CATÓLICA
FACULDADE DE MEDICINA DENTÁRIA
VISEU

FROM MOUTH TO MIND: MOLECULAR INSIGHTS INTO ORAL HEALTH AND NEURODEPRESSION

Dissertação apresentada à Universidade Católica Portuguesa
para obtenção do grau de Mestre em Medicina Dentária

Por:
Angelica La Vecchia

Viseu, 2025

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Por:
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Viseu, 2025

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Validação e confirmação pelos serviços escolares:

_____

e quasi sempre dietro la collina, è il sole

Lucio Battisti

In loving memory

of my grandmothers and grandfathers,

who are no longer with us,

but will forever remain my guardian angels.

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ABSTRACT

Objective: This thesis aims to explore the molecular mechanisms involved in the bidirectional relationship between oral health—particularly periodontitis—and depressive disorders. The main objective is to examine how inflammatory and immunological alterations associated with periodontitis may contribute to the onset and worsening of depressive symptoms, and, conversely, how molecular imbalances typical of depression may negatively affect oral health.

Materials and Methods: A systematic review of the scientific literature was conducted using the databases PubMed, Web of Science, and Scopus, in accordance with PRISMA and JBI guidelines.

Results: The analysis of 27 studies revealed a central role for pro-inflammatory cytokines as key biomarkers in the molecular mechanisms underlying this interrelationship. In the context of mental disorders, these molecules are implicated in alterations such as increased blood–brain barrier permeability and dysfunctions of the hypothalamic–pituitary–adrenal (HPA) axis—both of which are associated with cerebral dysregulation and the exacerbation of depressive states. In the field of oral health, the same cytokines influence the progression of periodontitis through changes in microbiota composition, hormonal levels, and local enzymatic activity. These findings highlight how the oral and neuropsychological systems are closely interconnected through shared biological pathways.

Conclusion: There is strong evidence that specific inflammatory and molecular pathways are simultaneously altered in patients with both depression and compromised oral health, compared to depressed individuals with preserved oral conditions. This interdependence underscores the need for an integrated clinical approach that considers the individual as a complex and unified psychophysical system. *Mens sana in corp(ore) sano*.

Keywords: Depressive Disorder, Cytokines, Biomarkers, Oral Health, Neuroinflammation.

RESUMO

Objetivo: Esta tese visa explorar os mecanismos moleculares envolvidos na relação bidirecional entre saúde oral, com ênfase na periodontite, e transtornos depressivos. O objetivo principal é analisar como alterações inflamatórias e imunológicas associadas à periodontite podem contribuir para o surgimento e agravamento de quadros depressivos, e, ao mesmo tempo, como desequilíbrios moleculares característicos da depressão podem impactar negativamente a saúde oral.

Materiais e Métodos: Realizou-se uma revisão sistemática da literatura científica, utilizando as bases de dados PubMed, Web of Science e Scopus, conforme as diretrizes PRISMA e JBI.

Resultados: A análise de 27 estudos revelou o papel central das citocinas pró-inflamatórias como biomarcadores-chave nos mecanismos moleculares dessa inter-relação. No contexto dos transtornos mentais, essas moléculas estão implicadas em alterações como o aumento da permeabilidade da barreira hematoencefálica e disfunções do eixo hipotálamo-hipófise-adrenal, ambos associados à desregulação cerebral e ao agravamento do quadro depressivo. No campo da saúde oral, essas mesmas citocinas influenciam a progressão da periodontite por meio de alterações na microbiota, nos níveis hormonais e na atividade enzimática local. Isso demonstra como os dois sistemas — oral e neuropsicológico — estão intimamente conectados por vias biológicas comuns.

Conclusão: Há evidências robustas de que vias inflamatórias-moleculares estão simultaneamente alteradas em pacientes com depressão e condição oral comprometida, em comparação com indivíduos depressivos com saúde oral. Esta interdependência reforça a necessidade de uma abordagem clínica integrada, que considere o indivíduo como um sistema complexo na sua totalidade psicofísica. *Mens sana in corp(ore) sano*.

Palavras-chave: Transtorno Depressivo, Citocinas, Biomarcadores, Saúde Oral, Neuroinflamação.

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LIST OF ABBREVIATIONS

- **ACTH** – Adrenocorticotropic Hormone
- **ANOVA** – Analysis of Variance
- **AOPP** – Advanced Oxidation Protein Products
- **BDNF** – Brain-Derived Neurotrophic Factor
- **BMS** – Burning Mouth Syndrome
- **cAMP** – Cyclic Adenosine Monophosphate
- **CB1** – Cannabinoid Receptor Type 1
- **CB2** – Cannabinoid Receptor Type 2
- **CD4** – Cluster of Differentiation 4
- **CD45RA** – Cluster of Differentiation 45, RA isoform
- **CMS** – Chronic Mild Stress
- **CRP** – C-Reactive Protein
- **EC** – Endocannabinoid System
- **ELISA** – Enzyme-Linked Immunosorbent Assay
- **EP+PS** – *Experimental Periodontitis* + *Psychological Stress*
- **EP+PS+DR** – Experimental Periodontitis + Psychological Stress + Drug(Fluoxetine)
- **GCF** – Gingival Crevicular Fluid
- **HPA** – Hypothalamic-Pituitary-Adrenal Axis
- **hsCRP** – High-Sensitivity C-Reactive Protein
- **IFN-γ** – Interferon-Gamma

- **IGF-2** – Insulin-Like Growth Factor 2
- **IL-1β** – Interleukin-1 Beta
- **IL-2** – Interleukin-2
- **IL-4** – Interleukin-4
- **IL-6** – Interleukin-6
- **IL-8** – Interleukin-8
- **IL-10** – Interleukin-10
- **IL-13** – Interleukin-13
- **JBI**- Joanna Briggs Institute
- **LPS** – Lipopolysaccharide
- **MDD** – Major Depressive Disorder
- **mBDNF** – Mature Brain-Derived Neurotrophic Factor
- **MMP8 -** Matrix Metalloproteinase 8
- **MMP9** – Matrix Metalloproteinase 9
- **NA** – Not Applicable
- **OLP** – Oral Lichen Planus
- **PANTHER** – Protein Analysis Through Evolutionary Relationships
- **PICO** – Population, Intervention, Comparison, Outcome
- **POMC** – Proopiomelanocortin
- **proBDNF** – Pro-Brain-Derived Neurotrophic Factor
- **pSS** – Primary Sjögren's Syndrome
- **RT-PCR** – Real-Time Polymerase Chain Reaction
- **SYNE1** – Spectrin Repeat Containing Nuclear Envelope Protein 1
- **TGF-β** – Transforming Growth Factor-Beta
- **TH1** – T Helper Cell Type 1
- **TLR-2 / 4** – Toll-Like Receptor 2 / 4
- **TNF-α** – Tumor Necrosis Factor-alpha
- **TRAP** – Total Radical-trapping Antioxidant Parameter
- **TRAP stain** – Tartrate-Resistant Acid Phosphatase stain

- **VEGF** – Vascular Endothelial Growth Factor
- **WNT** – Wingless-Related Integration Site

INTRODUCTION

1 INTRODUCTION

For this thesis, an in-depth investigation was conducted into the molecular mechanisms that influence oral health in patients suffering neurodepressive disorders, exploring how these processes directly impact oral health itself. The primary focus was to analyze how these seemingly distinct domains influence one another. Specifically, the study aimed to understand not only how the state of oral health significantly affects the development and progression of neurodepressive disorders, but also how certain molecular mechanisms, in turn, influence oral health.

The construction of this work was made possible through the analysis of a vast body of scientific literature, which was carefully reviewed, evaluated, and thoroughly discussed. Each examined article contributed to shaping a clearer and more comprehensive view of the complex interactions between oral health and molecular processes. This endeavor required not only systematic study, but also significant dedication to selecting and understanding the most relevant evidence, often navigating challenges related to fragmented knowledge.

This thesis, result of consistent effort and personal and scientific growth, aims to provide a current and meaningful contribution to the clinical landscape. Every page reflects the desire to delve into a complex and fascinating topic, uniting diverse disciplines within a single innovative perspective. It underscores the importance of in-depth exploration, the value of interdisciplinary connections, and the ambition to transcend traditional research boundaries.

1.1 What is meant by oral health?

Oral health is considered a fundamental component of overall well-being. Factors such as oral hygiene, condition of teeth, periodontal tissues, mucosal health, chewing efficiency, saliva production, and oral microbiology are key elements in maintaining good oral health.[1]

1.2 Interaction between oral health and psychological factors

Psychosocial factors play a crucial role in both the maintenance of health and the onset of diseases. These include psychological aspects, primarily dependent on the individual, and sociological profiles, which stem from external influences. Mental or emotional issues are often associated with various physical conditions. Traditionally, the mind and body have been considered separate entities, but how and where do they influence each other? [2]
Psychosomatic medicine, where emotional conflicts manifest as physical symptoms, holds fundamental importance in this context.[2]
In the oral domain, the oral mucosa is particularly sensitive to psychological events, and lesions may arise due to psychiatric influences. In cases of chronic pain, a psychological or behavioral component often intertwines with pathological symptoms. Addressing both physical and psychological aspects simultaneously can significantly enhance the likelihood of therapeutic success. [2]

1.3 Focus on periodontitis

Significant condition closely associated with neuropsychological disorders, particularly neurodepressive issues is periodontitis: the leading inflammatory disease of the oral mucosa. [3]
Periodontal diseases develop when gingival inflammation, triggered by a biofilm composed of Gram-negative bacteria and endotoxins, leads to the detachment of the periodontal ligament from the root cementum and dental structure. This process increases the depth of periodontal pockets, causes tooth loosening, and may ultimately result in tooth loss[4].
During the progression of periodontal disease, an imbalance between the local bacterial infection and the host's excessive inflammatory response plays a central role. This not only results in persistent chronic inflammation within the oral cavity but, through the dissemination of inflammatory mediators and bacterial components, may also contribute to systemic inflammatory burden, thereby promoting the development of extraoral diseases.

In this regard, current evidence suggests an association between systemic inflammation and an increased risk of developing depressive disorders.[5]
One of the most prominent hypotheses is that bacteria residing in periodontal pockets, such as *Porphyromonas gingivalis*, may enter the bloodstream, enabling the translocation of pathogenic products from the oral cavity to the brain via the blood–brain barrier.

While the pathology originates with the presence of periopathogenic bacteria, its progression depends on the host's immune response. Factors such as smoking, advanced age, systemic diseases, stress, depressive disorders, and anxiety can influence this response, exacerbating the disease.[6]
Periodontitis, in turn, can increase the risk of various physical conditions, including cardiovascular diseases, diabetes mellitus, and cancer.[7]

1.4 What is meant by depression and neurodepressive disorders?

Depression is a common mental disorder characterized by a persistently sadness, demotivated mood, a loss of interest and pleasure in daily activities, low self-- esteem, disturbed sleep, feelings of tiredness, and poor concentration.[8] It can negatively impact various aspects of life, including relationships and work performance. Estimates suggest that approximately 5% of adults suffer from depressive disorders, with a higher prevalence among women compared to men. The condition can occur at any age, with an average onset around 25 years old.[9]

Major depressive disorder is a complex condition with a multifaceted symptomatology involving somatic, psychological, and neuropsychological aspects.

1.5 What is meant by molecular mechanisms?

Molecular mechanisms are defined as a series of biochemical and cellular events that describe how molecules—such as proteins, genes, hormones, or lipids—interact to support and regulate specific biological functions within an organism.

These molecular mechanisms reflect complex signaling networks that regulate essential biological processes such as inflammation, cell survival, tissue regeneration, immune response, and intercellular communication. They highlight the complex interaction between systemic inflammation, oral health, and mental health. Alterations in these pathways may contribute to the development of pathological conditions both systemically and locally, affecting overall well-being.

1.6 Depression as a cause of periodontal and oral diseases: which mechanisms it implies?

Clinical depression can negatively affect the outcomes of oral treatment. This finding aligns with studies highlighting how psychosocial factors not only predict clinical outcomes, but also influence postoperative recovery.[10]

It is crucial to emphasize that not only periodontal disease, but also other general oral health issues, play a significant role in the development of depressive disorders. Moreover, depressive disorders may contribute to periodontal disease both through biological mechanisms related to stress and inflammation, and by negatively impacting health and treatment behaviors.[10]

Depressive disorders can disrupt the hypothalamic-pituitary-adrenal (HPA) axis, which regulates stress, leading to cortisol imbalances and impairing the immune system[11]. As supported by research, it has been demonstrated that various types of psychological stress, including depressive disorders, activate the HPA system, significantly increasing salivary cortisol levels.[12] This imbalance, in turn, can affect not only oral health but also its microbiome (as shown in Simpson et al. article [12]).

The result is an **increase in pro-inflammatory cytokines** (as will be analyzed through the studies, including IL-6, IL-2, IL-1B, and TNF-α) that leads to severe oral discomfort and potentially contributing to the progression of periodontal and oral infections, particularly in patients predisposed to periodontitis. Furthermore, can delay wound healing, worsening periodontal treatment outcomes.[10] This is driven by various mechanisms, such as:

a) **Chronic low-grade inflammatory response:** Persistent moderate elevation of pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α.[10]

b) **Activation of cell-mediated immunity:** Increased activation of T lymphocytes, macrophages, and other immune system cells. In depressive disorders, this activation has been reported to result in excessive cytokine production and an amplified inflammatory response.[10]

c) **Compensatory anti-inflammatory reflex system:** The body's attempt to counterbalance chronic inflammation and inflammatory responses through compensatory mechanisms, such as:

- Cortisol release by the HPA axis to reduce inflammation.
- Production of anti-inflammatory cytokines, such as IL-10, which aim to moderate the inflammatory response.

d) **Increased oxidative and nitrosative stress (inflammatory pathway):** These processes contribute to the neuropsychiatric progression of the disorder. Oxidative stress involves an accumulation of free radicals (reactive oxygen species, ROS) that damage cells, including neurons. Nitrosative stress involves reactive nitrogen species, such as peroxynitrite, which cause similar damage. Both processes lead to neuronal degeneration and synaptic dysfunction, exacerbating depressive symptoms and increasing the risk of neuropsychiatric comorbidities.[10]

Through these aspects, it is crucial to highlight the evidence of a cycle: everything is interconnected. Depressive disorders contribute to oral health problems through specific molecular mechanisms, which are at the core of the interaction between depressive disorders and oral health. Indeed, certain altered molecular pathways, resulting from oral health issues, could contribute to psychological distress and depressive disorders. The idea of a cycle is of paramount importance.

1.7 Oral disease as cause of depression: which mechanism it implies?

Periodontal disease is one of the main causes of edentulism, due to the inflammatory destruction of the supporting tissues of the tooth, such as the periodontal ligament and alveolar bone. Since the contours and aesthetics of the face depend on natural teeth and alveolar bone, tooth loss can negatively affect the quality of life, impairing not only masticatory function, but also body image, self-esteem, and social status. Numerous studies have highlighted a positive correlation between tooth loss and depressive disorders, emphasizing the importance of integrating psychological support into periodontal and prosthetic treatment to improve the overall well-being of patients.[10]

Going beyond a purely irrational interpretation and adopting a scientific perspective, it can be stated that among the primary mechanisms involved, inflammation can significantly impair immune system functionality[12].

Multiple mechanisms demonstrate how the deterioration of oral health can contribute to the development of severe mental disorders, including: inflammation mediated by chemokine and cytokine signaling pathways, interleukin signaling, corticotropin-releasing factor receptor signaling and Interferon-gamma signaling.

a. Presence of endotoxins in root canal

Individuals with chronic apical periodontitis show significantly elevated levels of endotoxins in the root canals. These increased levels of endotoxins in the root canals (CAP) are strongly associated with systemic markers of oxidative and nitrosative stress (O&NS), such as AOPP (advanced oxidation protein products) and NOx (nitrogen oxides). Activated O&NS processes can cause neuronal dysfunction, including neurotoxicity, neurodegeneration, and reduced neurogenesis and neuroplasticity (collectively referred to as neuroprogression). AOPPs, markers of protein oxidation, can trigger inflammation, monocytic cell activation, and processes related to AGEs (advanced glycation end products). The increase in nitrogen oxides can lead to hypernitrosylation, which is linked to neurodegeneration, neuronal dysfunction, and depressive disorders.[13]

b. Microglial Dysregulation

In the context of periodontitis, microglia adopt an activated, pro-inflammatory phenotype. This transition is accompanied by an increased microglial population in the frontal cortex, along with morphological changes in the cells themselves. Microglial activation alters synaptic plasticity and disrupts the homeostasis of the endocannabinoid system (EC), which has been found to be impaired in both major depressive disorder (MDD) and periodontitis. These conditions may therefore contribute to the onset of depressive symptoms.[14]

OBJECTIVES

2 OBJECTIVES

The main objective of this thesis is to explore the molecular mechanisms underlying the complex bidirectional relationship between oral health and neurodepressive disorders. Specifically, the thesis aims to analyze how oral health impairment may contribute to the development and progression of neurodepressive conditions through molecular pathways, and conversely, how the molecular processes associated with depressive disorders can affect oral health.

To this end, the work seeks to:

1. Identify and examine the key molecular mechanisms and pathways linking oral health and neurodepressive disorders, including those involving the oral microbioma, microglial function and receptors, cytokines, cortisol, nitrooxidative and oxidative courses and C-reactive protein.
2. Highlight shared factors that may serve as bridges between the two fields, such as inflammation, chronic stress (and its proinflammatory markers) and cellular immune dysfunction.
3. Propose a comprehensive framework that integrates current evidence, emphasizing the clinical implications for the interdisciplinary management of patients experiencing both neurodepressive disorders and oral health issues.

This analysis aims to provide new perspectives on the intricate, but critical interplay between depressive disorders and oral health, shedding light on how psychological suffering can influence oral health conditions, and equally, how chronic oral disorders may exacerbate or contribute to the development and persistence of depressive symptoms.

MATERIALS and METHODS

3 MATERIALS and METHODS

3.1 Overview

a. Initial work stages

In the "Materials and Methods" section of this thesis, an in-depth bibliographic research process was conducted using the following platforms: PubMed, Web of Science, and Scopus.

After several analyses and searches in defining a coherent and sensible strategy for identifying relevant studies, the decision was made to focus the work on depressive disorders, an interesting, current topic closely related to the neurological field. The simple correlation between oral health and depression did not seem sufficiently effective; therefore, the focus was shifted to the molecular mechanisms linking neurodepressive disorders to oral health. This approach allows for a more focused research scope and a deeper exploration of a specific area, ultimately improving the overall quality of the work.

b. Search terms and search strategies

Therefore, the formula used in the final instance was divided into 3 groups:

- the first concerning neurodepressive disorders,
- the second concerning molecular processes and pathways,
- and the third concerning oral health and oral disorders.

Even for this phase of work construction, reaching the final formula was not straightforward and several steps were required to reach a comprehensive conclusion.

A wide range of different search terms was initially selected to ensure a comprehensive search strategy. These terms were subsequently evaluated based on their relevance and the quality of results retrieved from the selected databases. Irrelevant or non-contributive terms were removed during this process, ultimately leading to the refinement of the final search formula.

Based on this refinement process, the final Pubmed search strategy was structured using MeSH terms and Boolean operators, as shown below:

("Depressive Disorder, Major"[Mesh] OR "Depressive Disorder"[Mesh] OR "Antidepressive Agents"[Mesh] OR "Depression"[Mesh] OR "Depressive Disorder, Treatment-Resistant"[Mesh])
AND
("Immunity"[Mesh] OR "Proteins"[Mesh] OR "Models, Animal"[Mesh] OR "Brain"[Mesh] OR "Neurotransmitter Agents"[Mesh] OR "Neural Pathways"[Mesh] OR "Biomarkers"[Mesh])
AND
("Oral Health"[Mesh] OR "Tooth Loss"[Mesh] OR "Mouth Diseases"[Mesh])

To ensure consistency and broaden coverage across databases, the search was also adapted and conducted on Scopus and Web of Science using the following string: *(“major depressive disorder” OR “antidepressive agents” OR depression OR “depression treatment-resistance” OR “depression disorder")* ***AND*** *(“animal model" OR brain OR "neurotransmitter agents" OR "neural pathway" OR biomarkers OR immunity OR proteins)* ***AND*** *("oral health" OR "tooth loss" OR "mouth disease")*

In all platforms, Boolean operators **AND** and **OR** were applied to enhance the search efficiency:

- **‘OR’** was used to broaden the search by including articles containing any of the listed terms.
- **‘AND**’ was used to narrow the results, selecting only those articles that included all the defined thematic areas.

This strategy enabled the identification of a broader range of relevant studies while focusing on those most pertinent to the topic addressed[15].

c. MeSH terms

The MeSH, which stands for Medical Subject Headings, is a controlled vocabulary system used to organize medical terms in a structured manner. These terms, also known as descriptors or subject headings, are arranged hierarchically: more specific terms are placed under broader terms within a hierarchical tree structure. This means that broader concepts are found at the top of the hierarchy, while related but more detailed concepts are located at the lower levels, forming a branching structure[14].

3.2 Research question with P.I.C.O. method

In patients diagnosed with depressive disorders (**population**), what molecular mechanisms are altered (**intervention**) when there is loss or aggravation (**outcome**) of oral health compared to patients who do not lose oral health (**comparison**)?

3.3 PRISMA principles

This thesis adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria, a set of guidelines recognized by the scientific community to enhance the quality of systematic reviews, ensuring they are transparent, comprehensive, and reproducible.

In alignment with PRISMA principles:

- A PRISMA flow diagram has been included to illustrate the study selection process
- The inclusion and exclusion criteria for the retrieved studies have been described to ensure a rigorous and justified analysis.
- A strategic search methodology was implemented to identify relevant studies.

3.4 Screening and labels

Subsequently, the Rayyan platform - a web-based tool designed to facilitate systematic review processes - was used to conduct a comprehensive screening of the retrieved articles.

During this phase, duplicate records were identified and removed. The remaining articles were categorized into three groups: included, excluded, and potentially eligible.
Excluded articles were assigned descriptive labels specifying the reason for their exclusion, ensuring transparency in the selection process:

1. Wrong population
2. Wrong type of study
3. Not full and open access
4. Systematic review or review
5. No molecular evidence
6. No depressive disorders evidence
7. No specific relationship between oral health and depressive disorders (in molecular terms)

The included articles underwent several screening stages. Subsequently, conflicts arising from the decisions of the two collaborators involved in the project were resolved. Only after this stage, was established a definitive base of included articles for the thesis.

To carry out this screening thoroughly, more stringent inclusion and exclusion criteria were adopted to ensure that the selected studies precisely addressed the research question. This process required critical reflection and continuous interactions, ultimately reaching a coherent and relevant synthesis of the existing literature.

3.5 Screening criteria

To ensure a rigorous and focused selection of studies, a predefined set of exclusion and inclusion criteria was applied during the screening process. These criteria were established based on the research objectives and methodological standards for systematic reviews. **Table 1** summarizes the specific parameters used to determine the eligibility of studies for inclusion in the thesis.

Table 1: Exclusion and Inclusion Criteria Applied to Study Selection

EXCLUSION	**INCLUSION**
1. Population a. Pacients without depressive disorders 2. Type of study a. Reviews b. Systematic reviews c. Opinion articles d. Observational studies 3. Area of study a. Articles that do not focus on molecular alterations or without laboratory or molecular evidence (may or may not be focused on drugs) b. Articles without any specific relationship or syndrome between oral health and depressive disorders	1. Population a. Animals b. Humans c. Adulthood 2. Type of study a. Longitudinal studies b. Experimental studies 3. Language a. English 4. Time span a. 30 years (1994-2024) 5. Acess a. Full and open access to the articles

3.6 Conflict Resolution

The process of data analysis and selection was carried out with careful attention to methodological consistency. A crucial aspect of this phase was the resolution of conflicts that arose during the evaluation of the studies. In some cases, discrepancies were addressed independently by the two reviewers through comparison of interpretations and critical consensus. However, certain divergences required external input to be resolved objectively. In such instances, the opinion of third parties was sought—namely, Professor Ana Sofia Duarte and Professor Raquel Monteiro Marques da Silva.

Their contribution was essential in ensuring that the selection process upheld scientific rigor and remained aligned with the research objectives, and that each decision was well substantiated.

This structured conflict resolution approach enhanced the precision and efficiency of the review process, providing a solid foundation for the subsequent analysis phases.

During the development of the characterization tables, additional articles were excluded. Each exclusion was duly justified and recorded within the Rayyan platform. Following this step, the final set of studies included in the thesis was identified.

3.7 Molecular Pathways Identification

Starting from the list of molecules extracted from the results of each article included in the thesis, the corresponding proteins were identified and subsequently analyzed to determine the specific genes encoding them. This process was carried out using the National Institutes of Health (NIH) software. Once the genes were identified and classified according to human or animal species (*Rattus norvegicus and Mus musculus*), they were entered into the PANTHER platforms to obtain a detailed overview of the molecular pathways involved. PANTHER (Protein Analysis Through Evolutionary Relationships) is a comprehensive, curated database used to classify genes and proteins by their functions, based on evolutionary relationships and biological pathways[16].

3.8 Methodological quality analysis

To ensure the reliability and methodological quality of the studies included in the thesis, the critical appraisal tool developed and validated by the Joanna Briggs Institute (JBI) [17] was employed. This instrument allows for the identification of potential biases in the design, conduct, and analysis of studies, representing an essential step for the synthesis and interpretation of results. The inclusion of this guideline reinforces the transparency, credibility, and overall quality of the evidence.

Each study was evaluated according to ten key questions, corresponding to the methodological criteria outlined in the JBI critical appraisal tool. For greater clarity and ease of understanding, the full wording of these questions is reported in the Results section, alongside the corresponding Table 7.

RESULTS

4 RESULTS

4.1 PRISMA flow diagram

The study selection process was conducted according to the PRISMA flow [18] and is graphically represented in the corresponding diagram (**Table 2**). A total of 488 record**s** were identified through three databases: Web of Science (n = 158), PubMed (n = 164), and Scopus (n = 166). After removing 76 duplicates**,** 412 records were screened.

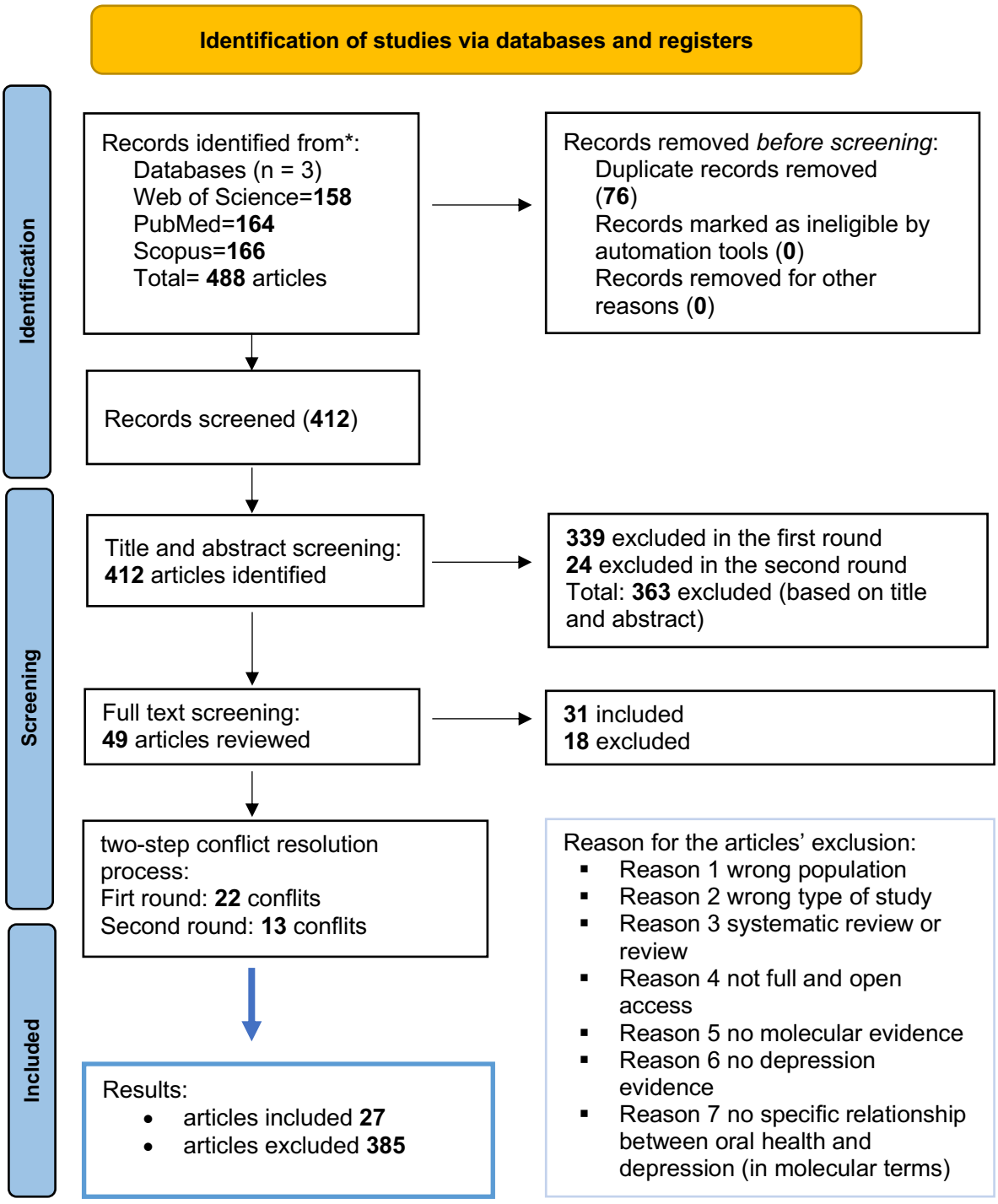
During the initial title and abstract screening phase, 363 records were excluded: 339 during the first review and 24 during the second, as they were deemed not relevant to the inclusion criteria. As a result, 49 articles were moved to the full-text review stage.

Following full-text analysis, 31 articles were initially included, while 18 were excluded. In a subsequent conflict resolution phase between reviewers, 22 articles were reassessed in the first round, during which some previously excluded articles were reconsidered and included. This was followed by a second resolution phase involving 13 articles, which required the intervention of third-party reviewers (the supervising professors), leading to the inclusion of 9 additional articles and the exclusion of 4**.**

In summary:

- Of the 31 initially included articles, 21 were confirmed, while 10 were excluded after further evaluation;
- After conflict resolution, 30 articles were ultimately included, and 14 excluded. These conflicts were resolved through discussion, with the involvement of a third reviewer when necessary;
- After the final quality assessment, **27 articles were definitively included** in the thesis.

Table 2: PRISMA Flow Diagram of Study Screening and Selection Process



4.2 Summary of Included Studies

The analysis of the results starts with an examination of the experimental models used in the included studies, as shown in the following **Figure 1**. The graph highlights that most of the selected research employed human subjects as the experimental model, while a smaller portion involved animal models (18 human studies *vs*. 9 animal studies using rats-*Rattus norvegicus*- and mice -*Mus musculus*-. This finding suggests a predominance of clinical approaches over preclinical ones in the context of the association between oral health and depressive symptoms, reflecting a tendency in the literature to prioritize findings with direct applicability to human experience.

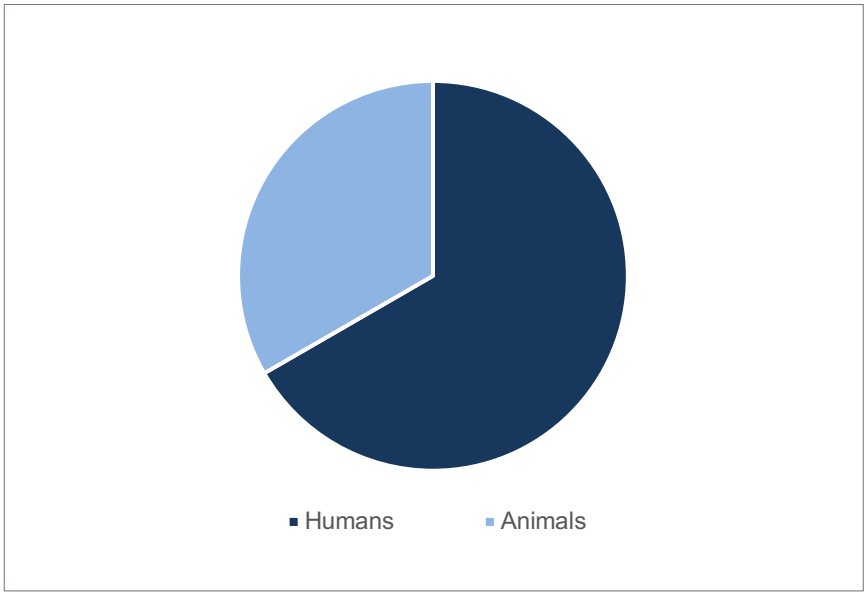


Figure 1: Frequency of Experimental Models used across the reviewed studies

Alongside the experimental models, the specific oral pathologies investigated also played a key role in achieving a comprehensive understanding of the most frequently studied disorders. **Figure 2** illustrates the prevalence of oral conditions studied across the included literature. As depicted, periodontitis emerged as the most correlated condition with depressive symptoms, followed by burning mouth syndrome, xerostomia, and, to a lesser extent, oral lichen planus.

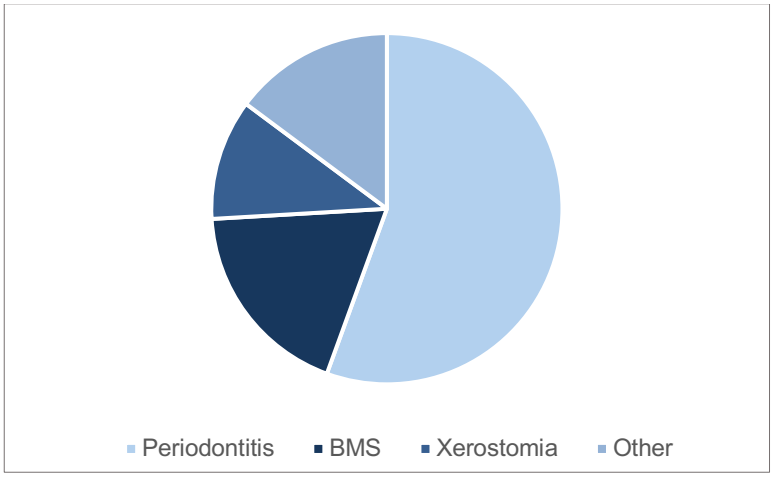


Figure 2: Most Common Oral Pathologies associated with Depressive Symptoms

To incorporate a more technical-operational dimension into the analysis, the most frequently employed molecular techniques were identified. These are presented in **Figure 3**, which highlights the Enzyme-Linked Immunosorbent Assay (ELISA) as the most used method (30%) to investigate the molecular connection between depressive disorders and oral diseases, followed by Western Blot (12%). The category "Others" (39%) includes techniques that were applied only once or twice across the studies considered in this thesis . It is worth noting that a single study may have employed more than one technique.

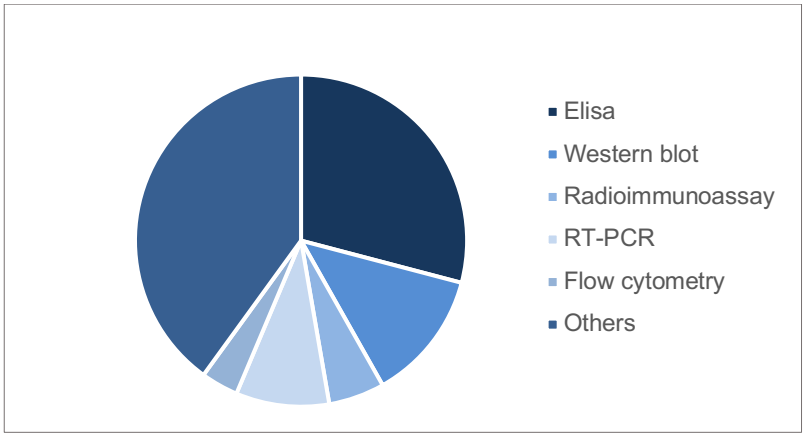


Figure 3: Main Techniques applied to explore molecular links between Depressive Disorders and Oral Diseases

To offer a clearer perspective of the key features of each study addressing the potential link between oral health and depressive disorders, the following tables have been created to support this aim.

For the analysis of experimental models, the **Table 3** shows the sample size, the number of patients with the condition, the number of healthy controls, the age range, the sex, and the geographic location of the studied population.
This information provides a clear overview of the methodological quality and consistency across the included studies, highlighting the robustness of experimental design, the comparability between pathological and control groups, and the representativeness of the sample (e.g., inclusion of both sexes versus female-only).

From the table, it is observed that studies involved a consistent number of samples, divided between disease and control groups. Sex distribution generally included both females and males, except for two studies that focused exclusively on female participants.

Shifting the focus to a more targeted perspective that enabled an understanding of biomarker expression patterns, **Table 4** provides a comprehensive overview of the studies included in this thesis that specifically focus on biomarker analysis. The table summarizes key methodological features, including the type of biological sample collected (e.g., saliva, blood, brain tissue), the biomarker detection techniques employed (e.g., ELISA, Western blot, PCR, colorimetric methods), the type of biomarkers investigated (e.g., proteins, hormones, genes, trace elements, and metabolites) and—most importantly—their expression variation (classified as increased [+], decreased [–], or unchanged [=]). Saliva and blood were the most common biological matrices, reflecting their relative accessibility and relevance in both oral and systemic health assessments. A wide range of techniques were utilized across studies, with ELISA emerging as the most frequently adopted method for protein quantification. This methodological diversity highlights the complexity of molecular investigations and underscores the importance of selecting appropriate detection methods based on study design, target molecules, and sample type.

This classification paved the way for more in-depth assessment to obtain an exhaustive framework on the molecular trends explored across the studies.

To support this, **Table 5** presents a summary of the “Prevalence of Molecular Change, Oral Disease Association, and Analytical Techniques” across studies, categorized by human and animal models. A broad spectrum of biomarkers was reported, although certain molecules

are cited with higher frequency across the literature and, as a result, more analyzed at the molecular level. These predominant biomarkers are discussed in detail in ‘Section 4.3‘, which also provides visual graphical representations to facilitate a clearer understanding of their expression trends.

Table 3: Summary of Experimental Models Used in the Included Studies

FOCUS ON EXPERIMENTAL MODELS						
AUTHORS	**SAMPLE SIZE**	**N with PATHOLOGY**	**N of CONTROLS**	**AGE RANGE**	**SEX**	**LOCATION**
Al-Bazaz et al., 2021	500	500 with depression (100% of participants showed some level of depression)	NA	17	Females and males	Baghdad City/Iraq.
Almeida et al., 2007	33 allocated to 4 groups	NA	NA	NA	Females and males	NA
Barry et al., 2018	20	10 with BMS	10	NA	Females and males	NA
Breivik et al., 2006	50	NA	Sham-operated rats	NA	NA	NA
Breivik T et al., 2005	Experiment 1: 18 females Experiment 2: 20 males	Experiment 1: 9 dexamethasone treated experiment 2 : 10 injected i.p. with 10 mg/(kg day) of tianeptine sodium salt	experiment 1: 9 controls experiment 2: 10 controls	NA	NA	Moolegaard Breeding Center (Ejby, denmark)
Chen et al., 2007	79	48 with BMS	31		Females and males	Department of Oral Medicine, West China College of Stomatology, Sichuan University.

Franco et al., 2020	61	35 with periodontitis, 26 with depressive symptomatology	NA	35 - 65	Females and males	Monterrey or its metropolitan area (Nuevo León, Mexico)
Giri et al., 2018	80	40 with depression	40	NA	Females and males	NA
Gomes et al., 2017	47	24 with depression	23	NA	Females and males	NA
Hernández et al., 2022	48	12 FOR P with CMS (P+CMS+), 12 for P without CMS (P+CMS) 12 for CMS without P(P CMS+)	12	NA	NA	NA
Johannsen et al., 2007	49	20 women with depression	29	mean ages: 48.5 ± 6.9 years for patient with depression 54.5 ± 2.9 years for controls	Females	Swedish insurance company
Jornet et al., 2020	82	51 with BMS	31	main age: 58	Females 71 and males11	NA
Kollera et al., 2000	NA	NA	NA	3, 12 and 24 months	F344 rats female	Harlan Sprague-Dawley (Indianapolis, U.S.A.)

Li et al., 2022	50	10 for EP group, rats with experimental periodontitis; 10 for the PS group rats exposed to psychological stress; 10 for the EP+PS group 10 for the EP+PS+DR group, rats with experimental periodontitis exposed to psychological stress and treated with fluoxetine.	10	8 weeks old	Male Sprague-Dawley rats	NA
Li et al., 2023	30	15 LPS-induced periodontitis (LPS group)	15	8-weeks-old male homozygous	Male homozygous rats	NA
Lutiana et al., 2018	40 for each of 3 behavioral tests total 120	Periapical lesion/saline (n = 10) periapical lesion/imipramine (n = 10)	10	NA	Wister male rats	NA
Milton et al., 2014	150	NA	NA	NA	Females and males	NA
Moss et al., 1996	164	79	85	36-71	Females and males	NA
Oliveira Solis et al., 2015	72	36 with MDD	36	NA	Females and males	NA
Pekiner et al., 2009	60	30 with BMS	30	NA	Females and males	NA
Robledo-Montaña et al., 2024	48	12 for each group: 1. Periodontitis + Stress (P + CMS+) 2. Periodontitis only (adm *P-gingivalis* and	12	NA	Wistar rats	NA

		F.nucleatum) 3. Stress only 4. Controls				
Sebastiani et al., 2020	132	patients with dentofacial deformities Class II (n44) or Class III (n44)	44	NA	Females and males	NA
Walther et al., 2023	6,209	1,453 with either none or mild periodontitis, 3,580 with moderate periodontitis 1,176 presented with severe periodontitis.	1,453 participants had either none or mild periodontitis,	mean age: 62 years	Females and males	Hamburg , Germany
Wang et al., 2019	200	100	100	mean ages: 48 for OLP patients, 44 for controls	OLP patients: Females 63 , males 37 Controls: Female 64 , males 36	Jiangsu Province Stomatological Hospital, Nanjing, China
Wanga et al., 2019	67	*32 with Porphyromonas gingivalis* , 9 with *Fusobacterium nucleatum*	26	NA	Mice- females	Guangzhou University of Chinese Medicine
Xie et al., 2014	88	31 with primary Sjögren's syndrome (pSS), 19 with rheumatoid arthritis (RA), 18 with anxiety and/or depression	20	NA	Females and males	NA
Zhang et al., 2024	1189	425 with moderate / severe periodontitis	764	mean age: 50.9 ± 0.9	Females	NA

Table 4: Focus on the Biomarkers Investigated and Their Expression Changes in the Presence of Oral and/or Mental Disorders

FOCUS ON BIOMARKERS				
AUTHORS	**SAMPLE**	**BIOMARKER DETECTION TECHNIQUE**	**TYPE**	**CHANGE OF EXPRESSION**
Al-Bazaz et al., 2021	Saliva	ELISA	Proteins	C-reactive protein(+)
Almeida et al., 2007	Saliva	Stimulated salivary flow rate assessment; Colorimetric methods; Titrimetry	Proteins	Total proteins (=), pH(=), saliva buffer capacity (urea, alfa amilase and calcium (=)
Barry et al., 2018	Blood	V-PLEX human pro-inflammatory-10-plex assays	Proteins	IL-8(+), IL-4(=), IL-2(+), IL-12p70(+), IL-13(=), IFN-y (+) IL-6(=), IL-10(=), TNF-a(+) obs: f IL-8 showed positive correlation with pain (r^2 = 0.252) and depressive symptoms (r^2 = 0.279).
Breivik et al., 2006	Blood and brain tissue	Radioimmunoassay (RIA); Coat-A-Count kit ,+ enzyme-linked immunosorbant assay; ELISA; RT-PCR	Proteins and hormons	Corticosterone (+), TNF-a (-), IL-10.(+), TGF-1b(+)
Breivik T et al., 2005	Blood	ELISA, Radioimmunoassay (RIA) Coat-A-Count kit, RNA-Whiz ANOVA	Proteins and RNA	Case I – Neonatal Dexamethasone Treatment: TNF-α (+); IL-6 (-); IL-10 (-); TGF-β1 (=); Corticosterone (-); Glucocorticoid receptor mRNA (hippocampus) (-) Case II – Chronic Tianeptine Treatment: TNF-α (+); TGF-β1 (+); IL-6 (+); IL-10 (+); Corticosterone (=)
Chen et al., 2007	Blood	ELISA	Proteins	IL-6 (-)

Franco et al., 2020	Saliva	SALIMETRICS® ELISA Kit (sandwich type); Human MMP8 SimpleStep ELISA® Kit (Abcam); Structural equation modeling (SEM)	Proteins	IL-1B (+), IL-6 (+), MMP-8(+) (collagen degradation activity in the periodontal tissue)
Giri et al., 2018	Saliva	Ion selective electrode method, Spectrophotometric	Proteins	Potassium(=), sodium(=), chloride(=), A-amylase(=), total protein(-), urea(=) calcium (-)
Gomes et al., 2017	Blood	ANOVA; Generalized Linear Model	Proteins	AOPP (+),Lipid Hydroperoxides (+), nitrogen oxides (+), SH (=), Paroxonase1 (=), TRAP (+)
Hernández et al., 2022	Frontal cortex	ELISA; fluoroscence; ANOVA	Proteins	In P+CMS+: Microglia (+), Zonula Occludens 1 (−), Occludin (−), ICAM-1 : Intercellular Adhesion Molecule 1 (+), Vascular Cell Adhesion Molecule (+), MMP9 (+), Sphk1 (−), Sphingosine-1-Phosphate Lyase 1(−). In P–CMS+: Microglia (+),Sphingosine-1-Phosphate Receptor 1 and 3 (+), Sphingosine Kinase 1 (−). In P–CMS: Sphingosine Kinase 2 (−).
Johannsen et al., 2007	Saliva and GCF	Intracrevicular washing technique ELISA and Radioimmunoassay (RIA)	Proteins	IL-6(+) cortisol GCF of depressed patients (-), IL-1β (=), MMP-8 (=) MMP-9 (=),
Jornet et al., 2020	Saliva	Multiplex Assay; Colorimetry; ELISA	Proteins and metabolic compounds	α-amylase (+), IgA (+), MIP4(+), Uric acid (-),Ferric Reducing Ability of Plasma (-)
Kollera et al., 2000	Saliva	SDS-PAGE (• Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis)	Proteins	α-amylase (-), Lactoferrin (=), Proline-rich proteins (+), Mucin-type glycoproteins (+), Lysozyme (+)

Li et al., 2022	Plasma	Openfield, Fluoroscence, Western blot; ELISA nad ANOVA	Proteins and hormones	Serum CORT (corticosterone) and ACTH levels: PS (+), EP+PS (+) IL-1β: EP (+), EP+PS (+) IL-6: EP (+), EP+PS (+) TNF-α: EP (+), EP+PS (+) IFN-γ: EP (+), EP+PS (+) HIF-1α: PS (+), EP (+), EP+PS (+) NF-κB (p-IκBα, IκBα, p-NF-κB p65): EP (+), EP+PS (+) mBDNF (-). ProBDNF and ratio proBDNF/mBDNF (+).
Li et al., 2023	Frontal cortex, cortex, hippocampus, and blood	Micro-CT; HE stain (Hematoxylin and Eosin); TRAP stain; ELISA Western Blot (WB); Immunofluorescenza (IF)	Proteins	IL-1β (hip, ctx, serum) (+); TNF-α, GFAP, Iba1 (hip) (+); Occludin, Claudin-5 (hip) (−); Occludin, Claudin-5 (ctx) (=); proBDNF (hip, PFC) (+); mBDNF (hip, PFC) (−); ratio (hip, PFC) (+); SorCS2, p75NTR (hip) (+); SorCS2, p75NTR (ctx) (=); c-Fos (hip) (−), (ctx) (=)
Lutiana et al., 2018	Serum and frontal cortex, blood	ELISA (Enzyme-Linked Immunosorbent Assay), with kit DuoSet di R&D Systems.	Hormones and proteins	TNF-a (+), IL-1B(+), IL-6(+), ACTH in serum (+) (→ indicated dysregulation of HPA axis, Corticosterone(=) obs: Imipramine significantly reduced IL-1β and TNF-α.
Milton et al., 2014	Saliva	Colorimetric method and Autopak kits; Photocolorimeter (540 nm); End-point method ; Enzymatic method (ultraviolet method) with Autopak kit	Proteins, ions and metabolites	α-amylase (+), calcium (+), total protein (+), and urea(+) sodium (=) potassium (=)
Moss et al., 1996	Blood	Serological Testing (Antibody testing); statistical analysis	Bacterias and proteins	IgG Bf (+), IgG Pg (=), IgG Aa(=)

Oliveira Solis et al., 2015	Blood and gingival crevicular fluid)	ANCOVA (Analysis of Covariance)	Proteins	In patients with MDD: cytokine(+) in GCF In the group stimulated with LPS: IL-6 (=) in GCF and blood In the unstimulated group:: IL-6 (=) in GCF and blood in MDD: IL-6 (-), IL-1β in blood (unstimulated) (-), IL-1β in CGF (-)
Pekiner et al., 2009	Saliva	Stimulated salivary flow rate (SSFR) assessment+ atomic absorbance spectrophotometr + Cytokine immunoassay kits	Trace elements and proteins	Mg levels (-), IL-2 (=), IL-6 (=), Zn (=) Cu (=)
Robledo-Montañet al., 2024	Frontal cortex tissues	Western blot fluorescence	Proteins	iNOS – Inducible Nitric Oxide Synthase-(+), CB2(=) CB1(-), synaptic proteins (BDNF, synaptophysis) (-) endocannibic system(CB1 receptor, PI3K, Akt (protein kinase B) , Extracellular Signal-Regulated Kinases 1/2, Monoacylglycerol Lipase, N-Acyl Phosphatidylethanolamine-specific Phospholipase D, Fatty Acid Amide Hydrolase) all (-)
Sebastiani et al., 2020	Buccal mucosa DNA	Real-time PCR using TaqMan technology	Proteins and genes	IL-6 polymorphism rs1800796 (CG genotype): Increased impact on "psychological discomfort" → +
Walther et al., 2023	Saliva	Human IL-6 Quantikine; HS ELISA Kit (R&D Systems); immunoturbidimetric method; Statistical analysis (multiple linear regression)	Proteins	IL-6 (+), hsCRP (+)

Wang et al., 2019	Blood	Real-time qPCR; Microarray analysis; Wes automatic western blot	Protein enzyme	PDE4B (+)→increased degradation of cAMP reducing cAMP levels, which may lead to increased production of pro-inflammatory cytokines (as TNF-α, IL-6, IL-1β), RGS2(-) Synaptogyrin 1 (-), SYNE1(-)
Wanga et al., 2019	Blood, brain and hippocampus	Western Blot; ELISA	Proteins and genes	Activated astrocyte (+), IL-6. (+), TNF-a(+), IL-1a(+) mBDNF(-), astrocytic p75NTR (-), Corticosterone/ cortisol (+)
Xie et al., 2014	Blood	ELISA; Flow cytometry	Proteins	P2X7R (+) in pSS (CD14+ e CD14−) without ATP (Adenosine Triphosphate) IL-1B (-), IL-6 (+)
Zhang et al., 2024	Blood	Cox proportional hazards: Weibull accelerated failure time (AFT) models for statistical analysis.	Proteins	White blood cells (=), C-reactive protein (=)

Table 5: Through the Included Studies: Comparative Summary of Molecular Alterations(+, -, =), Oral Disease Associations, and Analytical Methods

FOCUS ON MOLECULES									
	Humans N of studies			**Animals N of studies**			**Oral diseases**	**Techniques in humans**	**Techniques in animals**
Molecules	+	-	=	+	-	=			
CRP/ hsCRP	2		1				Caries, Periodontite	ELISA, immunoturbidimetric method	
iNOS - Inducible Nitric Oxide Synthase				1			Periodontitis		
CB2						1	Periodontitis		
CB1					1		Periodontitis		
BDNF					1		Periodontitis		
IL-6	4	2	3	4	1		Periodontitis, Sjögren's and BMS	PCR, vplex , flow cytometry system ELISA	ELISA, Openfield, Western blot, ANOVA
Costicosterone				2	1	2	Periodontitis, Sjögren's and BMS		ELISA and RNA-Whiz
Cortisol		1	1	1			Periodontitis	ELISA	Western Blot, ELISA
TNF-a.			1	5	1		Periodontitis, BMS	flow cytometry system, vplex	ELISA and RNA-Whiz
IL-1a				1			Periodontitis		
p75NTR				1	1	1	Periodontitis		Western Blot, ELISA

IL-1B	1	1	1	3			Periodontitis	ELISA, Structural equation modeling (SEM), Intracrevicular washing technique, ,Radioimmune assay	Western Blot (WB), Immunofluorescence (IF), Fluorescence, ELISA
ACTH				1			Periodontitis		
PDE4B -Phosphodiesterase 4B	1						OLP		
RGS2- Regulator of G-protein Signaling 2		1					OLP		
SYNGR1 – Synaptogyrin 1		1					OLP		
SYNE1		1					OLP		
PDE4B mRNA	1						OLP		
IL-8.	1						BMS		
IL-4			2				BMS		
IL-2.			3				BMS		
IL-13.			1				BMS		
IFN-y.			1	1			BMS for humanos and Periodontitis for animals		
IL-10			1	2			BMS for humanos and Periodontitis for animals	V-PLEX human pro-inflammatory-10-plex assays	RT-PCR, RIA; ELISA
AOPP.	1						Periodontitis		
LOOH- Lipid Hydroperoxides	1						Periodontitis		
Nitrogen oxides	1						Periodontitis		

			1				Periodontitis		
PON1 -Paraoxonase 1			1				Periodontitis		
TRAP	1						Periodontitis		
P2X7R- P2X purinoceptor 7	1						Sjögren's		
Mg		1					BMS		
Zn			1				BMS		
Cu			1				BMS		
Urea	1		2				Xerostomia		
A-amylase	1		2		1		Xerostomia		
Calcium	1	1	1				Xerostomia		
MMP-8.	1		1				Periodontitis		
MMP-9			1	1			Periodontitis		
TGF-1b	1			1		1	Periodontitis		
mRNA	1				1		Periodontitis		RTPCR ELISA, Radioimmunoassay, Coat- A-Count kit, RNA-Whiz ANOVA
IgG Bf.	1						Periodontitis		
IgG Pg.			1				Periodontitis		
IgG Aa.			1				Periodontitis		
Sodium.		1	1				Salivary issues		
Potassium.		1	1				Salivary issues		
Total proteins	1	1					Salivary issues		
Lactoferrin						1	Salivary issues		
Proline-rich proteins				1			Salivary issues		

Lysozyme				1			Salivary issues		
mBDNF					3		Periodontitis		Micro-CT, HE stain, TRAP stain, ELISA, Western Blot (WB), Immunofluorence
ProBDNF and ratio proBDNF/mBDNF				1			Periodontitis		
ZO-1- Zonula Occludens 1					1		Periodontitis		
Occludin.					2		Periodontitis		
Sphk1 Sphingosine Kinase 1					1		Periodontitis		
SGPL1- Sphingosine-Phosphate Lyase 1					1		Periodontitis		
S1PR1- Sphingosine-1-Phosphate Receptor 1						1	Periodontitis		
S1PR3 - Sphingosine-1-Phosphate Receptor 3				1			Periodontitis		
ICAM-1 Intercellular Adhesion Molecule				1			Periodontitis		
VCAM-1- Vascular Cell Adhesion Molecule				1			Periodontitis		
(TGF)-1B.				1		1	Periodontitis		
Adrenocorticotropic				1			Periodontitis		
p-IκBα- Phosphorylated Inhibitor of NF-kB alpha				1			Periodontitis		
p-NF-κB p65- Phosphorylated NF-kB p65				1			Periodontitis		
IκBα- Inhibitor of NF-kB alpha					1		Periodontitis		
ROS- Reactive Oxygen Species				1			Periodontitis		
MDA- Malondialdehyde				1			Periodontitis		
SOD- Superoxide Dismutase					1		Periodontitis		
CAT- Catalase					1		Periodontitis		
GSH-Px- Glutathione Peroxidase					1		Periodontitis		
MIP4- Macrophage Inflammatory Protein 4	1						BMS		

IgA	1						BMS		
sAA- Serum Amyloid A	1						BMS		
Uric acid		1					BMS		
FRAP -Ferric Reducing Ability of Plasma		1					BMS		
Chloride			1				Periodontitis		
TGF-b							Periodontitis		
CD4+CD45RA-	1						Periodontitis		
CD4+CD45RA+	1						Periodontitis		
CD69			1				Periodontitis		
CD4+CD62L+	1						Periodontitis		
CgA- Chromogranin A	1						Periodontitis		
β-endorphin	1						Periodontitis		
Claudin 5					1		Periodontitis		
Microglia				1			Periodontitis		
FOXP-3 (CD4+CD25+)			1				Periodontitis		
CD28+		1					Periodontitis		
CD4+CD152: =			1				Periodontitis		
CD4NegCD152: =			1				Periodontitis		
CD4+CD184: =			1				Periodontitis		
CD4NegCD28+:		1					Periodontitis		
CD25			1				Periodontitis		
CD4+			1				Periodontitis		
CRP/ hsCRP – C-reactive protein (high sensitivity)			1				Periodontitis		

4.3 Frequently Reported Biomarkers and Their Expression Patterns

Elaborating on the analysis of molecular expression dynamics, the present thesis focused on biologically relevant molecules that were consistently reported in the literature in the literature as reliable biomarkers of the mechanisms under investigation. The selection criteria prioritized molecules with a clear biological signal, reproducible results, and consistent findings across studies. In contrast, molecules that were only sporadically identified or lacked a significant and coherent association across the analyzed studies were excluded from the central analysis, due to insufficient biological or interpretative relevance. Nonetheless, their presence should not be entirely discounted or overlooked, as they may still play a supporting role in signaling the interaction between the two pathological domains examined: oral health disorders and psychological or depressive conditions.

The following is a list of the most frequently investigated molecules, which are therefore most emphasized in this thesis:

- TNF-α
- CRP
- mBDNF
- proBDNF
- Interleukin-6 (IL-6), the most frequently cited cytokine in the reviewed studies.
- Interleukin-1 beta (IL-1β), also widely analyzed for its potential pro-inflammatory role.
- Interleukin-10 (IL-10), considered for its anti-inflammatory function.
- Cortisol, a stress hormone relevant to evaluating hypothalamic-pituitary-adrenal (HPA) axis responses.
- Corticosterone, mainly analyzed in animal models for its role in neuroendocrine stress mechanisms.

This molecular analysis formed the basis for the development of graphical representations aimed at visually highlighting expression patterns and facilitating interpretation.

Regarding IL-6, **Figure 4** shows that its levels (blood and saliva samples) tend to increase in both animal (using rats, *Rattus norvegicus*) and human studies. This recurring elevation suggests that IL-6 may represent a key pro-inflammatory marker involved in the shared pathophysiology mechanisms of oral diseases and depressive disorders. However, some findings report stable or even decreased levels, indicating variability that may depend on the clinical or experimental conditions. This duality, further explored in the discussion section, positions IL-6 as a potential "double-edged sword," with context-dependent roles.

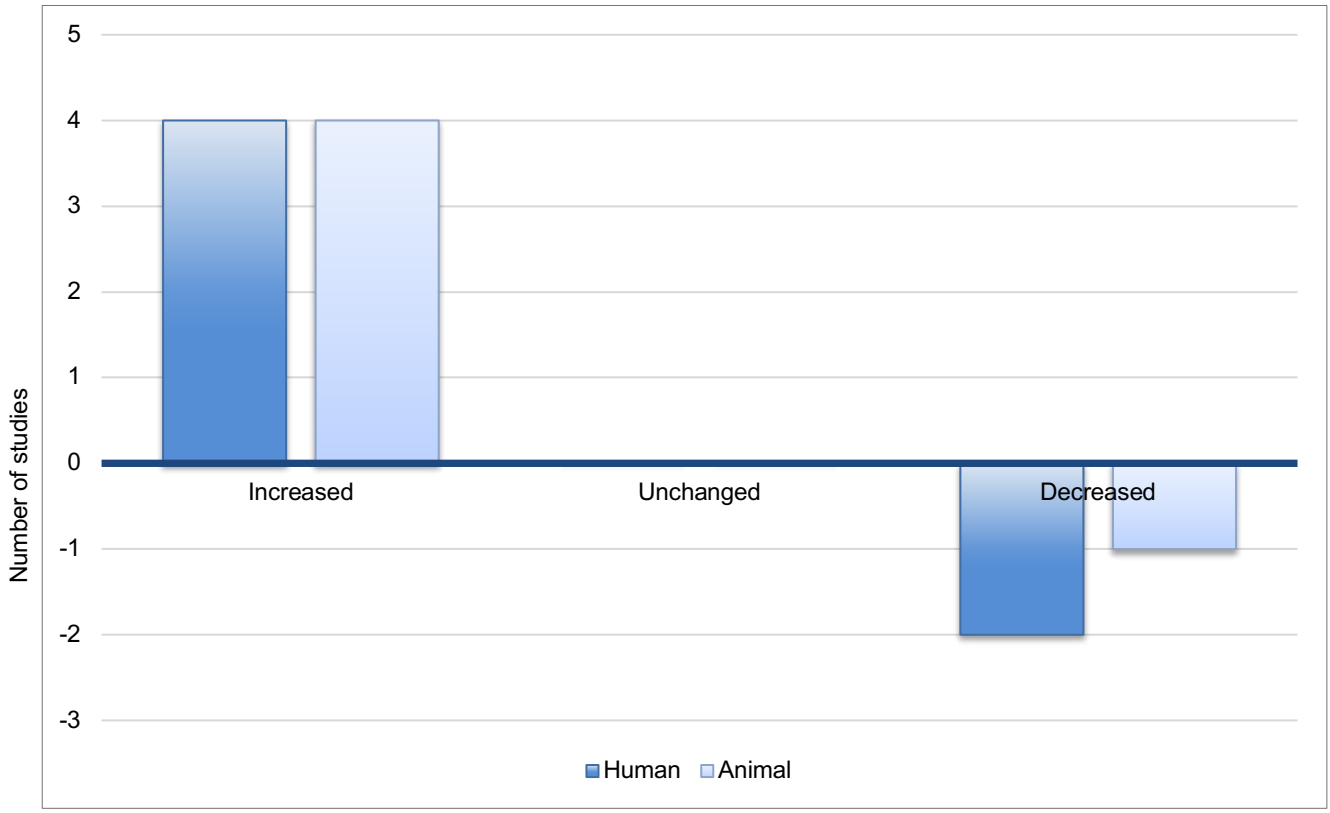


Figure 4: ***IL-6 Expression patterns across the analyzed studies in the context of Periodontal and/or Depressive Conditions****. Summary of IL-6 expression trends (increased, decreased, or unchanged) reported in the selected literature, including both human studies and studies conducted on Rattus norvegicus under conditions of periodontitis, depressive disorders, or their comorbidity.*

Similarly, in the case of IL-1β (blood and saliva samples), the second most frequently studied cytokine, **Figure 5** reveals a general trend toward increased expression, especially in animal studies (using rats, *Rattus norvegicus*), where three investigations reported elevated levels. In contrast, findings from human studies are more variable: one study observed an increase,

one reported stable level, and noted a decrease. Despite this variability, the overall pattern supports the hypothesis that IL-1β functions as a pro-inflammatory mediator potentially involved in the pathophysiological mechanisms linking oral and depressive pathologies.

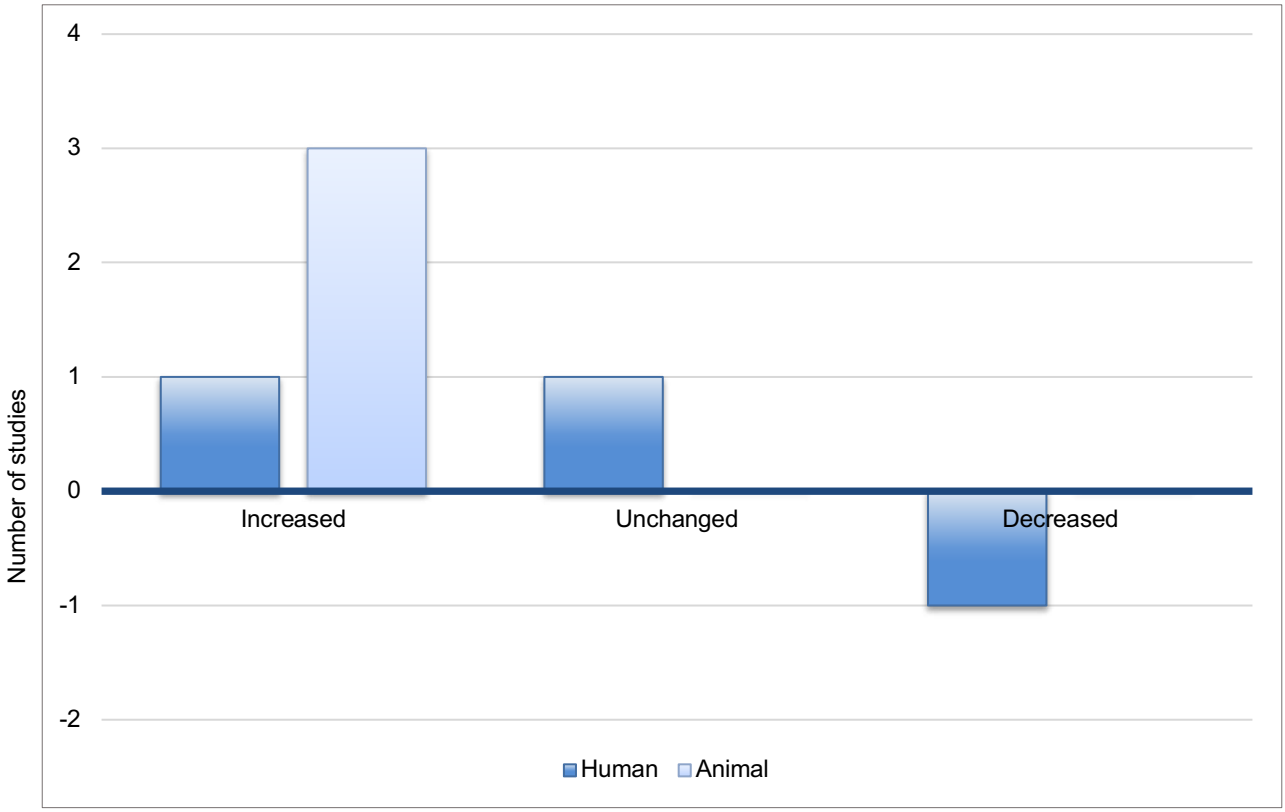


Figure 5: ***IL-1β Expression Trends in relation to Depression and Oral Health****. Summary of reported IL-1β expression changes (increased, decreased, or unchanged) across human and Rattus norvegicus studies investigating periodontal disease, depressive disorders, or their coexistence.*

The role of TNF-α, a key pro-inflammatory cytokine involved in immune response regulation, also warrants attention in blood samples. As shown in **Figure 6**, TNF-α expression is markedly elevated in animal models (using rats, *Rattus norvegicus*) with five studies reporting increased levels. In human subjects, however, findings are less consistent: one study reported a decrease, while another found no significant change. Despite this inconsistency, TNF-α remains a relevant inflammatory biomarker, particularly in preclinical models, suggesting its potential involvement in the biological mechanisms linking oral health and depressive disorders. A more detailed examination of TNF-α and its implications will be provided in the discussion section.

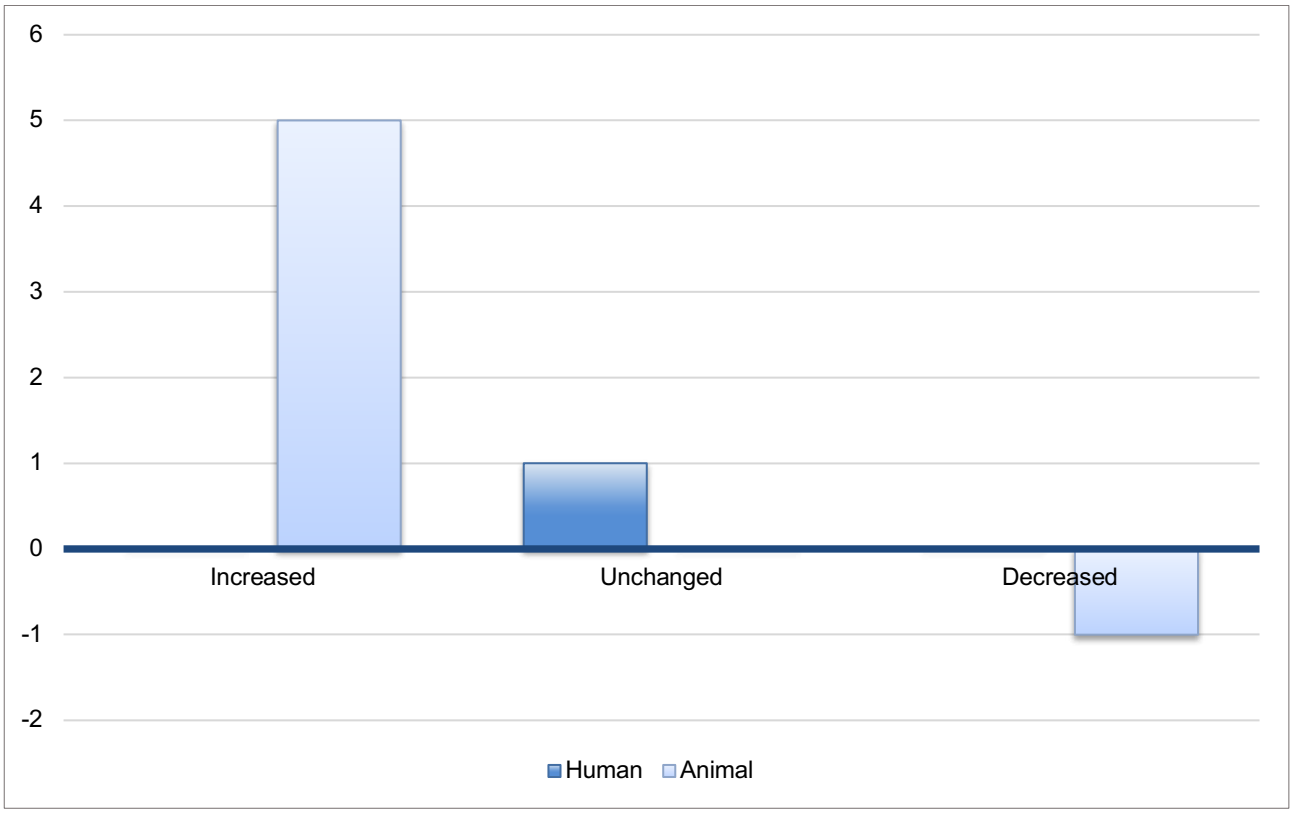


Figure 6: ***TNF-α Expression Dynamics in the reviewed research under Periodontal and/or Depressive Conditions.*** *Overview of TNF-α expression patterns as reported in human and Rattus norvegicus studies focused on periodontitis, depression, or their combination, categorized by direction of change (increase, decrease, unchanged).*

In contrast, IL-10 in blood samples, known for its anti-inflammatory role, displays a distinct behavior compared to the previously discussed cytokines (**Figure 7**). IL-10 remained unchanged in one human study. In animal models (using rats, *Rattus norvegicus*), two studies demonstrated an increase.

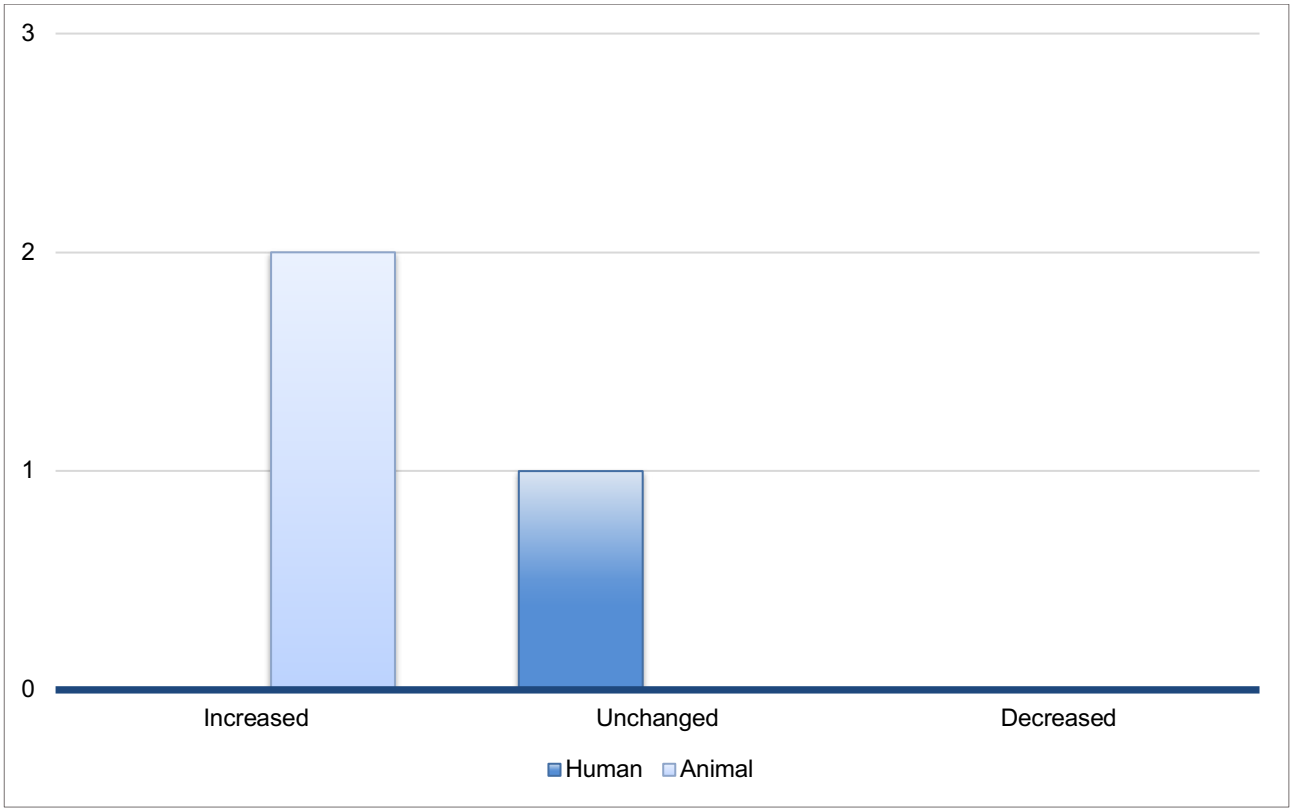


Figure 7: ***IL-10 Expression variation in the context of Depression-associated Periodontal Conditions****. Synthesis of IL-10 expression findings from human and Rattus norvegicus studies, indicating whether levels were found to be increased or unchanged in the presence of depressive and/or periodontal conditions.*

From a different perspective, a particularly significant element in the pathophysiology of mood disorders is Brain-Derived Neurotrophic Factor (BDNF), a neurotrophic factor essential for neuronal survival, growth, and plasticity. Reduced BDNF levels have been associated with depressive symptoms and several neuropsychiatric disorders, highlighting its central role in mood regulation and stress response.[10]

In this context, BDNF emerges as a relevant biomarker of inflammatory processes both in the brain and peripherally. Specifically, in oral inflammation linked to periodontitis, decreased BDNF levels indicate a connection between chronic inflammation – caused by pathogens such as *Porphyromonas gingivalis* – and neuronal health impairment,

contributing to synaptic dysfunction and the onset of depressive symptoms, as well as the dysregulation of mood and stress responses.[10]

Focusing on hormonal markers, as shown in **Figure 8**, cortisol levels in human subjects (blood and saliva samples) present a heterogeneous pattern: one study reports an increase, one reports stability, and another reports a decrease. In animal models, the single available study shows an increase.

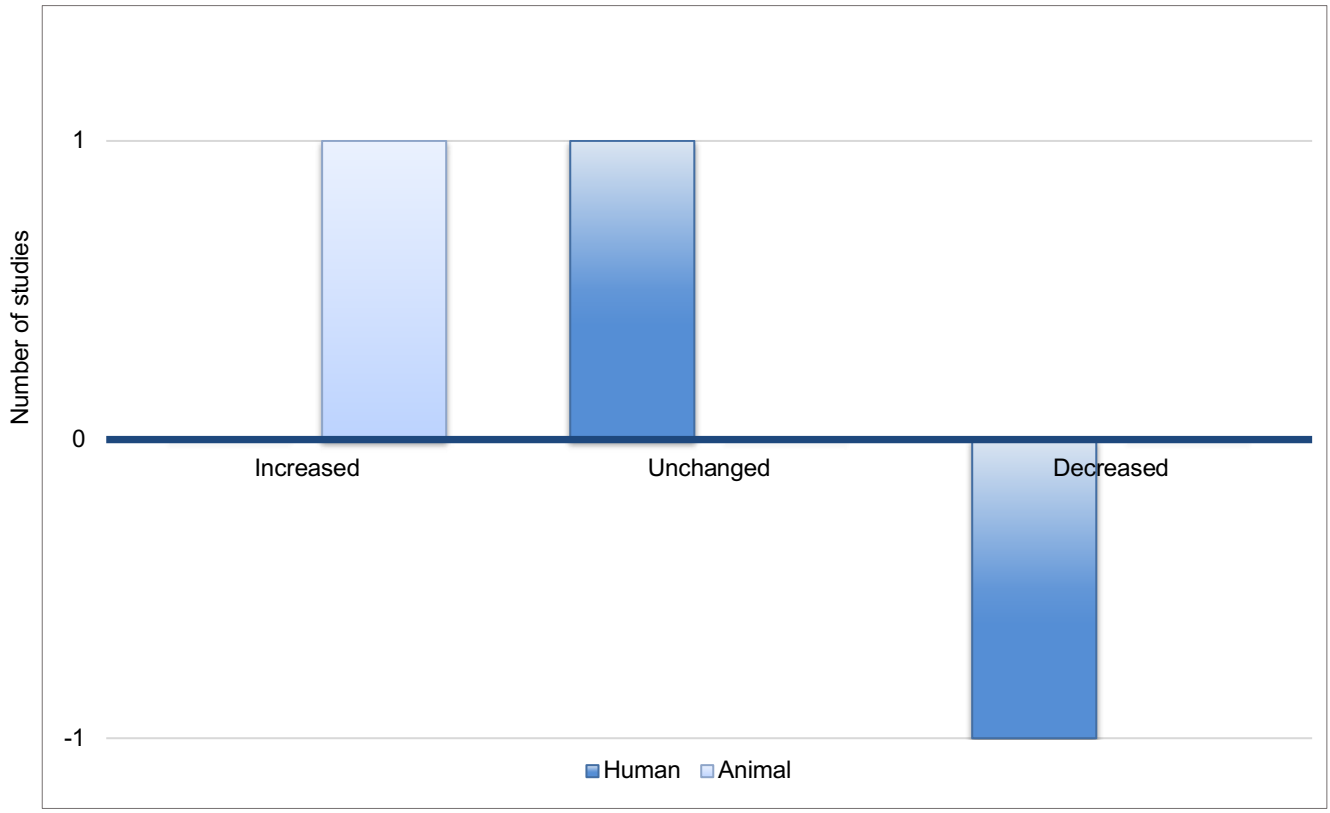


Figure 8: ***Cortisol Levels in studies investigating Psychobiological Interactions in Periodontal and/or Depressive Conditions.*** *Summary of reported cortisol level variations (increased, decreased, or unchanged) in human studies and studies involving Rattus norvegicus, within experimental or clinical contexts characterized by periodontitis, depressive disorders, or their comorbidity.*

Lastly, corticosterone in blood sample, assessed exclusively in animal models (**Figure 9)**, exhibits a variable expression pattern. Among the reviewed studies, two reported increased levels, two noted stable trends, and one observed a decrease.

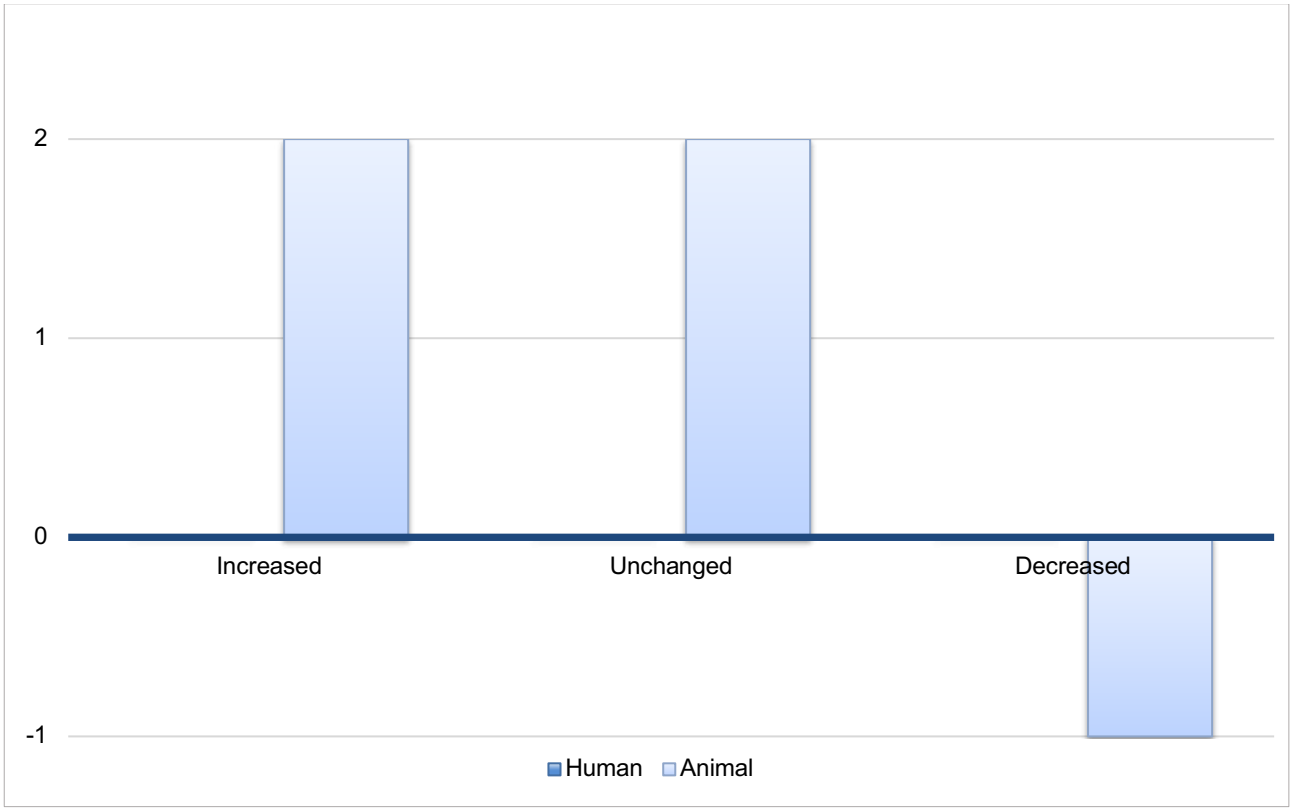


Figure 9: ***Corticosterone Trends observed in animal models under Periodontal and/or Depressive Conditions****. Overview of corticosterone expression patterns (increased, decreased, or unchanged) as reported in studies conducted on Rattus norvegicus, under experimental conditions modeling periodontitis, depression, or their coexistence.*

4.4 Pathway Analysis of Protein-Coding Genes

Once a clearer view of the relationship between oral health and depressive disorders was established, it became both interesting and engaging to explore the molecular mechanisms behind this connection. **Figures 10** and **11** show the main pathways found using the PANTHER platform, as described in the Materials and Methods section, for human and animal models respectively.

It is important to emphasize that this is a functional classification of the included genes, as no *p*-values were reported—an essential requirement for defining a proper enrichment analysis. Nevertheless, the functional classification remains valuable, as it allows for the

organization and interpretation of the data based on known biological functions, providing a conceptual foundation for future investigations and hypothesis generation.

Figure 10, which focuses on data from human subjects, highlights the primary biological pathways involving protein-coding genes identified across the reviewed studies. The main pathways include:

- Alzheimer disease-presenilin pathway (P00004)
- Apoptosis signaling pathway (P00006)
- CCKR signaling map (P06959)
- Heterotrimeric G-protein signaling pathway - Gi alpha and Gs alpha mediated (P00026)
- Heterotrimeric G-protein signaling pathway - Gq alpha and Go alpha mediated (P00027)
- Inflammation mediated by chemokine and cytokine signaling pathway (P00031)
- Interferon-gamma signaling pathway (P00035)
- Interleukin signaling pathway (P00036)
- Plasminogen activating cascade (P00050)
- Wnt signaling pathway (P00057)

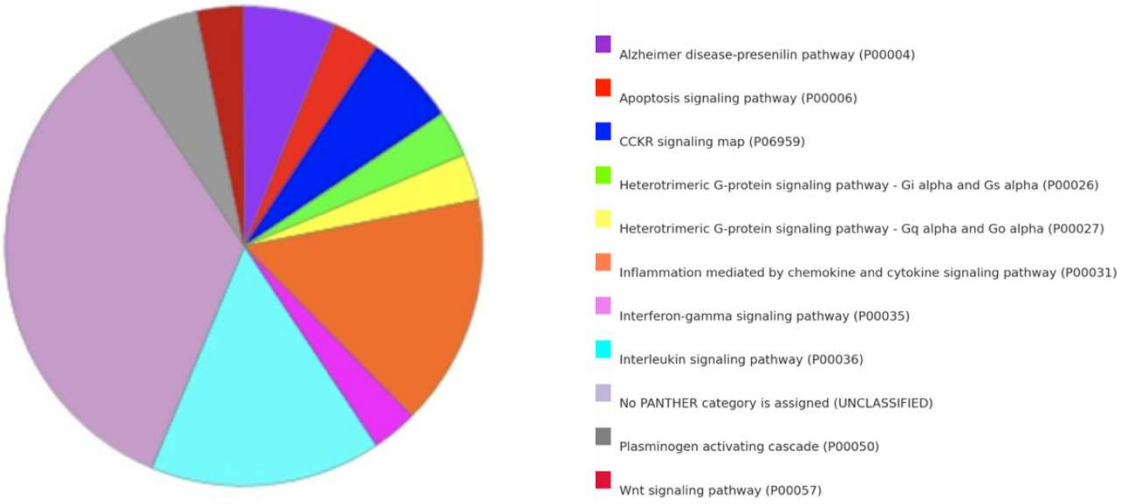


Figure 10: Key Molecular Pathways Linking Oral and Mental Domains identified in Human datasets via Panther Analysis

Figure 11, which presents data from animal models, highlights the principal biological pathways involving protein-coding genes identified in the analyzed studies. The major pathways include:

- Alzheimer disease-presenilin pathway (P00004)
- Angiogenesis (P00005)
- Apoptosis signaling pathway (P00006)
- CCKR signaling map (P06959)
- Cadherin signaling pathway (P00012)
- Corticotropin releasing factor receptor signaling pathway (P04380)
- Endogenous cannabinoid signaling (P05730)
- Gonadotropin-releasing hormone receptor pathway (P06664)
- Huntington disease (P00029)
- Inflammation mediated by chemokine and cytokine signaling pathway (P00031)
- Interferon-gamma signaling pathway (P00035)
- Interleukin signaling pathway (P00036)
- Metabotropic glutamate receptor group II pathway (P00040)
- Opioid proopiomelanocortin pathway (P05917)
- PI3 kinase pathway (P00048)
- Plasminogen activating cascade (P00050)
- TGF-beta signaling pathway (P00052)
- VEGF signaling pathway (P00056)
- Wnt signaling pathway (P00057)

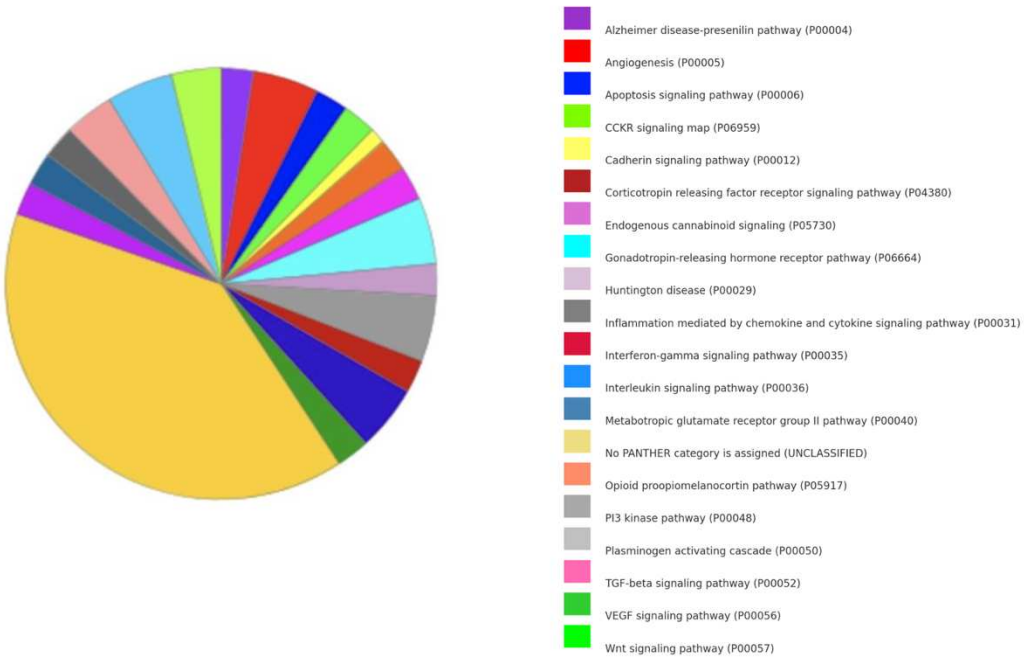


Figure 11: Key Molecular Pathways Linking Oral and Mental Domains identified in Animal datasets via Panther Analysis

The collected data indicate that pathways related to neurodegenerative processes, inflammation, and cell signaling are common to both species, with some differences attributable to biological specificity.

The molecular mechanisms common to humans and animal models, most of which are involved in inflammatory responses and immune signaling pathways, are as follows:

- Alzheimer disease-presenilin pathway (P00004)
- Apoptosis signaling pathway (P00006)
- CCKR signaling map (P06959)
- Inflammation mediated by chemokine and cytokine signaling pathway (P00031)
- Interferon-gamma signaling pathway (P00035)
- Interleukin signaling pathway (P00036)
- Plasminogen activating cascade (P00050)
- Wnt signaling pathway (P00057)

4.5 Quality Assessment of Included Studies

As anticipated in the Materials and Methods section, **Table 6** below presents an assessment of the quality of the included studies, based on the critical appraisal tool validated by the Joanna Briggs Institute (JBI). This tool evaluates methodological soundness through 10 key criteria, allowing for a structured appraisal of potential bias across the studies examined. Specifically, each study was assessed according to the following questions:

1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?
2. Were cases and controls matched appropriately?
3. Were the same criteria used for identification of cases and controls?
4. Was exposure measured in a standard, valid and reliable way?
5. Was exposure measured in the same way for cases and controls?
6. Were confounding factors identified?
7. Were strategies to deal with confounding factors stated?
8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?
9. Was the exposure period of interest long enough to be meaningful?
10. Was appropriate statistical analysis used?

The studies were assigned a quality score, based on the JBI criteria, which allowed for the classification of risk of bias into three categories:

- Low or negligible risk: score between 8 and 9
- Moderate risk: score between 6 and 7
- High risk: score below 6

Table 6: Risk of Bias and Studies Quality Assessment

Study ID	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	SCORE
Al-Bazaz et al., 2021	Yes	No	Yes	Yes	Yes	Na	No	Yes	No	Yes	6, MODERATE RISK
Almeida et al., 2007	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9, LOW RISK
Barry et al., 2018	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Not Applicable	Yes	7, MODERATE RISK
Breivik et al., 2006	Unclear	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8, LOW RISK
Breivik T et al., 2005	Yes	Yes	Yes	Yes	Yes	Na	No	Yes	Yes	Yes	8, LOW RISK
Chen et al., 2007	Yes	Yes	No	Yes	Yes	No	No	Yes	No	Yes	6, MODERATE RISK
Franco et al., 2020	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	8, LOW RISK
Giri et al., 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10, NO RISK
Gomes et al., 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not Applicable	Yes	9, LOW RISK
Hernández et al., 2022	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	8, LOW RISK
Johannsen et al., 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10, NO RISK
Jornet et al., 2020	Yes	Yes	Yes	Yes	Yes	Na	No	Yes	No	Yes	7, MODERATE RISK
Kollera et al., 2000	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7, MODERATE RISK
Li et al., 2022	Yes	Yes	Yes	Yes	Yes	Na	No	Yes	Yes	Yes	8, LOW RISK
Li et al., 2023	Yes	Yes	Yes	Yes	Yes	Na	No	Yes	Yes	Yes	8, LOW RISK
Lutiana et al., 2018	Yes	Yes	Yes	Unclear	Yes	No	No	Yes	Yes	Yes	7, MODERATE RISK
Milton et al., 2014	Yes	No	No	Yes	Yes	No	No	Yes	Yes	Yes	6, MODERATE RISK

Moss et al., 1996	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9, LOW RISK
Oliveira Solis et al., 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not Applicable	Yes	9, LOW RISK
Pekiner et al., 2009	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Not Applicable	Yes	7, MODERATE RISK
Robledo-Montaña et al., 2024	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	8, LOW RISK
Sebastiani et al., 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not Applicable	Yes	9, LOW RISK
Walther et al., 2023	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	8, LOW RISK
Wang et al., 2019	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	8, LOW RISK
Wang et al., 2019	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Not Applicable	Yes	7, MODERATE RISK
Xie et al., 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not Applicable	Yes	9, LOW RISK
Zhang et al., 2024	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9, LOW RISK

Based on the conducted analysis, 18 studies were found to be associated with a low or negligible risk of bias, while 9 studies presented a moderate risk. No studies were classified as having a high risk of bias.

Articles with a moderate risk most frequently exhibited methodological uncertainties related to the identification and management of confounding factors, as well as issues regarding the definition of exposure duration. The latter was particularly common in studies without a longitudinal design, where the exposure timeframe was not adequately described in relation to the observation period.

The distribution of quality scores supports the assumption of high robustness and reliability of the evidence analyzed in this thesis.

The analysis of the results concludes with the Supplementary **Table S1** (*Overview of Included Studies: Authors, Publication Year, Title, and Research Objectives*) and **Table S2** (*Supplementary Study Characteristics and Methodological Details)* in the 'appendices paragraph' that summarize others key data from the included studies.

DISCUSSION

5 DISCUSSION

To address the established P.I.C.O. question, the studies included in this thesis consisted of both longitudinal and experimental designs, involving human and animal models published over the past 30 years. Longitudinal studies followed subjects over time to monitor molecular variations within the association between oral health and depressive disorders , while experimental studies were based on controlled interventions to study the effects of molecular mechanisms at the basis of this relationship. All selected studies focused on molecular alterations or provided laboratory-based molecular evidence supporting a specific relationship between oral health and depressive disorders.

Unlike other reviews that have followed a similar line of inquiry but focused exclusively on the clinical manifestations of oral health in individuals with depressive disorders, the present work aimed to investigate the underlying molecular mechanisms of this association, thereby offering a more integrated and pathophysiological perspective. For instance, in the meta-analysis conducted by Kisely et al.[19], a clear increase in the risk of dental caries and periodontitis is reported among individuals suffering from depressive disorders; however, the potential mediating role of inflammatory markers or dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis is not explored. Similarly, the systematic review by Alimoradi et al [20] demonstrates a statistically significant association between oral health-related quality of life and depressive disorders, yet it confines the analysis to a subjective dimension, without addressing the involvement of biomarkers or biological pathways.

In contrast, the present thesis distinguishes itself by including studies that specifically examine biochemical parameters, thereby allowing for the hypothesis of a circular relationship between chronic oral inflammation and the neurobiological alterations typically associated with depressive disorders. Furthermore, while some reviews (such as that by Kloeckner et al [21]) encompass many observational studies, this thesis also includes experimental articles and research involving animal models, thus broadening the analytical perspective, and helping to bridge a gap in the more traditional literature. This multidimensional approach enables a more nuanced and comprehensive understanding of

the phenomenon- moving beyond the mere clinical observation of comorbidity to explore its possible biological and pathogenetic foundations.

It is important to emphasize that, although excluded from the functional analysis, certain molecules (**Table 5**) retain scientific relevance. These include, e.g., neurotransmitters, cytokines, etc., which act as biomarkers indicating the presence of, and connection between the two pathological domains under investigation: oral disorders and psychological-depressive conditions.

5.1 Cytokines

a. Their presence

This review highlights a general increase in cytokine levels in inflammatory contexts, as evidenced by the expression changes reported in **Table 4**. These findings are consistent with previous literature. Agrawal et al.[22] reported a significant rise of these molecules in inflamed oral tissues. In line with this, Sachin et al [23] observed an increased concentration of chemokines in response to *E. coli* supernatant, the bacterial peptide FMLP, and LPS-activated serum in patients with chronic periodontitis. However, the same research group also noted that there are not significant differences in chemokine responses to inflammatory stimulus, highlighting variability in outcomes depending on the parameters assessed.
Ball et al.[24] stated that individuals with major depressive disorder show elevated levels not only of pro-inflammatory cytokines, but also of their respective receptors, such as IL-6, IL-8, TNF-α, as well as TLR-3 and TLR-4. They further noted that other studies have detected increases in IL-1β, IL-6, and IL-8 in the gingival crevicular fluid of patients with periodontal disease, with a positive correlation to psychosocial stress. Moreover, the same authors' group (Ball et al.[24]) highlighted a possible association between high cortisol levels (in serum and saliva) and the worsening of periodontal clinical parameters, particularly bleeding on probing, clinical attachment loss, and pocket depth.
An additional contribution is provided by Dumitrescu et al[25], who identified periodontal disease as being associated. with low-grade systemic inflammation, marked by elevated levels of IL-6, TNF-α, and CRP. According to the authors, this inflammatory state may trigger

oxidative and nitrosative stress, both implicated in neuroprogressive processes typical of depressive disorders, as discussed later.

A different perspective is offered by Li et al[26], who demonstrated that rats exposed exclusively to psychological stress did not exhibit significant changes in the expression levels of key inflammatory cytokines, including IL-1β, IL-6, TNF-α, or IFN-γ. In contrast, rats in the experimental periodontitis (EP) group showed significantly elevated protein levels of these inflammatory markers in periodontal tissues.

Although most studies lead to similar conclusions, some report partially divergent data: Solis et al.[27] observed a slight reduction in IL-6 and IL-1β levels in unstimulated white blood cells from patients with major depression, compared to controls. Similarly, Pekiner et al.[28] found that salivary levels of IL-2 and IL-6 in patients with Burning Mouth Syndrome (BMS) did not significantly differ from those of controls, although IL-6 values were slightly elevated.

In contrast, Chen et al.[29] reported lower serum IL-6 levels in BMS patients than in controls.

Chiappelli et al.[11] linked IL-2 production to an altered immune response in patients with oral lichen planus (OLP), particularly in the erosive form, highlighting an increase in memory T cells (CD4+CD45RA−) and a reduced ability to produce IL-2.

b. Cytokines and Psychological Disorders

Cytokines are key players in immune activation and can directly influence neuronal function, contributing to the onset or exacerbation of depressive disorders through several mechanisms described in the literature, all inside the inflammatory setting:

1. The increase in pro-inflammatory cytokines promotes oxidative and nitrosative stress, leading to the accumulation of advanced oxidation protein products (AOPPs). This process triggers the activation of macrophages and monocytes by endotoxins such as lipopolysaccharides (LPS). At the same time, elevated levels of advanced glycation end products (AGEs) are observed, accumulating in tissues. These biological conditions lead to excessive production of reactive oxygen and nitrogen species (ROS and RNS), thereby worsening neurodegeneration and depressive symptoms.[23]

2. Depressive disorders are often associated with alterations in the gut microbiota, characterized by dysbiosis and increased intestinal permeability (leaky gut). This condition compromises the mucosal barrier, facilitating the systemic translocation of endotoxins such as LPS. These endotoxins, produced by Gram-negative bacteria, activate toll-like receptors TLR-2 and TLR-4, stimulating T-helper cell type 1, M1 macrophages, and—similarly to the first mechanism—reactive species (ROS/RNS). This results in systemic inflammation and oxidative/nitrosative stress, both of which contribute to neurodegeneration and depressive pathology.[23]

   Although the paragraph refers to gut microbiota dysbiosis, similar mechanisms have also been described in the context of oral dysbiosis, particularly in periodontal disease. The oral and gut microbiota are ecologically distinct, but functionally interconnected: oral pathogens such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum* can contribute to elevated systemic LPS levels and activate the same immune-inflammatory pathways (TLRs, T-helper cell type 1, ROS/RNS) implicated in intestinal permeability. Therefore, disturbances in oral health may converge with gut-related pathways in promoting systemic inflammation and neurodegeneration.

3. Cytokines can disrupt neurotransmission and neuronal plasticity by interfering with the metabolism of neurotransmitters such as serotonin, noradrenaline, and dopamine.[30] They also modulate corticotropin-releasing hormone (CRH), thus activating the hypothalamic-pituitary-adrenal (HPA) axis and promoting excessive secretion of ACTH and cortisol. This hyperactivation is associated with immunosuppression and elevated cortisol levels, a common finding in major depressive disorder. [31]

c. Cytokines and Oral Disorders (Periodontitis, OLP, BMS)

Beyond their effects on mental health, pro-inflammatory cytokines also contribute to the development and progression of oral pathologies such as periodontitis, oral lichen planus (OLP), and burning mouth syndrome (BMS), through the following molecular mechanisms:

1. The increase in Gram-negative bacterial antigens, favored by dysbiosis associated with depressive states, stimulates the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), thereby increasing the endotoxin load in root canals. This process triggers an inflammatory cascade mediated by pro-inflammatory cytokines, leading to tissue damage and a marked delay in healing processes. [13]
2. Cytokines influence aromatase enzyme activity in peripheral tissues, increasing the conversion of androgens into estrogens. Elevated estrogen levels, often seen in autoimmune disorders, have been associated with the onset of oral lichen planus. According to study of Agrawal et al [22], this association suggests a potential use of estrogens as biomarkers for OLP.

In a broader perspective, elevated IL-6 levels have been linked to alveolar bone resorption and have been detected not only in gingival crevicular fluid, but also in biopsies of inflamed periodontal tissue. This increase may be induced by depressive states and, in turn, worsen depressive symptoms by impairing immune competence, thereby promoting the onset of infections (both oral and systemic) and neoplastic processes. [27]

d. The Dual Role of IL-6

Although elevated IL-6 is generally associated with pathological processes—as reported by Ball et al.[24]—the study by Chen et al.[29] highlighted a potential protective role of this cytokine in certain clinical contexts. In patients with burning mouth syndrome (BMS), lower serum IL-6 levels were correlated with increased pain intensity. This finding suggests that reduced IL-6 may contribute to hyperalgesia by weakening its neurotrophic and neuroprotective effects on the trigeminal nociceptive pathway. [29]

However, the opposite effect must also be considered: excessive IL-6 expression can impair central nervous system function, suppress immune responses, and promote the onset or worsening of depressive symptoms, infections, and tumors.

As a final point, IL-6 plays a dual role in cerebral immune response. It acts as a "double-edged sword," exerting neuroprotective effects in some contexts while contributing to pathology in others, depending on the timing and conditions of its expression.

e. TNF-α

Tumor necrosis factor-alpha (TNF-α), produced by macrophages, plays a critical role in both systemic inflammation and the modulation of neuronal activity. It is also involved in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis. Elevated TNF-α levels have frequently been observed in individuals with periodontitis as well as in those suffering from depressive disorders, suggesting a potential shared biological mechanism between the two conditions.

Within this framework, an additional molecular mechanism highlights how periodontitis may contribute to the development of depressive disorders: the microglial response to periodontal inflammation.

- **Periodontitis → Pro-inflammatory microglial activation**

  Chronic periodontal inflammation leads to the release of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6), which may reach the central nervous system via the trigeminal nerve and systemic circulation. This mechanism aligns with molecular pathways identified through the Panther database, particularly inflammation mediated by chemokine and interleukin signaling pathways in both humans and animals, and TGF-beta signaling exclusively in animals. These signals trigger microglial activation, particularly in the prefrontal cortex—a brain region central to mood regulation.

- **Activated microglia → Synaptic plasticity alterations**

  Hyperactive microglia not only release more pro-inflammatory cytokines, but also alter synaptic pruning processes, reducing neuronal connectivity. This disrupts the excitatory/inhibitory balance essential for mood regulation.

- **Additionally: Role of the endocannabinoid (EC) system**

  The EC system (CB1, CB2, anandamide, 2-AG) plays a crucial role in inflammation control and synaptic plasticity. In both periodontitis and depressive disorders, the EC system appears disrupted, often showing decreased anandamide levels and

desensitization of CB1 receptors, which are essential for mood tone. This exacerbates synaptic dysfunction and neuroinflammation, promoting the progression toward major depressive disorder (MDD).[14]

Although several studies have reported increased TNF-α levels in both periodontitis and depressive disorders—pointing to a common inflammatory mechanism—other experimental data suggest a more nuanced scenario. In animal models of depressive disorders, such as olfactory bulbectomy (OB) rats [32], the exposure to a pro-inflammatory agent like lipopolysaccharide (LPS) induced a blunted inflammatory response, with a decreas of circulating TNF-α levels. This phenomenon may be explained by the chronic activation of the HPA axis, typical of depressive disorders, which exerts immunosuppressive effects by downregulating pro-inflammatory cytokine production and, on the contrary, promoting anti-inflammatory mediators such as IL-10 and TGF-β1. This pattern may suggest a compensatory mechanism by the organism to regulate and counteract inflammatory responses.

In this context, TNF-α should not be regarded simply as "always elevated" inflammatory marker, but rather as a molecule whose expression is modulated by the individual's neuroendocrine and immune status.

The normalizing effect of certain antidepressants, such as tianeptine—which restores TNF-α levels along with anti-inflammatory cytokines—underscores the central role of immuno-neuroendocrine balance in inflammation regulation.[33]

The **molecular mechanisms** identified via Panther database relative to the cytokines are: Inflammation mediated by chemokine signaling, Interleukin signaling pathway, Wnt signaling pathway (in both humans and animals' species, associated with IL-6, TNF-α, and cytokines) Interferon-gamma signaling and TGF-beta signaling (exclusive to animal models).

- **Inflammation-mediated chemokine and interleukin signaling pathway**→As reported by Warren et al.[34], chronic stress—whether psychological, environmental, or physical—acts as a systemic trigger. It activates the HPA axis, leading to altered immune responses and increased susceptibility to periodontal infections. Pro-

inflammatory cytokines such as IL-1β, TNF-α, and IL-6 play a central role in this process, contributing to both periodontitis pathogenesis and the neuroinflammatory mechanisms underlying depressive disorders.

- **Wnt signaling pathway**→ The Wnt pathway, particularly the Wnt/β-catenin axis, is involved in inflammation regulation and tissue regeneration. In the oral environment, it contributes to bone regeneration and periodontal immune responses. At the same time, it is essential for the development and homeostasis of the central nervous system (CNS). Its dysfunction has been associated with neurological disorders, suggesting a potential link between chronic oral inflammation and vulnerability to depressive conditions.[35]
- **Interferon-gamma signaling pathway** → Interferon-gamma (IFN-γ) plays a key role in both systemic and local inflammatory regulation. In chronic oral infections (e.g., periodontitis), this pathway may lead to a hyperactive immune response that compromises the integrity of the blood-brain barrier. This dysfunction is often exacerbated by pathogens such as *F. nucleatum*, which facilitate the entry of inflammatory mediators into the central nervous system, promoting neuroinflammation.[14]
- **TGF-beta signaling pathway** → Transforming growth factor-beta (TGF-β) is a essential regulator of inflammatory responses and tissue regeneration, influencing both periodontal healing and neuroprotective mechanisms. Such that as highlighted by Breivik et al.[32], treatment with tianeptine in OB rats significantly increased TGF-β1 levels, leading to the inhibition of periodontal bone loss and normalization of behavioral responses.

5.2 C-Reactive Protein (CRP)

Regarding C-reactive protein (CRP), the study by O'Neil et al.[36] found no significant influence of systemic inflammation on the relationship between depressive disordersand oral health, although a positive correlation between poor oral health and depression was observed, regardless of the inflammatory markers assessed.

The authors acknowledge that CRP may not be a sufficiently sensitive marker. To address this limitation, they suggest the use of more advanced testing methods, such as high-sensitivity CRP (hs-CRP), which may provide a more detailed picture of subclinical inflammatory levels.

As previously discussed in the context of cytokines, Dumitrescu et al.[25] reported a substantial increase in CRP levels in systemic inflammation related to periodontal disease. This condition, through neurobiological mechanisms such as oxidative and nitrosative stress, may contribute to the onset or worsening of depressive symptoms. This scenario is supported by the present thesis, as two included studies—Walther et al [5] and Al-Bazaz et al.[37], —found elevated CRP levels in both depressive disorders and periodontitis conditions.

The CRP-relates **molecular mechanisms** identified through Panther database are: Inflammation mediated by chemokine signaling, Interleukin signaling pathway (in both humans and animals' species), and VEGF signaling pathway (exclusive to animal models)

- **VEGF signaling pathway** → According to Sun et al.[38], activation of the IGF2 gene and its crosstalk with PTGS2- Prostaglandin-Endoperoxide Synthase 2- (which encodes cyclooxygenase 2, a key enzyme in prostaglandin synthesis) are implicated in chronic inflammatory contexts, particularly in neurodegenerative damage and tumor progression. Furthermore, PTGS2 stimulates the expression of VEGF (vascular endothelial growth factor), which promotes angiogenesis by facilitating the formation of new blood vessels necessary for supplying nutrients and oxygen to inflamed or neoplastic tissues.

5.3 Cortisol

Cortisol emerges, through the analysis of the following study, as one of the central mediators in the link between psychological stress and periodontal health. Under physiological conditions, cortisol regulates inflammation and immune function; however, its imbalance—whether in excess or deficiency—can negatively influence the onset and progression of periodontitis. These observations suggest, furthermore, a possible dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, consistent with the alterations in chronic stress

often associated with both depressive and oral inflammatory conditions. Supporting this, studies such as that by Sachin et al.[23] highlight that stress-induced elevated cortisol levels suppress neutrophil activity and worsen gingival inflammation. Similarly, Rai et al.[39] emphasize salivary cortisol as a key predictor of tooth loss. In contrast, Johannsen et al.[39] present an opposing perspective, showing that patients with depressive disorders exhibit lower cortisol levels in the gingival crevicular fluid compared to controls. This suggests a possible alteration in the distribution or local metabolism of cortisol, rather than a mere systemic increase.

Overall, these findings indicate that it is not only the absolute level of cortisol that impacts oral health, but also its balance and regulation across different body compartments.

According to the Panther database, the **molecular mechanisms** linked to cortisol include**:** PI3 kinase pathway, Corticotropin-releasing factor receptor signaling (in both humans and animals' species), and Opioid proopiomelanocortin pathway (exclusive to animals' model)

- **PI3 kinase pathway** → This pathway, activated as a second messenger by cannabinoid receptors CB1 and CB2, stimulates cAMP production, a molecule involved in cellular surveillance and plasticity. It thus plays an essential role not only in cell survival, but also in neuroprotection and the maintenance of tissue integrity, both at the oral and cerebral level[14]
- **Corticotropin-releasing factor receptor signaling pathway** → This pathway is closely linked to the stress response, as it activates the HPA axis, leading to increased cortisol production. Persistent oral inflammation may chronically activate this mechanism, thereby contributing to prolonged stress states and increasing vulnerability to depressive symptoms[28.]
- **Opioid proopiomelanocortin (POMC) pathway** → The POMC pathway is a major neuroendocrine axis involved in modulating pain, mood, and stress response. POMC is a precursor protein that is processed into several active peptides, including β-endorphin, ACTH (adrenocorticotropic hormone), and MSH (melanocyte-stimulating hormone). An excessive production of endorphins, induced by

psychosocial/depressive stress conditions, may contribute to increased vulnerability to periodontal tissue destruction[40].

5.4 BDNF

Brain-Derived Neurotrophic Factor (BDNF) is a key element in the pathophysiology of mood disorders, as it supports neuronal survival, neural growth, and synaptic plasticity. A reduction in BDNF levels has been associated with the emergence of depressive symptoms, confirming its critical role in mood modulation and stress response.

In animal models, as shown by Wang et al.[41], exposure to *P. gingivalis (Pg)*—a major pathogen in periodontitis—leads to a significant decrease in BDNF levels, consequently promoting depressive-like behaviors. However, therapeutic interventions such as BDNF injection or overexpression of p75NTR—a neurotrophic receptor (including BDNF) involved in the regulation of neuronal survival, apoptosis, and inflammatory responses within astrocytes (glial cells supporting neurons in the central nervous system)—have been shown to alleviate these behaviors, highlighting the protective effect of restoring BDNF signaling. This evidence reinforces the concept of a pathological connection between oral health, neuroinflammation, and depressive disorders: once again highlighting how molecular balance is crucial for the maintenance of systemic health.

The proposed molecular mechanism describes a causal sequence whereby *Pg,* through the release of lipopolysaccharides, activates TLR-4 receptors, leading to a reduction not only in p75NTR, but also in mature BDNF (mBDNF), resulting in neuronal dysfunction and the onset of depressive symptoms.

It is important to distinguish between proBDNF and mBDNF. ProBDNF is the immature form of the neurotrophin, which promotes neuronal atrophy and cell death. In contrast, mBDNF is the biologically active form that interacts with the TrkB (Tropomyosin Receptor Kinase B) receptor to support neuronal survival, growth, and synaptic plasticity. According to Li et al[26]., animal models of depressive disorders show increased levels of proBDNF alongside a concomitant reduction in mBDNF in both the hippocampus and the prefrontal cortex, indicating a shift toward neurodegenerative signaling.

An additional perspective on the link between oral inflammation and depressive disorders emerges from the work of Robledo-Montaña et al.[14], who hypothesized the involvement of microglia in the disruption of synaptic plasticity associated with depressive disorders. Specifically, periodontitis promotes a pro-inflammatory microglial activation profile, with an increase in microglial populations in the frontal cortex and qualitative morphological changes. This altered microglial state, through disruptions in the homeostatic endocannabinoid system, contributes to synaptic plasticity deterioration. The dysfunctional interaction of these mechanisms ultimately supports the emergence of depressive symptoms.

In conclusion, the consistency across the findings of Wang et al., Robledo-Montaña et al., and Li et al. outlines a pathological axis linking oral inflammation, neuroinflammation, and mood disorders.

The **molecular pathways** associated with BDNF, as identified by the Panther database, are: PI3 kinase pathway, Wnt signaling (in both humans and animals' species, also involved in cytokine-related mechanisms) and Cadherin signaling (exclusive to animals' models)

- **Cadherin signaling pathway**→ The stabilization of VE-cadherin (Vascular Endothelial Cadherin) strengthens adherents' junctions between endothelial cells, thus supporting the integrity and stability of the vascular barrier. It also helps regulate inflammation by limiting the infiltration of inflammatory cells into the endothelium. In pathological contexts such as periodontitis or psychological disorders, reduced expression of this pathway may exacerbate negatively clinical outcomes[42].

5.5 Microbiome

Regarding the microbiome, Mendes et al [4] describe the progression of periodontal disease as a chronic inflammatory process initiated by a bacterial biofilm composed primarily of Gram-negative bacteria and endotoxins. This leads to detachment of the periodontal ligament, deepening of gingival pockets, and tooth loss.

In the present thesis, it was found that periodontitis (Walther et al[5]), in addition to generating local inflammation in the oral cavity, may also activate a systemic response through the dissemination of inflammatory mediators and bacterial products into the bloodstream. This increased systemic inflammatory load has been linked to a higher risk of developing extra-oral conditions, including neurological and psychological disorders.

Within this context, it is proposed that bacteria residing in the periodontal pocket—particularly *P. gingivalis*—as well as inflammatory mediators, can enter the systemic circulation, leading to the translocation of pathogenic products from the oral cavity to the brain through the blood-brain barrier (BBB). Indeed, this barrier may be altered or impaired by the systemic release of pro-inflammatory cytokines in response to periodontal inflammation. This scenario consequently accelerates inflammatory and degenerative processes at the cerebral level, facilitating the development of disorders such as Alzheimer's disease and depressive disorders[5]. These processes are supported by molecular pathways identified through the Panther database, including interferon-gamma signaling pathway and Alzheimer disease – presenilin pathway (**Figures 10 and 11).**

These findings provide a valuable foundation for compare other studies, investigating the role of periodontitis in cognitive dysfunction and mood disorders.

Simpson et al[12] describe how changes in the oral microbiome may disrupt microbial adhesion and contribute to the onset of oral inflammatory diseases, which—as previously discussed—can induce a chronic inflammatory state that precedes the occurence of depressive disorders. At a taxonomic level, cortisol has been shown to moderate associations between specific microbial groups (such as Actinomycetales and Actinomycetaceae) and symptoms of anxiety or depressive disorders. Alterations in CRP have influenced the important relationship between anxiety and bacteria belonging to families such as *Campylobacteraceae* and *Streptococcaceae,* as well as species like *Haemophilus, Alloprevotella rava, Rothia mucilaginosa,* and *Prevotella oulorum*[12].

Another interesting aspect of the microbiome is presented by Malan-Muller et al.[43], who bring attention to a possible role of the gut microbiota in post-traumatic stress disorder (PTSD). The authors identified significant correlations with bacterial genera also associated

with periodontal disease, including Mitsuokella, Olsenella, Catenibacterium, and Odoribacter.

Molecular mechanisms identified, via Panther database, related to the microbiome are: Inflammation mediated by chemokine signaling, Wnt signaling + Alzheimer disease – presenilin pathway (in both humans and animals) Cadherin signaling (exclusive to animals' models, as observed in the case of BDNF)

- **Alzheimer disease – presenilin pathway** → The presenilins (PSEN1 and PSEN2) are genes strongly implicated in the pathogenesis of Alzheimer's disease. They encode proteins involved in the cleavage of amyloid precursor protein (APP), leading to the production of beta-amyloid, the main component of neuritic plaques characteristic of Alzheimer's pathology. However, recent evidence—including that reported by Olsen et al.[44] —suggests that beta-amyloid formation may also be exacerbated by chronic oral inflammation, particularly periodontitis caused by *P. gingivalis*, as well as by oxidative stress. These factors intensify neuronal damage and increase the risk of developing depressive symptoms.

5.6 Functional Validation of Mechanisms via Panther

Following the in-depth analysis of molecular mechanisms associated with each macro-theme, it is useful to objectively frame and contextualize the results obtained through the Panther classification system.

Regarding cytokines, the pathways identified align with expectations: a strong association emerges with major inflammatory mediators — including IL-6, TNF-α, and interferons — confirming the activation of molecular circuits that are well-established in immune response modulation.

Similarly, for C-reactive protein (CRP), the findings reflect the underlying biological rationale of the analysis: pathways involving chemokines and interleukins were identified, consistent with CRP's recognized role as a marker of systemic inflammation. An exception is represented by the emergence of the VEGF-related pathway, observed exclusively in animal

models. Although not a canonical pathway directly linked to CRP, its presence appears biologically plausible, as previously discussed.

In the case of cortisol, the identified mechanisms are coherent with the expected signaling pathways. The detection of PI3K (Phosphoinositide 3-Kinase) signaling supports the activation of the HPA axis and the stress response in both human and animal models. The POMC opioid pathway, detected only in animal models, while less anticipated, remains biologically consistent due to the role of ACTH in regulating cortisol secretion. The absence of pathways directly involving glucocorticoid receptors is noteworthy, though it does not compromise the overall interpretation; rather, it may reflect current limitations in database annotation. Overall, the results support the robustness of the model in reflecting cortisol physiology and its involvement in neurological disorders.

For BDNF, the findings capture the functional complexity of this molecule. The presence of cadherin signaling in animal models, although not typically associated with BDNF, is compatible with neuroplastic processes and cellular adhesion. No major absences were observed, and the overall pathway profile reflects BDNF's neurotrophic role.

Finally, the results concerning the microbiome are largely consistent with current knowledge. Inflammatory pathways mediated by chemokines and Wnt signaling are fully aligned with the microbiome's known role in immune modulation and chronic inflammatory processes. The identification of the presenilin pathway, although not initially hypothesized, is increasingly recognized in this context. The detection of cadherin signaling exclusively in animal models, as also seen with BDNF, may reflect tissue structural changes associated with cell-to-cell communication[41].

Overall, these data strengthen the hypothesis of significant cyclical relationship between oral status, inflammatory processes, and neuropsychological vulnerability.

FINAL CONSIDERATIONS AND FUTURE PERSPECTIVES

6 FINAL CONSIDERATIONS AND FUTURE PERSPECTIVES

The interconnection between oral and mental health represents an extremely broad and complex field, where multiple biological pathways intertwine and influence one another. It is essential to highlight the evidence of a dynamic cycle in which the relationship between the two domains becomes central—the real core of the link between oral health and mental disorders. Depressive disorders contribute to the onset and worsening of oral conditions through specific molecular mechanisms, while, in parallel, altered pathways triggered by compromised oral health may, in turn, fuel or exacerbate depressive states.

This study aimed to identify and examine the relationship between oral health and neurodepressive disorders, focusing on the principal molecular mechanisms underlying this bidirectional connection:

1. Pro-inflammatory cytokines as key biomarkers

   The analysis identified key biomarkers within the sphere of inflammation, specifically cytokines such as IL-6, IL-1β, and TNF-α. These markers are indicative of chronic inflammatory states, representing crucial warning signals. Notably, they are associated with both neurological and oral disorders. In the context of depressive diseases, these cytokines contribute to mechanisms involving oxidative stress, increased permeability of mucosal and blood-brain barriers, neurotransmission dysregulation (e.g., microglial activity), and alterations in the HPA axis. In the case of oral diseases, they play a pivotal role in disease progression, marked by shifts in the microbiome composition—such as the increase in *P. gingivalis* or *F. nucleatum* in connection with interferon-gamma signaling—along with altered enzymatic and hormonal activities. Among these, IL-6 was frequently elevated in both depressive and periodontal conditions—particularly in animal models and several human studies—supporting its role as a shared pro-inflammatory biomarker at the intersection of these two pathological domains.

2. Hormonal indicators of disease progression

   Hormones such as corticosterone in animal models and cortisol in humans were identified as potential indicators, given their association with mechanisms affecting the progression of both oral and neuropsychiatric disorders. This is mediated through

mechanisms involving receptor interactions, gene crosstalk, stress response pathways, HPA axis alterations, and peptide activity.

As dental professionals, this scenario reinforces the awareness of promoting and maintaining oral hygiene as a fundamental preventive strategy. This approach not only helps to slow the progression of periodontal disease—often associated to co-occurring psychological symptoms—but also contributes significantly to preserving the patient's psychological well-being.

Oral health cannot be viewed as an isolated element, but rather must be understood within the broader context of integrated well-being. Adopting a healthy lifestyle—encompassing regular physical activity, quality sleep, a balanced diet, and positive social relationships—represents an effective preventive strategy for protect systemic health, including oral and mental health.

The main limitation of this study lies in the lack of consistently homogeneous trends across the various molecules analyzed.

Studies such as those analyzed in this thesis have proven particularly effective in identifying biomarkers in animal models. However, it is important not to hastily conclude that these biomarkers are exclusive to animal systems; they may also be present in humans. The key difference is that research involving human subjects requires more complex and less standardized experimental protocols, with outcomes that are often less direct and predictable compared to *in vivo* studies conducted on small animal models.

Although this review provides strong scientific evidence identifying specific clinical indicators that link oral diseases and depressive disorders, and its predominantly strong methodological quality supports the credibility of the findings, future investigations are deemed necessary. These should aim to deepen the understanding of the underlying biological processes, improve the control of confounding variables, and clarify exposure timelines.

Advancing this knowledge will improve the reliability and reproducibility of findings in this growing field, which holds important diagnostic and preventive implications and supports interdisciplinary approaches to patient care.

The human being must be understood as a complex system, made up of delicate yet deeply interconnected balances. Only when each component—both physical and psychological—integrates in harmony, coherence, and synergy can a true state of well-being be achieved. ***Mens sana in corp(ore) sano.***

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7 BIBLIOGRAPHY

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APPENDICES

8. APPENDICES

Table S1: Overview of Included Studies: Authors, Publication Year, Title, and Research Objectives

OVERVIEW				
LINK	**AUTHORS**	**YEAR**	**TITLE**	**OBJECTIVE**
https://pubmed.ncbi.nlm.nih.gov/17956468/	A. Johannsen, I. Rydmark, B. Sçder, M. Sberg	2007	Gingival inflammation, increased periodontal pocket depth and elevated interleukin-6 in gingival crevicular fluid of depressed women on long-term sick leave	To investigate periodontal status, in relation to inflammatory markers and cortisol, in the gingival crevicular fluid and saliva of a homogenous group of women on long-term sick leave for job-stress related depression in comparison to nondepressed women
https ://doi.org/10.1007/s11136-020-02581 -8	Aline Monise Sebastiani, Maria Fernanda Pivetta Petinati, Nelson Luis Barbosa Rebellato, Katheleen Miranda dos Santos, Luciana Signorini, Erika Calvano Küchler, Rafael Correia Cavalcante, Livia Azeredo Alves Antunes, Rafaela Scariot	2020	Depression, temporomandibular disorders, and genetic polymorphisms in IL6 impact on oral health-related quality of life in patients requiring orthognathic surgery	To assess oral health-related quality of life (OHRQoL) in patients requiring orthognathic surgery, and evaluate if depression, temporomandibular disorders (TMD), and genetic polymorphisms in interleukin-6 (IL6) influence their OHRQoL.

https://pubmed.ncbi.nlm.nih.gov/29194773/	Alison Barry, Ken D. O'Halloran, Joseph P. McKenna, Christine McCreary, Eric J. Downer	2018	Plasma IL-8 signature correlates with pain and depressive symptomatology in patients with Burning Mouth Syndrome: results from a pilot study	To correlate depressive symptomatology and oral cavity pain with plasma cytokine/chemokine signatures in a cohort of patients with BMS. + to understand the systemic inflammatory mechanisms associated with the occurrence of BMS and in doing so we have identified a chemokine signature in blood plasma that potentially correlates with clinical symptoms in patients with the disorder
http://dx.doi.org/10.1016/j.bbi.2015.11.014	Ana Cristina de Oliveira Solis, Andrea Horvath Marques, Wagner Vasques Dominguezc,Euthymia Brandão de Almeida Prado, Cláudio Mendes Pannutia, Roberto Fraga Moreira Lotufoa, Francisco Lotufo-Neto	2015	Evaluation of periodontitis in hospital outpatients with major depressive disorder. A focus on gingival and circulating cytokines	To determine the following: IL-6, IL-1b, INF-c levels in white blood cells; and IL-6, IL-1b levels in the GCF and the correlation between IL-6 and IL-1b levels in WholeBlood Culture and in the Gengival Crevicula rFluid
https://pubmed.ncbi.nlm.nih.gov/25083039/	Annette Milton, Ajay Bhambal, Preeti Nair	2014	Sialochemical Analysis: Windfall to the Oral Physician (A Hospital-based Clinical Cross-Sectional Study in Depressive Disorders	To investigate the sialochemical variations in healthy and patients with depressive disorders (To compare the qualitative differences of stimulated saliva between healthy individuals and depressed patients. To check for correlation between important biochemical parameters in saliva. To compare these results with other studies and see for differences in the results.)

https://pubmed.ncbi.nlm.nih.gov/24480517/	B. Xie, Y. Chen, S. Zhang, X. Wu, Z. Zhang, Y. Peng, X. Huang	2014	The expression of P2X7 receptors on peripheral blood mononuclear cells in patients with primary Sjögren's syndrome and its correlation with anxiety and depression	To study surface expression of P2X7 receptors (P2X7R) on peripheral blood mononuclear cells (PBMC) in patients with primary Sjögren's syndrome (pSS), and its correlation with anxiety and/or depression.
https://pubmed.ncbi.nlm.nih.gov/16820034/	Breivik T, Gundersen Y, Myhrer T, Fonnum F, Osmundsen H, Murison R, Gjermo P ,von Horsten S, Opstad PK.	2006	Enhanced susceptibility to periodontitis in an animal model of depression: reversed by chronic treatment with the anti-depressant tianeptine	To test the hypothesis that the olfactory bulbectomy model of depression in rats could influence susceptibility to ligature-induced periodontitis, and that chronic treatment with the anti-depressant drug tianeptine could attenuate this effect
https://pubmed.ncbi.nlm.nih.gov/16409252/	Breivik T, Gundersen Y, Osmundsen H, Fonnum F, Opstad PK.	2005	Neonatal dexamethasone and chronic tianeptine treatment inhibit ligature-induced periodontitis in adult rats	To investigated the effects of two different treatment strategies, which have been found to down-regulate the HPA axis, on ligature-induced periodontitis
https://pubmed.ncbi.nlm.nih.gov/37822872/	Carolin Walther, Berit Lieske , Katrin Borof, Simone Kühn, Martin H,Bernd L, Thomas Beikler,Guido Heydeckee, Piotr Kuta, Udo Seedorf , Kristin Spinlera, Jürgen Gallinat , Ghazal Aarabi.	2023	Association between periodontitis and depression severity – A cross-sectional study of the older population in Hamburg	To investigate the association between periodontitis (exposure variable) and depression severity (outcome variable) in an older German population
https://pubmed.ncbi.nlm.nih.gov/30229893/	Chen Wang , Shan Li, Chen Shen , Jing Shan, Yuan Fan	2019	Expression and significance of phosphodiesterase 4B gene in peripheral blood	To investigate the molecular mechanism of mental factors in the development of OLP

			of patients with oral lichen planus	
https://pubmed.ncbi.nlm.nih.gov/28455694/	Cinthya Gomes, Frederico Canato Martinho, Décio Sabbatini Barbosa, Leonardo Santos Antunes, Helvécio Cardoso Corrêa Póvoa, Thiago Hissnauer Leal Baltus, Nayara Rampazzo Morelli , Heber Odebrecht Vargas, Sandra Odebrecht Vargas Nunes, George Anderson, Michael Maes	2017	Increased Root Canal Endotoxin Levels are Associated with Chronic Apical Periodontitis, Increased Oxidative and Nitrosative Stress, Major Depression, Severity of Depression, and a Lowered Quality of Life	To understand the associations among chronic apical periodontitis (CAP), root canal endotoxin levels (lipopolysaccharides,(LPS), O&NS pathways, depressive symptoms, and quality of life
https://pubmed.ncbi.nlm.nih.gov/36644813/	David Martín-Hernández, María Martínez, Javier Robledo-Montaña, Marina Muñoz-Lopez, Leire Virto, Nagore Ambrosio, Maria José Marín, Eduardo Montero, David Herrera, Mariano Sanz, Juan C. Leza, Elena Figuero, Borja García-Bueno	2022	Neuroinflammation related to the blood–brain barrier and sphingosine-1-phosphate in a pre-clinical model of periodontal diseases and depression in rats	To explore the potential mechanisms of neuroinflammation (microglia, blood–brain barrier [BBB] permeability, and the sphingosine-1-phosphate [S1P] pathways) resulting from the association between periodontitis and depression in rats.

https://pubmed.ncbi.nlm.nih.gov/19141055/	F. N. Pekiner, B. Gumru, Y. Demirel, S. Ozbayrak	2009	Burning mouth syndrome and saliva: detection of salivary trace elements and cytokines	To compare the levels of salivary trace elements [magnesium (Mg), zinc (Zn), copper (Cu)] and interleukin (IL)-2 and IL-6, and to search for a correlation between depression/anxiety and salivary trace elements and cytokines in BMS patients and controls.
https://jneuroinflammation.biomedcentral.com/articles/10.1186/s12974-024-03213-5	Javier Robledo-Montaña, César Díaz-García, María Martínez, Nagore Ambrosio, Eduardo Montero, María José Marín, Leire Virto, Marina Muñoz-López, David Herrera, Mariano Sanz, Juan Carlos Leza, Borja García-Bueno, Elena Figuero*† e David Martín-Hernández	2024	Microglial morphological/inflammatory phenotypes and endocannabinoid signaling in a preclinical model of periodontitis and depression	To obtain a deeper understanding of the association between periodontitis and depression, conducting an exten- sive morphological and inflammatory phenotypic analysis of the microglial population.
https://doi.org/10.1016/j.pharep.2018.08.003	Lutiana R. Sim, Soraia Netto, Jaqueline S. Generoso, Renan A. Ceretta, Rodrigo F. Valim, Diogo Dominguini, Monique Michels, Gislaine Z. R, Samira S. Valvassori, Felipe Dal-Pizzol, Tatiana Barichello	2018	Imipramine treatment reverses depressive- and anxiety-like behaviors, normalize adrenocorticotropic hormone, and reduces interleukin-1 in the brain of rats subjected to experimental periapical lesion	To observe anxiety- and depressive-like behavioral in rodent subjected to periapical dental lesion, analyzing (TNF-α), interleukin-1β (IL- 1β), IL-6 and serum levels of adrenocorticotropic hormone (ACTH).

https://pubmed.ncbi.nlm.nih.gov/8910824/	Mark E. Moss, James D. Beck/ Berton H. Kaplan/ Steven Offenbacher, Jane A. Weintraub, Gary G. Koch Robert J. Genco Eli E. Machtet, Lisa A.	1996	Exploratory Case-Control Analysis of Psychosocial Factors and Adult Periodontitis	To explore the role ofpsychosocial factors including social strain, depression, and copingas host factors that influence adult Periodontitis with the use of self-reported questionnaire data
https://pubmed.ncbi.nlm.nih.gov/11205893/	Markus M. Kollera, Karnam R. Purushothamb, Nobuko Maedae, Philip J. Scarpacec, Michael G. Humphreys-Behe	2000	Desipramine induced changes in salivary proteins, cultivable oral microbiota and gingival health in aging female NIA Fischer 344 rats	To assess the effects of the long-term administration of the tricyclic antidepressant desipramine and the reversibility of this treatment following a 15 d washout period on specific salivary proteins, composition of oral microbiota, and oral health (gingivitis) of aging female F344 rats
https://doi.org/10.26477/jbcd.v33i1.2921	Noor A. Al-Bazaz, Nada Jafer MH Radhi	2021	Depression status in relation to dental caries and salivary C- Reactive Protein among 17 years old secondary school female in Baghdad City/Iraq.	To assess the effect of depression status on dental caries among 17 years old secondary school female students in relation to salivary C-Reactive Protein.
https://pubmed.ncbi.nlm.nih.gov/32098025/	Norma Idalia Rodríguez Franco , José Moral de la Rubia, Andrea Guadalupe Alcázar Pizañ	2020	Predictive Model of Clinical Attachment Loss and Oral Health-Related Quality of Life through Depressive Symptomatology, Oral Hygiene Habits, and Proinflammatory Biomarkers: A Pilot Study	To test a predictive model of clinical attachment loss and oral health-related quality of life in a pooled sample of dental patients with periodontitis and mental health patients with depressive symptomatology, and test the invariance of the model across both types of patients

https://pubmed.ncbi.nlm.nih.gov/18329910/	Patrícia Del Vigna de Almeida, Ana Maria Trindade Grégio, João Armando Brancher, Sérgio Aparecido Ignácio, Maria Angela Naval Machado, Antônio Adilson Soares de Lima, Luciana Reis Azevedo	2007	Effects of antidepressants and benzodiazepines on stimulated salivary flow rate and biochemistry composition of the saliva	To evaluate the effect of psychotropics on stimulated salivary flow rate (SSFR), total proteins, urea and calcium concentration, -amylase activity, pH, saliva buffer capacity (SBC), and the prevalence of xerostomia in psychotropic users and its relationship with low SSFR and/or hyposalivation
https://pubmed.ncbi.nlm.nih.gov/32231113/	Pia Lopez-Jornet, Candela Castillo Felipe, Luis Pardo-Marin, Jose J. Ceron, Eduardo Pons-Fuster, Asta Tvarijonaviciute	2020	Salivary Biomarkers and Their Correlation with Pain and Stress in Patients with Burning Mouth Syndrome	To evaluate a panel of salivary analytes involving biomarkers of inflammation, stress, immune system and antioxidant status in patients with burning mouth syndrome (BMS) and to study their relationship with clinical variables.
https://doi.org/10.1155/2022/6447056	Qiang Li ,Yajuan Zhao , Daokun Deng , Jiuhui Yang,3 Yongjin Chen, Jia Liu , Min Zhang	2022	Aggravating Effects of Psychological Stress on Ligature-Induced Periodontitis via the Involvement of Local Oxidative Damage and NF-κB Activation	To elucidate the adverse effects of psychological stress on the inflammatory process and redox status of periodontitis tissue, fifty male Sprague-Dawley rats
https://pubmed.ncbi.nlm.nih.gov/17641729/	Qianming Chen, Juan Xia, Mei Lin, Hongmei Zhou, and Bingqi Li	2007	Serum Interleukin-6 in Patients with Burning Mouth Syndrome and Relationship with Depression and Perceived Pain	To examine alteration of serum interleukin-6 and its clinical significance in burning mouth syndrome (BMS) patients

https://www.jcdr.net/ReadXMLFile.aspx?id=11456	Umamaheswari Giri, Vezhavendhan Nagaraj, Avudaippan Sankaran, R Ramesh, Suganya Rajaram, Sivaramakrishnan Muthanandam, Santhadevy Arumugam, Vidyalakshmi Santhanam	2018	Sialochemical Profile in Depressive Individuals under Antidepressant Therapy	To study the sialochemical alteration in depressive individuals and to compare the effect of antidepressant therapy (selective serotonin reuptake inhibitors-two month course) on the same patients.
https://doi.org/10.1016/j.bbi.2019.07.012	Yi-Xi Wanga, Xiao-Ning Kanga, Yang Caoa, De-Xiu Zhenga, Ye-Ming Lua,b, Chun-Feng Panga,Zhi Wanga, Bin Chenga, Yun Penga.	2019	Porphyromonas gingivalis induces depression via downregulating p75NTR-mediated BDNF maturation in astrocytes	To understand that p. gingivalis is a modifiable risk factor for depression and uncovers a novel therapeutic target for the treatment of depression.
https://pubmed.ncbi.nlm.nih.gov/36738676/	Yingxue Li, Xiaoyue Guan, Yani He, Xiangbin Jia, Lifei Pan, Yuting Wang, Yue Han, Rui Zhao, Jianmin Yang, Tiezhou Hou	2023	ProBDNF signaling is involved in periodontitis-induced depression-like behavior in mouse hippocampus	To mechanistically investigate the regional roles of proBDNF (the precursor of brain-derived neurotrophic factor) in periodontitis induced depression-like behavior in mice.
https://www.nature.com/articles/s41598-024-72297-z	Yonghuan Zhang, Shanfeng Lin, Xuzhuo Chen, Hongbing Lan, Weiqi Li, Li Lin	2024	Association of periodontitis with all-cause and cause-specific mortality among individuals with depression: a population-based study	To detect the association between periodontitis and all-cause as well as cause-specific mortality rates among adults diagnosed with depression

Table S2 below reports additional information, including therapies, diagnostic tools (e.g., questionnaires), neuronal alterations, and specific oral diseases, in order to provide a more detailed contextualization of each study.

Table S2 Supplementary Study Characteristics and Methodological Details

SUPPLEMENTARY DETAILS					
AUTHORS	**STUDY TYPE**	**THERAPIES**	**DIAGNOSTIC TOOLS**	**NEURONAL ISSUES**	**ORAL PATHOLOGY or ISSUE**
Al-Bazaz et al., 2021	Cross-sectional observational study	NA	Children Depression Inventory (CDI) questionnaire to assess depression Dental examinationusing the Decay (1-4) Missing-Filled Surface (DMFS) index	Psychological stress and depression	Dental caries , oral complications
Almeida et al., 2007	clinical studi cross sectional	Newer psychotropic medications (SSRIs)	NA	Antidepressants and benzodiazepines	Xerostomia
Barry et al., 2018	Clinical-pilot study	NA	Visual analogue scale (VAS) for pain intensity 16-item Quick Inventory of Depressive Symptomatology (QIDS-SR16) for depressive symptomatology	Depression	Oral cavity pain, BMS
Breivik et al., 2006	Animal study (Experimental, Preclinical study)	Tianeptine	Open field test (to assess behavioral responses to stress	Stress and depression	Periodontitis

Breivik T et al., 2005	Animal study , in vivo	Neonatal dexamethasone and chronic tianeptine	NA	Stress	Periodontitis
Chen et al., 2007	ross-sectional observational study	NA	Hamilton Rating Scale for Depression (HRSD) → Assessment of depressive symptoms Visual Analogue Scale (VAS) → Measurement of pain levels	Depression and chronic pain	BMS
Franco et al., 2020	Observational cross-sectional study	NA	Self-report scales for assessing depression, oral health-related quality of life (OHRQoL), and oral hygiene habits Clinical examination → Measurement of clinical attachment loss (CAL)	Depression (mental health patients with depressive symptomatology)	Oral Hygiene and periodontitis
Giri et al., 2018	Case control	NA	Hospital Anxiety and Depression Scale (HADS)	Depression	Salivary issues
Gomes et al., 2017	Case control study	NA	Questionnair of sociodemographic (data, smoking history, and data on family history of psychiatric disease) and Beck Depression Inventory	Psychological, environmental and social domains affected, depression	Periodontitis Apical cronica
Hernández et al., 2022	Animal study , in vivo	NA	NA	Depression and cronic mild stress (CMD)	Periodontitis

Johannsen et al., 2007	Clinical study (Cross-sectional observational study)	NA	Clinical periodontal examination (pocket depth, gingival inflammation)+ Diagnostic and Statistical Manual for Mental Disorders	Chronic stress and depression	Oral hygiene / gingival inflammation / periodontal pocket stauts
Jornet et al., 2020	Cross sectional study	NA	Visual analogue scale (VAS), the Hospital Anxiety and Depression (HAD) score and the Oral Health Impact Profile-14 (OHIP14) score.	Anxiety and depression	BMS
Kollera et al., 2000	Animal study , in vivo	Desipramine	Oral microbiota composition assessment Clinical evaluation of gingivitis	Depression	Oral microbiota,salivary gland dysfunction (oral dryness, xerostomia)
Li et al., 2022	Preclinical experimental study, animal in vivo study	NA	NA	Chronic unpredictable mild stress (CUMS)	Periodontitis and toooth loss
Li et al., 2023	Animal study , in vivo	NA	NA	Depression	Periodontitis
Lutiana et al., 2018	Animal study , in vivo	Imipramine	Behavioral tests,	Anxiety, Depression-like behavior, Anhedonia	Periapical lesions, periodontitis
Milton et al., 2014	Cross-sectional clinical study	CAs, SSRIs and TeCAs)	NA	Depression	Personal hygiene, salivary health
Moss et al., 1996	cohort study	NA	Daily Strains Scale+ The Brief Symptom Inventory-an abbreviated version of the SCL-90-R-was used to measure psychological dis tress	Stress	Periodontitis

Oliveira Solis et al., 2015	Clinical study (case-control study)	NA	NA	Depression	Periodontitis
Pekiner et al., 2009	Clinical study case control	NA	Spielberger State-Trait Anxiety Inventory (SAI-TAI) Zung Self-Rating Depression Scale	Psychological distress	BMS
Robledo-Montaña et al., 2024	Animal study, in vivo	NA	NA	Mild chronic stress (CMS)	Periodontitis
Sebastiani et al., 2020	Transversal study	NA	14-item Oral Health Impact Profile (OHIP-14).	Depression, stress and psychological discomfor	Temporomandibular disorders (TMD), dentofacial deformity (DFD)
Walther et al., 2023	Prospective cohort study	NA	Clinical periodontal examination (probing depth, gingival recession, plaque index, bleeding on probing) Depression assessment using the 9-item Patient Health Questionnaire (PHQ-9)	Depression	Periodontitis
Wang et al., 2019	Case control study	NA	Zung self-rating anxiety scale and self-rating depression scale (SAS & SDS)	Anxiety anddepression	OLP
Wanga et al., 2019	Animal study , in vivo	The Pg-LPS/TLR4 pathway affecting p75NTR and BDNF	Behavioral analysis: To assess depression-like behavior in mice	Stress	Periodontitis due to *P.gingivalis* exposure

Xie et al., 2014	Clinical and experimental	NA	Hamilton Anxiety Rating Scale (HAMA), Hamilton Rating Scale for Depression HRSD	Anxiety, Depression	Primary Sjögren's syndrome (pSS)→xerostomia
Zhang et al., 2024	Cohort study	NA	National Health and Nutrition Examination Survey (NHANES)	Depression	Periodontitis