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INFLUENCE OF HUMAN EVOLUTION ON SUSCEPTIBILITY TO CHRONIC INFLAMMATORY ORAL DISEASES

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Figure 1 – Graphic abstract: Evolutionary Mismatch and the Emergence of Periodontal Disease

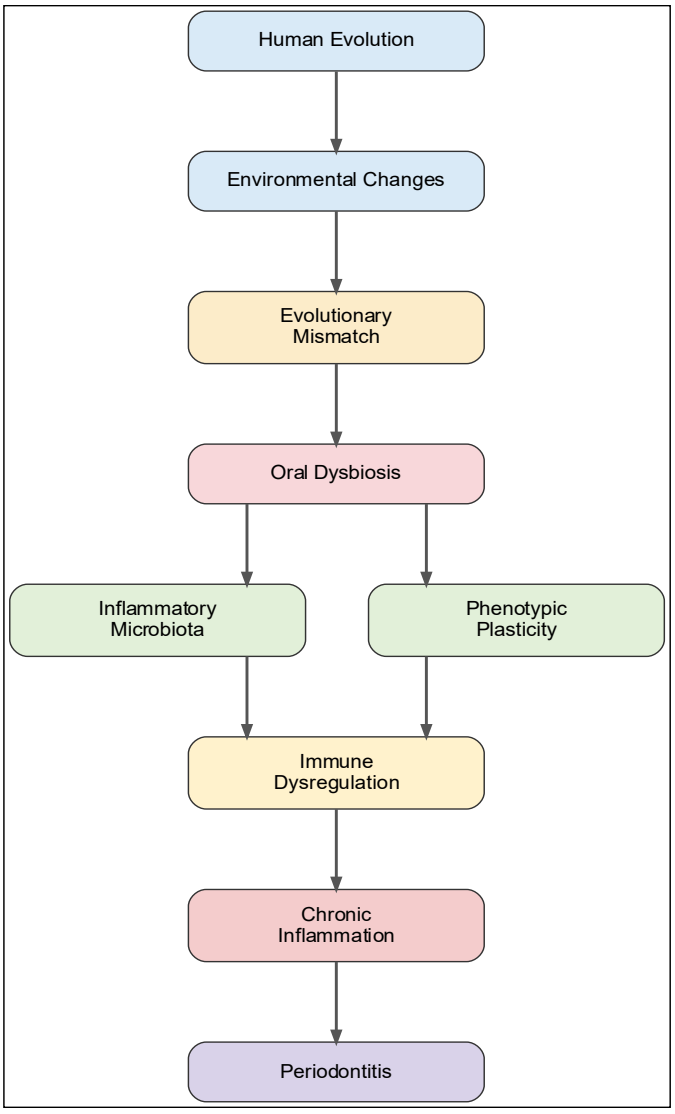

Figure 1. Environmental and behavioral changes associated with modern human lifestyles may create a mismatch between ancestral biological adaptations and current conditions, favoring oral microbial dysbiosis, enhanced inflammatory responses, immune dysregulation, and chronic inflammation, which contribute to the development and progression of periodontitis.

ABSTRACT: Periodontitis is a multifactorial chronic inflammatory disease resulting from the interaction among the oral microbiota, host immune response, genetic susceptibility, and environmental factors. Although traditionally associated with specific pathogenic microorganisms, growing evidence indicates that its pathogenesis is driven by ecological and evolutionary processes involving microbial dysbiosis and host adaptation to environmental changes. This narrative review aimed to analyze the influence of human evolution on susceptibility to chronic inflammatory oral diseases, with particular emphasis on periodontitis. A literature search was conducted in the PubMed, Scopus, and Google Scholar databases, including studies published between 2014 and 2025 addressing human evolution, the oral microbiome, host–microorganism coevolution, immune response, and periodontal inflammation. The analyzed evidence indicates that periodontal susceptibility results from the dynamic interaction among microbial adaptations, evolutionarily conserved immune mechanisms, and environmental changes associated with modern lifestyles. Mechanisms such as inflammophilic microbiota, bacterial phenotypic plasticity, and evolutionary mismatch contribute to the establishment of dysbiosis, the persistence of chronic inflammation, and the progression of periodontal disease. Overall, adopting an evolutionary perspective expands the traditional pathogen-centered model of periodontitis and provides a broader framework for understanding its biological mechanisms, with potential implications for future preventive, diagnostic, and therapeutic strategies.

Keywords: Dysbiosis; Human Evolution; Oral microbiome; Periodontal inflammation; Periodontitis.

1 INTRODUCTION

Chronic inflammatory oral diseases, particularly periodontitis, represent major public health concerns due to their high prevalence and the functional and systemic impacts associated with the loss of periodontal support. Traditionally, periodontitis was primarily understood as an infectious disease caused by the accumulation of bacterial biofilm. However, recent studies have demonstrated that its progression involves a complex interaction among the oral microbiota, host immune response, genetic factors, and environmental conditions (HAJISHENGALLIS, 2015; KINANE *et al*., 2017; WEYRICH, 2021).

Evidence from molecular anthropology and paleomicrobiology indicates that the composition of the human oral microbiome has undergone significant modifications throughout evolution. Studies based on the analysis of archaeological dental calculus demonstrate that prehistoric populations exhibited a microbiome predominantly associated with eubiosis and apparently lower occurrence of periodontitis compared with contemporary populations. These findings suggest that the evolution of the oral microbiome occurred alongside the biological and behavioral changes that shaped the evolutionary history of the human species (SHANMUGASUNDARAM *et al*., 2024).

In this context, evolutionary theory has contributed to expanding the understanding of the mechanisms involved in chronic periodontal diseases. Host–microorganism coevolution has enabled the development of microbial adaptations that promote bacterial persistence within inflammatory environments, while human immune mechanisms originally selected for protection against infections may become dysregulated and contribute to excessive inflammatory responses in chronic conditions (NAGASAWA *et al*., 2014; CHEN, 2019).

Recent studies further support this perspective by demonstrating that periodontitis pathogenesis results from the ability of specific pathobionts, particularly *Porphyromonas gingivalis*, to modulate the expression of virulence-related genes in response to environmental and host immune conditions. This phenotypic plasticity represents an important evolutionary adaptation, promoting bacterial persistence, immune evasion, and the maintenance of the dysbiotic state characteristic of periodontal disease (SHARAF; HIJAZI, 2023).

The Agricultural Revolution and, subsequently, the Industrial Revolution represented major milestones in the modification of the human oral ecosystem. The increased availability of foods rich in refined carbohydrates, combined with lifestyle changes and greater exposure to modern environmental factors, promoted alterations in oral microbiome composition, contributing to increased dysbiosis and a higher prevalence of periodontitis in contemporary populations (SHANMUGASUNDARAM *et al*., 2024).

The composition of the oral microbiome is influenced by factors such as diet, smoking, alcohol consumption, systemic conditions, and lifestyle, reinforcing the multifactorial nature of periodontitis (RAJASEKARAN *et al*., 2024). These modern lifestyle-related factors have also modified the interaction between the host and the oral microbiota. Within this framework, the concept of evolutionary mismatch describes the incompatibility between biological adaptations selected in ancestral environments and the conditions of contemporary environments, increasing susceptibility to chronic inflammatory diseases, including periodontitis (GANCZ; WEYRICH, 2023).

Simultaneously, advances in molecular microbiology techniques and next-generation sequencing have expanded the understanding of periodontal etiopathogenesis, demonstrating that the disease does not result from the isolated action of a single microorganism, but rather from the disruption of the ecological balance of the oral microbiome. Therefore, contemporary models emphasize microbial dysbiosis and interactions among bacterial communities and host immune responses, gradually replacing the classical infectious model with an ecological and evolutionary perspective of periodontitis (MANOIL *et al*., 2024).

From this perspective, periodontitis is understood as a multifactorial disease whose development results from the dynamic interaction among evolutionary, microbiological, immunological, and environmental factors. This approach expands the understanding of the biopathological mechanisms underlying the disease and provides a basis for the development of more targeted preventive and therapeutic strategies. Therefore, understanding the influence of human evolution on susceptibility to chronic inflammatory oral diseases allows for a broader biopathological perspective of periodontitis, extending beyond the classical infectious model. Thus, the present study aimed to analyze the relationship between evolutionary mechanisms, oral microbiota, and immune responses in susceptibility to chronic inflammatory oral diseases.

2 METHODS

This study is a narrative literature review conducted to analyze the influence of human evolution on susceptibility to chronic inflammatory oral diseases, with particular emphasis on periodontitis.

A literature search was conducted in the PubMed, Scopus, and Google Scholar databases using combinations of the following English keywords: *periodontitis*, *oral microbiome*, *oral dysbiosis*, *host–microbial coevolution*, *human evolution*, *evolutionary mismatch*, *immune response*, *periodontal inflammation*, and *periodontal disease*. The descriptors were combined using the Boolean operators AND and OR, according to the search strategy adopted for each database.

Studies published between 2014 and 2025 were considered eligible if they were available in full text, written in English, and addressed evolutionary mechanisms related to susceptibility to chronic inflammatory oral diseases. Preference was given to original research articles, systematic reviews, and narrative reviews investigating interactions among the oral microbiota, host immune response, genetic factors, and environmental changes associated with human evolution.

Studies focusing exclusively on the clinical management or treatment of periodontitis without discussing evolutionary mechanisms were excluded, as were duplicate publications, conference abstracts, letters to the editor, and articles without full-text availability.

The retrieved studies were screened by title, abstract, and full-text reading. Their selection was based on relevance to the objectives of this review and their contribution to understanding the evolutionary mechanisms involved in susceptibility to chronic inflammatory

oral diseases. The selected evidence was synthesized narratively, and the principal studies are summarized in Table 1.

3 DISCUSSION

The findings synthesized in this review indicate that susceptibility to chronic inflammatory oral diseases cannot be explained solely by the presence of pathogenic microorganisms but rather by the complex interaction among the oral microbiota, host immune response, genetic susceptibility, and environmental factors shaped throughout human evolution. Accordingly, periodontitis should no longer be viewed exclusively as a localized infectious disease but as the outcome of biological processes driven by evolutionary interactions between the host and the oral microbiota (NAGASAWA *et al*., 2014; HAJISHENGALLIS *et al*., 2015).

Table 1 summarizes the main studies included in this review, highlighting their principal findings and their contributions to understanding how evolutionary mechanisms influence susceptibility to chronic inflammatory oral diseases.

TABLE 1 (1/2) – Main selected studies and their contributions to understanding the influence of human evolution on susceptibility to chronic inflammatory oral diseases.

AUTHOR/YEAR	MAIN FINDINGS	RELATIONSHIP WITH PERIODONTAL SUSCEPTIBILITY
NAGASAWA *et al*., 2014	Host–microorganism coevolution	Promotes bacterial adaptations associated with the persistence of periodontal inflammation
HAJISHENGALLIS *et al*., 2014	Inflammophilic microbiota	Selection of bacteria adapted to inflammatory environments, contributing to dysbiosis
HAJISHENGALLIS *et al*., 2015	Subversion of the immune response by the periodontal biofilm	Maintenance of chronic inflammation and progression of periodontal disease
WANG, 2015	Functional signatures of dysbiosis during periodontitis progression	Demonstrates that functional alterations in the microbiome promote oral ecological imbalance and periodontal disease progression
KINANE *et al*., 2017	Influence of genetic factors on host response	Individual modulation of susceptibility and intensity of the inflammatory response

Source: Research data (2026).

TABLE 1 (2/2) – Main selected studies and their contributions to understanding the influence of human evolution on susceptibility to chronic inflammatory oral diseases.

AUTHOR/YEAR	MAIN FINDINGS	RELATIONSHIP WITH PERIODONTAL SUSCEPTIBILITY
PAN; WANG; CHEN, 2019	Role of pro-inflammatory cytokines	Amplification of tissue damage and periodontal bone resorption
PEREIRA *et al*., 2019	Antagonistic pleiotropy of the APOE gene and its relationship with periodontal diseases and atherosclerosis	Suggests that genetic variants selected throughout evolution may influence individual susceptibility to periodontal inflammation
HIRSCHFELD, 2020	Role of neutrophils in the periodontal immune response	Alterations in neutrophil function promote inflammation and periodontitis progression
GANCZ; WEYRICH, 2023	Oral microbiome alterations associated with evolutionary mismatch	Influence of environmental and dietary changes on periodontal susceptibility
SHARAF; HIJAZI, 2023	Phenotypic plasticity and virulence modulation mechanisms in *Porphyromonas gingivalis* and other periodontal pathobionts	Promotes bacterial persistence, immune evasion, and maintenance of periodontal dysbiosis
MANOIL *et al*., 2024	Advances in microbial diagnosis and consolidation of the ecological model of periodontitis based on dysbiosis	Demonstrates that the disease results from interactions between microbial communities and host immune responses rather than from the action of a single pathogen
ASHRAF *et al*., 2025	Use of microRNAs and aptamers as biomarkers for early diagnosis of periodontitis	Highlights molecular mechanisms associated with inflammatory responses and perspectives for early diagnosis and disease monitoring
TANG, 2025	Role of pyroptosis and necroptosis in periodontitis	Intensification of inflammatory responses and periodontal tissue destruction

Source: Research data (2026).

Collectively, the evidence indicates that susceptibility to chronic inflammatory oral diseases arises from the interplay among microbiological, immunological, genetic, and environmental factors. Mechanisms including host–microorganism coevolution, oral microbiota dysbiosis, interindividual variability in immune responses, and environmental changes associated with human evolution collectively help explain differences in individual susceptibility, disease onset, and the progression of periodontitis.

FIGURE 2 – Proposed model illustrating how evolutionary mismatch contributes to oral dysbiosis, immune dysregulation and periodontitis susceptibility.

Source: Elaborated by the author (2026) with the assistance of the Python programming language.

The coevolutionary relationship between humans and periodontopathogenic bacteria provides an important framework for understanding periodontal susceptibility. Host–microorganism coevolution has promoted the development of adaptive mechanisms that enhance bacterial persistence within the periodontal environment, indicating that periodontitis is better understood as the result of long-term biological interactions rather than merely the consequence of the presence of specific pathogens (NAGASAWA *et al*., 2014).

This evolutionary perspective is further supported by the findings of SHARAF and HIJAZI (2023), who demonstrated that *Porphyromonas gingivalis* exhibits remarkable phenotypic plasticity, dynamically modulating the expression of virulence-associated genes in response to environmental cues and host immune conditions. Such adaptive capacity favors microbial persistence, facilitates immune evasion, and contributes to the maintenance of dysbiosis, highlighting the role of microbial evolution in the pathogenesis and progression of periodontitis.

Another key concept emerging from the analyzed studies is the inflammophilic nature of the periodontal microbiota. Rather than merely tolerating inflammatory environments, specific bacterial communities are capable of exploiting inflammation as a selective advantage. HAJISHENGALLIS *et al.* (2014; 2015) proposed that inflammation alters nutrient availability and creates ecological conditions that favor the proliferation of microorganisms adapted to these environments, thereby sustaining microbial dysbiosis. Consequently, a self-perpetuating feedback loop is established, in which inflammation promotes shifts in microbial composition, while the dysbiotic microbiota further amplifies the host inflammatory response.

This ecological perspective has been reinforced by recent advances in periodontal microbiology. MANOIL *et al.* (2024) emphasized that developments in next-generation sequencing and metagenomic analyses have shifted the understanding of periodontitis from a pathogen-centered model to one based on microbial ecology, in which disease results from functional disruption of the microbial community and its interactions with the host immune system. Consistent with this concept, WANG (2015) demonstrated that functional alterations within the oral microbiome drive ecological imbalance and contribute to periodontal disease progression, further supporting dysbiosis as a central mechanism in the etiopathogenesis of periodontitis.

In addition to microbiological factors, interindividual variability in the host immune response represents another key determinant of periodontal susceptibility. KINANE *et al.* (2017) emphasized that genetic factors directly influence the magnitude of inflammatory responses to microbial challenges, contributing to differences in disease susceptibility and progression among individuals. From an evolutionary perspective, this variability may be partly explained by mechanisms such as antagonistic pleiotropy. PEREIRA *et al.* (2019) suggested that variants of the *APOE* gene, particularly the *APOE4* allele, may have conferred adaptive advantages under ancestral environmental conditions despite being currently associated with an increased susceptibility to chronic inflammatory diseases.

The importance of host immune regulation is further highlighted by the role of innate immune cells, particularly neutrophils, in maintaining periodontal homeostasis and controlling bacterial biofilms. HIRSCHFELD (2020) demonstrated that alterations in neutrophil function compromise immune homeostasis, favor persistent inflammation, and contribute to periodontal tissue destruction. Together, these findings reinforce that individual susceptibility to periodontitis depends not only on microbial composition but also on genetically and evolutionarily influenced variations in the host immune response.

Within this framework, pro-inflammatory cytokines play a central role in linking host defense to periodontal tissue destruction. Cytokines such as IL-1β, TNF-α, and IL-6 are essential components of the innate immune response against microbial challenges; however, their persistent production promotes connective tissue degradation and amplifies periodontal inflammation (PAN; WANG; CHEN, 2019). This dual role illustrates an important evolutionary paradox, in which immune mechanisms originally selected to protect the host become detrimental when chronically activated, a hallmark of chronic inflammatory diseases.

The sustained inflammatory response also promotes molecular events associated with periodontal tissue breakdown and alveolar bone loss. Persistent immune activation increases the expression of receptor activator of nuclear factor kappa-B ligand (RANKL), a key regulator of osteoclast differentiation and activity, thereby intensifying alveolar bone resorption, one of the defining features of advanced periodontitis. Consequently, biological pathways that were evolutionarily conserved to control infections may inadvertently contribute to tissue destruction under chronic inflammatory conditions, reinforcing the role of host immune dysregulation in periodontal disease progression (PAN; WANG; CHEN, 2019; KINANE *et al.*, 2017).

Environmental changes throughout human history represent another important factor influencing periodontal susceptibility. The transition from hunter-gatherer societies to agricultural and, later, industrialized populations profoundly altered dietary patterns, lifestyle, and consequently the composition of the oral microbiota. GANCZ; WEYRICH (2023) argued that modern diets rich in processed carbohydrates have favored microbial shifts associated with dysbiosis and periodontal inflammation. These findings support the concept of evolutionary mismatch, whereby biological adaptations that evolved under ancestral environmental conditions are no longer fully compatible with contemporary lifestyles, increasing susceptibility to chronic inflammatory diseases such as periodontitis.

Despite the growing body of evidence supporting an evolutionary perspective of periodontitis, most available studies are observational, experimental, or theoretical, limiting the establishment of direct causal relationships between evolutionary mechanisms and disease susceptibility. Furthermore, the complexity of host–microbiome interactions and the influence of contemporary environmental factors make it challenging to isolate the contribution of evolutionary processes. Future multidisciplinary studies integrating evolutionary biology, genomics, and longitudinal microbiome analyses are needed to strengthen this conceptual framework.

The evidence discussed thus far indicates that susceptibility to chronic inflammatory oral diseases arises from the dynamic interaction among microbial adaptations, host immune

mechanisms, and environmental changes that have accompanied human evolution. More recently, studies investigating regulated cell death pathways have further expanded the understanding of periodontal pathogenesis. TANG (2025) demonstrated that pyroptosis and necroptosis actively contribute to the amplification of inflammatory responses and periodontal tissue destruction. Because these mechanisms are evolutionarily conserved, their involvement in periodontitis reinforces the concept that ancestral biological processes continue to influence host inflammatory responses under contemporary environmental conditions.

Advances in molecular biology have also broadened the understanding of periodontitis beyond its pathogenic mechanisms by providing new opportunities for early diagnosis and disease monitoring. ASHRAF *et al.* (2025) highlighted that microRNAs detected in saliva and gingival crevicular fluid act as important regulators of immune responses and periodontal homeostasis, reflecting molecular alterations associated with inflammation before the onset of clinical manifestations. These findings suggest that molecular biomarkers may contribute to the early identification of periodontitis and improve disease monitoring, complementing the evolutionary and immunological perspectives discussed throughout this review.

Collectively, the evidence synthesized in this review supports a broader interpretation of periodontitis as a multifactorial disease shaped by the dynamic interaction among microbial adaptation, evolutionarily conserved immune mechanisms, genetic susceptibility, and environmental changes throughout human history. Rather than representing solely an infectious condition, periodontitis should be understood as the outcome of long-term interactions between the host and the oral microbiota under changing environmental conditions. This evolutionary perspective expands the traditional pathogen-centered model and provides a conceptual framework for future advances in prevention, diagnosis, and personalized periodontal care (HAJISHENGALLIS, 2015; KINANE *et al.*, 2017; GANCZ; WEYRICH, 2023).

4 FINAL CONSIDERATIONS

The present review demonstrated that susceptibility to chronic inflammatory oral diseases, particularly periodontitis, results from the complex interaction among the oral microbiota, host immune responses, and adaptive mechanisms shaped throughout human evolution.

The analyzed evidence indicates that processes such as host–microorganism coevolution, microbial adaptation to inflammatory environments, and evolutionary mismatch

contribute to the establishment of oral dysbiosis, the persistence of chronic inflammation, and the progression of periodontal disease.

Despite the growing body of evidence supporting this evolutionary perspective, studies directly investigating the relationship between human evolution and chronic inflammatory oral diseases remain limited, with the available literature consisting predominantly of observational and theoretical studies. Therefore, future research integrating molecular biology, genomics, microbiome analysis, and evolutionary biology is needed to further clarify the mechanisms underlying periodontal susceptibility and to support the development of more precise preventive, diagnostic, and therapeutic strategies.

Overall, the evidence synthesized in this review supports an evolutionary framework for understanding periodontitis. Rather than representing solely an infectious disease, periodontitis should be interpreted as the outcome of long-term interactions among microbial adaptation, host immune regulation, genetic susceptibility, and environmental changes throughout human history. This integrated perspective expands the traditional pathogen-centered model and may contribute to future advances in precision prevention, early diagnosis, and personalized periodontal care.

CONFLICT OF INTEREST

The author declares that there are no conflicts of interest related to this study.

DATA AVAILABILITY STATEMENT

No original datasets were generated or analyzed during this study. All information supporting the findings is contained within the manuscript and is based on published literature.

ARTIFICIAL INTELLIGENCE USE STATEMENT

Artificial intelligence tools were used exclusively to assist in the generation of the figures through code executed in the Python environment on Google Colab. No artificial intelligence tools were used to generate, interpret, or analyze the scientific content of this manuscript. The author is solely responsible for the study conception, manuscript writing, revision, and final version of the work.

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