et al., 2009; Iob et al., 2020). Elevated cortisol has been associated with a wide range of symptoms of depression, including fatigue, sleep disturbances, and cognitive impairments (Adam et al., 2017). Moreover, prolonged high cortisol levels can lead to neuronal damage, particularly in the hippocampus, a brain region involved in mood regulation (McEwen, 2007). Charalambous et al. (2024) examining the relationship between the oral microbiome and stress response in a cohort of 115 adults, including individuals who had experienced institutionalisation and adoption as well as non-adopted controls found that specific oral microbial signatures were linked to differential cortisol responses to psychosocial stress, suggesting that the composition of the oral microbiome may influence HPA axis reactivity.

Collectively, these findings support a bidirectional interaction between the oral microbiome and the neuroendocrine stress system, with potential implications for mood regulation and mental health.

5.2.6. Oral Microbiome's role in oxidative stress

The oral microbiome contributes to oxidative stress through several mechanisms. Oxidative stress, defined as an imbalance between the generation of free radicals (reactive oxygen species, ROS) and the body's capacity to neutralise them, has been linked to the development of depression (Barbosa et al., 2020; Bhatt et al., 2020b). For instance, certain oral bacteria, such as *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*, are known to produce ROS, that can induce lipid peroxidation and DNA damage, contributing to oxidative stress and inflammation (Gualtero et al., 2023; Pietro et al., 2017). Inflammation-driven ROS production can result in oxidative stress, causing structural and functional alterations in proteins, lipids, and nucleic acids (Nathan and Cunningham-Bussel, 2013). Therefore, oxidative stress in the body has a detrimental effect on neuronal health and function. It leads to neuronal injury, mitochondrial dysfunction, and impaired synaptic plasticity—all processes linked to depression (Bansal and Kuhad, 2016; Innes et al., 2019; Rahmani et al., 2022). Furthermore, oxidative stress can also impair the function of neurotransmitter systems, particularly serotonin and dopamine, which are crucial for mood regulation (Delva and Stanwood, 2021; Moncrieff et al., 2023). Studies show that saliva from patients with periodontitis or caries has elevated oxidative stress and inflammatory markers (Džunková et al., 2018). For instance, recurrent major depressive disorder has been associated with elevated oxidative markers (e.g., malondialdehyde) and reduced antioxidant enzymes like superoxide dismutase (SOD) and glutathione peroxidase (GPx), suggesting a shared pathogenic mechanism between oral and neuropsychiatric conditions (Ciobica et al., 2020). This suggests that immune response markers could help precisely identify pathogenic bacteria linked to oral diseases.

6. Salivary biomarkers and the role of oral health in early detection and monitoring of depression

Growing evidence supports the potential of saliva as a non-invasive diagnostic fluid for the early detection and monitoring of depression. Saliva contains a wide range of biologically active molecules—such as cortisol, inflammatory cytokines (e.g., IL-6, TNF-α), neurotrophic factors, and microbial components—that reflect systemic physiological and psychological states (Chojnowska et al., 2021; Dongiovanni et al., 2023). Among these, salivary cortisol has been extensively studied as a biomarker of hypothalamic–pituitary–adrenal (HPA) axis dysregulation in individuals with depression, showing altered diurnal patterns and heightened stress reactivity (Hellhammer et al., 2009). Although blood remains the gold standard for systemic biomarker detection, saliva offers a valuable, non-invasive alternative that provides insight into inflammatory, neuroendocrine, and microbial dynamics linked to both oral and mental health (Slavich and Irwin, 2014).

Importantly, oral health status modulates the salivary biomarker profile. Chronic periodontal diseases and oral dysbiosis increase levels of salivary inflammatory mediators, potentially amplifying systemic inflammation and contributing to neuroinflammatory processes (Visentin et al., 2023). As such, salivary biomarkers related to oral dysbiosis may serve as early indicators for identifying individuals at risk for depression or monitoring its progression, particularly in those with poor oral health (Maes et al., 2008; Neupane et al., 2022b). Oral microbes and their byproducts—such as LPS—may influence brain function indirectly by promoting systemic inflammation and blood-brain-barrier dysfunction or directly via neuroanatomical routes.

Monitoring salivary biomarkers over time may also help track the effectiveness of interventions. For example, successful periodontal therapy or psychological treatment may result in reduced levels of salivary cortisol, C-reactive protein (CRP), and proinflammatory cytokines, reflecting improvements in both physical and mental health (Neupane et al., 2022b; Zheng et al., 2025). These salivary markers, especially when combined with clinical and psychological assessments, could contribute to more sensitive, personalised approaches in depression screening and management.

7. Conclusions

This review has highlighted the oral microbiome as a critical but often overlooked component of the microbiota-brain axis, with growing evidence linking oral dysbiosis to systemic inflammation, gut-brain axis, neuroinflammation, HPA axis, oxidative stress and subsequent depressive symptoms. One of the main pathways linking oral dysbiosis to depression involves chronic low-grade inflammation triggered by oral pathogens releasing virulence, which activates the immune system and elevates systemic levels of proinflammatory cytokines that are associated with depressive symptoms (Eltokhi and Sommer, 2022; Martínez et al., 2022c). Additionally, inflammatory mediators can cross the BBB, leading to neuroinflammation, synaptic dysfunction, and disruptions in neurotransmitter systems, including serotonin, dopamine, and GABA.

Furthermore, the oral-gut-brain axis is a critical pathway by which oral dysbiosis may influence mental health. The translocation of oral pathogens into the gut can disrupt the gut microbiota balance, exacerbating gut dysbiosis and impairing the production of key metabolites such as SCFAs (Paudel et al., 2022). These metabolites are essential in regulating neuroinflammation, maintaining BBB integrity, and modulating neurotransmitter synthesis. Thus, disruptions in the oral cavity can have far-reaching consequences on brain function and mood regulation.

Maintaining good oral hygiene and controlling periodontal disease may support mental well-being by modulating inflammatory and neurochemical pathways (Kisely, 2016; Skallevold et al., 2023). Closer collaboration among dentistry, psychiatry and microbiology could yield microbiome-informed therapies tailored to each patient's oral microbial and inflammatory profile.

Key research priorities include identifying microbial signatures linked to depression, confirming causal relationships through longitudinal studies, and testing probiotics, prebiotics and targeted antimicrobials to correct oral dysbiosis. Overall, the oral microbiome stands out as a crucial bridge between systemic and mental health, encouraging us to frame depression as partly biological rather than purely psychological.

CRediT authorship contribution statement

Claudio Singh Solorzano: Writing – review & editing, Writing – original draft, Visualization, Resources, Project administration, Methodology, Investigation, Conceptualization. **Floriana De Cillis:** Writing – review & editing, Visualization, Supervision, Methodology, Investigation. **Elisa Mombelli:** Writing – review & editing, Supervision, Investigation. **Samantha Saleri:** Writing – review & editing, Investigation. **Moira Marizzoni:** Writing – review & editing, Visualization, Supervision, Investigation. **Annamaria Cattaneo:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Disclosures

The authors have no conflict of interest to report.

Statement

During the preparation of this work the author(s) did not use generative AI and AI-assisted technologies.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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