J Oral Res
research in oral sciences

REVIEW

ASSOCIATION OF PERIODONTITIS AND HEPATOCELLULAR CARCINOMA: A SYSTEMATIC EXPLORATORY REVIEW

Asociación entre Periodontitis y Carcinoma Hepatocelular: una Revisión Sistemática Exploratoria

Valentina Gallardo,[1] Constanza Gómez,[1] Dominga Rivera,[2] Karen Kasztan,[2] Alejandra Fernández,[1,2] Constanza Jiménez.[1,2]

Received: December 12, 2025. | **Accepted:** January 26, 2026. | **Published online:** September 23, 2026.

ABSTRACT

Introduction: Periodontitis is a highly prevalent oral disease characterized by chronic inflammation and microbial dysbiosis. Hepatocellular carcinoma (HCC) is the most common primary liver cancer worldwide. Emerging evidence suggests a potential association between these diseases; however, current evidence remains scarce and fragmented. **Objective:** To systematically map and synthesize the available human evidence regarding the association between periodontitis and HCC.

Materials and Methods: A scoping review was conducted following the Joanna Briggs Institute guidelines. Electronic searches were performed across *PubMed, Scopus, Web of Science, Cochrane library*, and *OVID databases*. Eligibility was restricted to primary human studies.

Results: six studies met the inclusion criteria. Epidemiological findings regarding initiation risk were inconsistent. Conversely, clinical and microbiological studies converged on a plausible association of periodontitis with HCC progression and severity. Overall, HCC patients exhibited reduced oral immunity and microbial diversity, with enrichment of specific pathogens such as *Fusobacterium nucleatum, Porphyromonas gingivalis* and Cyanobacteria. Furthermore, periodontitis was clinically associated with advanced HCC staging, and increased serum reactive oxygen metabolites, indicating synergistic oxidative burden.

Conclusions: While epidemiological evidence on periodontitis as a risk factor for HCC remains conflicting, growing clinical research supports periodontitis may contribute to HCC progression and severity. Further longitudinal and mechanistic research are needed to clarify this relationship, explore its underlying mechanisms, and determine its implications for cancer prevention and multidisciplinary care.

Keywords: *Periodontitis; Hepatocellular carcinoma; Association; Risk factor; Immunity; Systematic review*

1. Department of Oral Medicine and Pathology, Faculty of Dentistry, Universidad Andres Bello, Santiago, Chile.
2. Dermoral, Laboratory of Translational Dentistry, Faculty of Dentistry, Universidad Andres Bello, Santiago, Chile.

Corresponding Author:
Constanza Jiménez. Department of Oral Medicine and Pathology, Faculty of Dentistry, Universidad Andres Bello, Echaurren 237, Santiago, Chile. **Phone:** (+56-9) 95095269. **E-mail:** c.jimenezlizama@uandresbello.edu

Gallardo V, Gómez C, Rivera D, Kasztan K, Fernández A & Jiménez C. Association of Periodontitis and Hepatocellular Carcinoma: a Systematic Exploratory Review. J Oral Res. 2026; 15(1):192-211. https://doi.org/ 10.17126/joralres.2026.016

ISSN Print 0719-2460 - ISSN en línea 0719-2479

RESUMEN

Introducción: La periodontitis es una enfermedad oral altamente prevalente, caracterizada por inflamación crónica y disbiosis microbiana. El carcinoma hepatocelular (CHC) es el cáncer primario de hígado más frecuente del mundo. Evidencia emergente sugiere una posible asociación entre ambas enfermedades; no obstante, la evidencia disponible es limitada y fragmentada. **Objetivo:** Mapear y sintetizar sistemáticamente la evidencia humana disponible sobre la asociación entre periodontitis y CHC.

Materiales y métodos: Se realizó una revisión de alcance siguiendo las directrices del Instituto Joanna Briggs. Se efectuaron búsquedas electrónicas en las bases de datos *PubMed, Scopus, Web of Science, Cochrane Library* y *OVID*. Se incluyeron únicamente estudios primarios en humanos.

Resultados: Seis estudios cumplieron con los criterios de inclusión. Los hallazgos epidemiológicos sobre riesgo de inicio fueron contradictorios. Los análisis clínicos y microbiológicos coincidieron en una posible asociación entre periodontitis y la progresión y severidad del CHC. En general, los pacientes con CHC mostraron una inmunidad oral reducida y menor diversidad bacteriana, con enriquecimiento de patógenos específicos como *Fusobacterium nucleatum, Porphyromonas gingivalis* y Cianobacterias. Además, la periodontitis se asoció con CHC de mayor severidad y mayores niveles séricos de metabolitos reactivos del oxígeno, sugiriendo mayor carga oxidativa sistémica.

Conclusión: Si bien la evidencia epidemiológica de la periodontitis como factor de riesgo para CHC sigue siendo contradictoria, estudios clínicos recientes respaldan que la periodontitis podría contribuir a la progresión y severidad del CHC. Se requieren más estudios longitudinales y mecanísticos para dilucidar la naturaleza de esta relación y explorar sus implicancias en la prevención del cáncer y su abordaje multidisciplinario.

Palabras clave: *Periodontitis; Carcinoma hepatocelular; Asociación; Factor de Riesgo; Inmunidad; Revisión sistemática*

INTRODUCTION

Periodontitis is a highly prevalent chronic inflammatory oral disease initiated by microbial dysbiosis and sustained by a dysregulated host immune response, resulting in irreversible destruction of the periodontal attachment apparatus.[1] It is one of the leading causes of tooth loss worldwide.[2,3] In Chile, more than 90% of adults are affected, with periodontal tissue damage accumulating progressively over time.[3] Clinically, periodontitis is characterized by bleeding on probing (BOP), loss of the clinical attachment level (CAL), periodontal pocket formation, and alveolar bone resorption, the latter typically identified radiographically as marginal bone resorption.[4,5] From an etiopathogenic perspective, periodontitis begins with the formation of an acquired pellicle, a thin film of salivary proteins that coats the tooth surfaces, followed by bacterial adhesion, colonization, and subsequent biofilm formation.[2] Over time, the biofilm undergoes dysbiotic shifts, favoring the predominance of periodontal pathogens such as *Porphyromonas gingivalis*.

These microorganisms trigger a persistent and dysregulated host inflammatory response, ultimately leading to progressive destruction of the periodontal supporting tissues.[2]

Beyond its oral manifestations, periodontitis has been associated with an increased risk of several systemic diseases (e.g., diabetes mellitus, cardiovascular disease, and chronic kidney disease), as well as with certain cancers.[6,7] Epidemiological evidence suggests that individuals with periodontitis may have a two- to five-fold higher risk of developing cancer compared with periodontally healthy counterparts.[8] In addition, periodontal pathogens such as *P. gingivalis* and *Fusobacterium nucleatum* have demonstrated carcinogenic potential, which may contribute to tumorigenesis and further amplify cancer risk in affected individuals.[9]

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and the third leading cause of cancer-related mortality worldwide, representing a major global public health challenge.[10] Its development is multifactorial, with well-established risk factors, including diabetes mellitus, chronic viral hepatitis (B, C, and D), excessive alcohol consumption, cirrhosis, exposure to aflatoxin B1, non-alcoholic fatty liver disease (NAFLD), and metabolic syndrome.[11] Among these, cirrhosis remains the strongest and most consistent predictor of HCC development.[12] Prognosis is generally poor, largely because most cases are diagnosed at advanced stages when treatment options are limited and less effective.[13]

Emerging evidence indicates a potential association between periodontitis and HCC, likely mediated by mechanisms involving chronic low-grade systemic inflammation, the oral-gut-liver axis, and overproduction of reactive oxygen species (ROS).[14]

More recently, research has turned to the prospective role of microRNAs (miRNAs), which regulate key biological processes in both diseases. In periodontitis, MiRNAs contribute to tissue homeostasis, bone resorption, and immune responses,[14-17] while in cancer, they influence tumorigenesis by either promoting or inhibiting tumor suppressors and oncogenes.[18]

To explore shared molecular pathways, recent bioinformatic analyses have constructed competing endogenous RNA networks between both diseases. Notably, one such analysis identified three crosstalk genes common to both periodontitis and HCC.[19] These genes participated in immune modulation, cell cycle regulation, and liver metabolism; serving as potential prognostic biomarkers for HCC.[19] However, despite these insights, the biological mechanisms linking periodontitis and HCC remain poorly understood. Current evidence is limited and fragmented, underscoring the need for a comprehensive synthesis.

Therefore, this exploratory scoping review aimed to systematically map and synthesize the available human evidence on the association between periodontitis and HCC.

MATERIALS AND METHODS

Protocol and registration

The protocol for this scoping review was reviewed and approved by Ethics and Scientific Committee at the Faculty of Dentistry,

Universidad Andres Bello, Santiago, Chile (Approval 08-2024 #PROPRGFO_2024_66).

The study was conducted in accordance with the Joanna Briggs Institute (JBI) manual for Evidence Synthesis, specifically the chapter on scoping reviews.[20]

The complete protocol is publicly available on the Open Science Framework platform (available at: *https://osf.io/u9nz6/overview*).

Research question

The guiding research question was: *"What human evidence exists in the scientific literature regarding the association between periodontitis and HCC?"*

Eligibility criteria

Eligibility criteria were defined using the Population/Concept/Context (PCC) framework.

1. **Population:** Primary human studies involving participants of any age or sex with periodontitis and/or HCC.
2. **Concept:** Studies reporting epidemiological or clinical evidence addressing the association between periodontitis and HCC.
3. **Context:** All clinical and population-based settings, without restrictions by geographic location, language or publication date.

Only primary human studies were eligible for inclusion. Animal studies, *in vitro* experiments, and bioinformatics analyses were excluded from results and considered solely supporting mechanistic evidence in the discussion.

Exclusion criteria included

(a) non-primary publications (e.g., reviews, editorials, letters to the editor, conference abstracts, etc.), (b) studies not explicitly addressing the association between periodontitis and HCC, (c) studies lacking a clearly defined methodology, and (d) studies for which the full text was unavailable.

Information sources and electronic literature search

A systematic literature search was performed across *PubMed, SCOPUS, Web of Science (WOS), Cochrane Library*, and *OVID* from March to May 2024. The search was updated in January 2026 prior to resubmission. Final search strategies incorporated appropriate Medical Subject Headings and were adapted for each database:

1. **PubMed:** (*"Periodontitis"* [Mesh] OR *"Periodontitis"* [All]) AND (*"Carcinoma, Hepatocellular"* [Mesh] OR *"Carcinoma, Hepatocellular"* [All]).
2. **Scopus:** TITLE-ABS-KEY (*periodontitis*) AND TITLE-ABS-KEY (*carcinoma, hepatocellular*).
3. **WOS:** (ALL=(*periodontitis*)) AND ALL= (*carcinoma, hepatocellular*).
4. **Cochrane Library:** ([mh *Periodontitis*] OR *Periodontitis*) AND ([mh *"Carcinoma, Hepatocellular"*] OR *"Carcinoma, Hepatocellular"*).
5. **OVID:** (*Periodontitis* and *Carcinoma, Hepatocellular*). *af.*

Selection of sources of evidence

Records were imported into Rayyan for screening (https://www.rayyan.ai/). Two reviewers (V.G., C.G.) independently screened titles, abstracts, and full texts against eligibility criteria. To ensure inter-reviewer consistency, calibration exercises were performed and screening only commenced after achieving an inter-rater agreement >0.6. Disagreements were resolved by consensus or by consultation with the lead supervisor (C.J).

Data charting and items

The reviewers (V.G., C.G.) performed data extraction. A standardized Excel form was used to capture author(s), year, country, journal, language, study design, study objective, key outcomes and conclusions.

Data synthesis and reporting

Results were synthesized descriptively and

grouped thematically into three categories:
(a) Epidemiological evidence from large-scale prospective studies;
(b) Microbial and Immunological findings from Cross-sectional and Case-control Studies, and;
(c) Periodontitis, oxidative stress, and HCC Severity.
Consistent with JBI guidance, no formal risk-of-bias assessment was performed, as this is not a mandatory component of scoping reviews.[20] A meta-analysis was not conducted due to the exploratory nature of this review, the small number of eligible human studies, substantial clinical and methodological heterogeneity across study designs, and the absence of sufficiently comparable outcomes and effect measures to allow meaningful quantitative synthesis.

RESULTS

A total of 69 records were initially identified through database searches. After removing 27 duplicates, 42 records were screened. Of these, 37 were excluded for being secondary studies or not meeting the "Concept" eligibility criteria (Figure 1).
Five reports were retrieved and assessed for eligibility, with 3 excluded for failing to meet the "Concept" criteria, resulting in 2 being included from this phase.[21,22]
An additional 13 records were identified through other sources, including manual retrograde reference screening (n = 3) and an updated literature search conducted in January 2026 (n = 10). Of these, 9 reports were excluded failing to meet the "Concept" criteria. The remaining four studies.[23-26] were included, bringing the total number of studies in this review to 6.
All selected studies had an observational design, comprising one case-control study.[26] two prospective cohort studies.[22,25] and three cross-sectional studies.[21,22,25] All available evidence comes from human studies conducted in Japan, the United States, and the United Kingdom (Tables 1 and Table 2).

Epidemiological evidence from large-scale prospective studies

Jordao *et al.*,[22] examined the association between self-reported poor oral health and the risk of gastrointestinal cancers, including HCC, using data from the UK Biobank cohort. The analysis included 469,628 adults aged 40 to 69 years, who were followed from 2006 until cancer diagnosis, death or the end of the study. Oral health status was self-reported based on symptoms such as gingival pain, bleeding gums, or tooth mobility.
Participants were classified as having either adequate or poor oral health and completed standardized questionnaires covering demographic, socioeconomic, and lifestyle factors, including smoking status, alcohol consumption, fruit and vegetable intake, educational level, waist circumference, and body mass index (BMI).[22] Over a mean follow-up of six years, 4,069 cases of gastrointestinal cancer were identified, 13% of which occurred among individuals who self-reported poor oral health at baseline.[22] No significant association was observed between poor oral health and overall gastrointestinal cancer risk in the fully adjusted model (Table 2).
In contrast, site-specific analyses demonstrated a statistically significant association between poor oral health and HCC, along with a non-significant trend toward an increased risk of hepatobiliary cancers after adjustment for relevant confounders.[22] Notably, the association between periodontitis and HCC remained particularly robust among smokers even after multivariable adjustment (Table 2).
Collectively, these findings indicate that while poor oral health is not associated with

Figure 1

PRISMA-ScR flow diagram illustrating the search and selection of the scientific articles included in this study

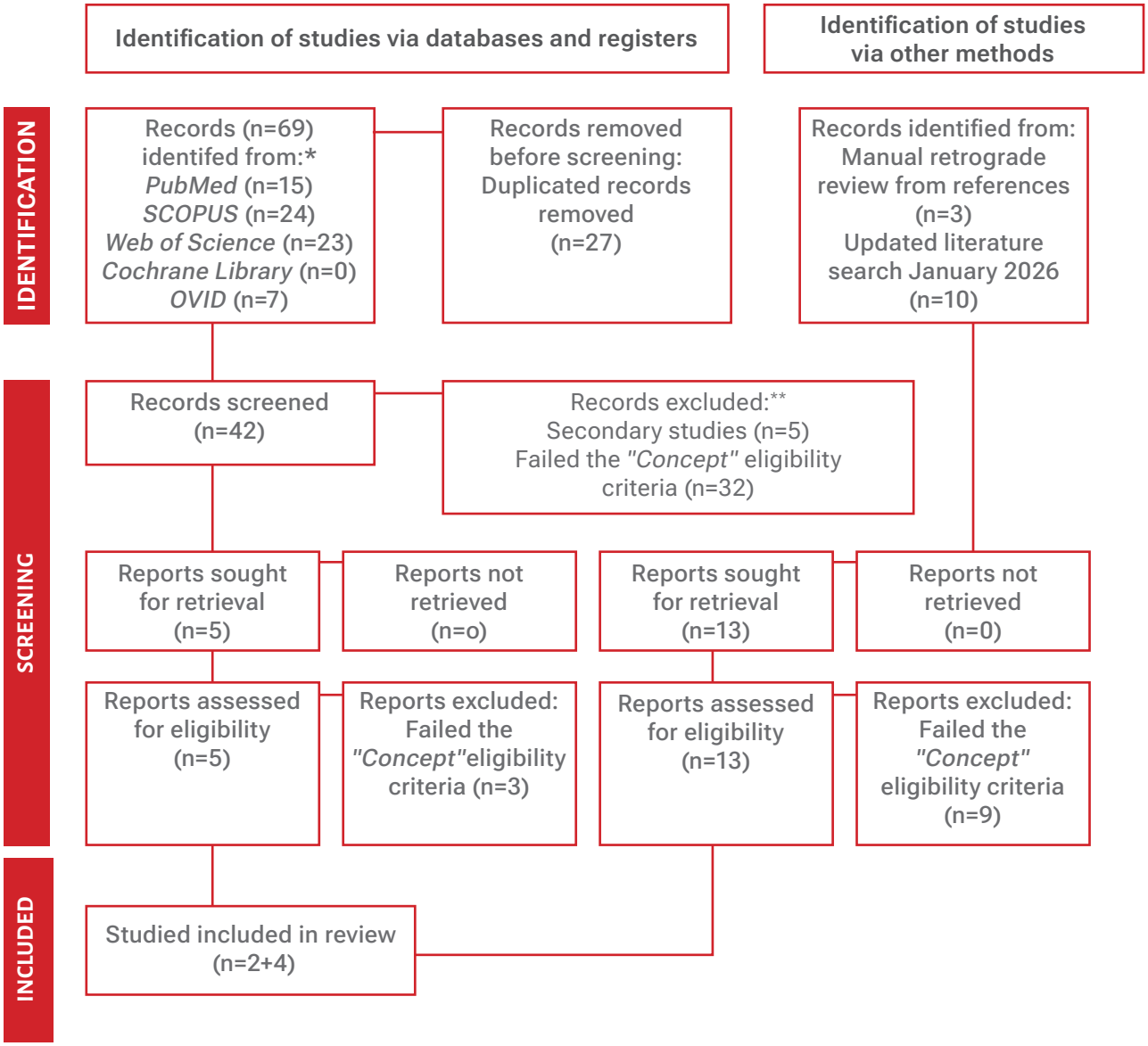


Table 1

Characteristics of the included studies

Author	Year	Country	Journal	Study Design
Matsui et al.,[24]	2024	Japan	Medicina	Observational, Cross-sectional
Nwizu et al.,[25]	2017	USA	Cancer Epidemiology, Biomarkers & Prevention	Observational, Prospective cohort.
Hernández et al.,[26]	2022	USA	Cancer Epidemiology, Biomarkers & Prevention	Observational, Case-control.
Jordao et al.,[22]	2019	United Kingdom	United European Gastroenterology Journal	Observational, Prospective cohort.
Takuma et al.,[23]	2023	Japan	Applied Sciences	Observational, Cross-sectional
Tamaki et al.,[21]	2011	Japan	Journal of Clinical Periodontology	Observational, Cross-sectional.

gastrointestinal cancer risk overall, it may represent a site-specific risk factor for HCC, especially among individuals with a history of tobacco exposure.[22]

Conversely, another high-volume investigation using the Women's Health Initiative cohort found no association between periodontitis and HCC.[25] In this study, authors investigated the relationship between periodontal disease history and incident cancer risk among post-menopausal women. The research included 65,869 women, aged 54 to 86 years, who were followed for a mean period of 8.32 years and a maximum of 15 years.[25]

Periodontitis status was determined through self-reported questionnaires, regarding whether participants had been professionally diagnosed by a dentist or dental hygienist. Participants completed assessments covering numerous potential confounders, including age, race, smoking status, BMI, educational level, alcohol consumption, and physical activity.[25]

In total, 7,149 cancers were identified during the follow-up period. While self-reported periodontal disease history was associated with a significant 14% increase in the risk of overall cancer (Table 2), site-specific analyses showed no significant association between periodontitis and HCC.[25]

These findings remained consistent in analyses focused on never-smoking participants, suggesting the null association was not influenced by residual confounding such as tobacco use. Notably, authors mention that specific associations with HCC could not be further explored or stratified by smoking status due to the insufficient number of events in this population.[25]

Microbial and Immunological findings from Cross-sectional and Case-control Studies

Hernández *et al.*,[26] evaluated the link between the oral bacterial microbiome and HCC using 16S rRNA gene sequencing of saliva samples from 180 participants, including 90 HCC cases and 90 controls. Significant baseline differences between groups were observed for age, ethnicity, education, viral liver disease, smoking, diabetes, fatty liver disease, cirrhosis, and NSAID use (p>0.05). Compared with controls, individuals with HCC showed significantly reduced alpha diversity and a distinct beta diversity profile in their oral microbiome.[26] After multivariable adjustment, Cyanobacteria emerged as the only taxon independently associated with an increased risk of HCC (Table 2). Notably, this association was observed exclusively among individuals with negative histories of established HCC risk factors, suggesting oral Cyanobacteria may be a novel and independent contributor to HCC development.[26]

Furthermore, functional metagenomic inference showed enrichment of genes involved in microcystin production (a potent hepatotoxic tumor promoter), as well as genes typically involved in response to microcystin exposure (Table 2). Collectively, these findings support a potential role for oral *Cyanobacteria* in HCC through toxin-mediated mechanisms.[26]

Takuma *et al.*,[23] investigated the role of *P. gingivalis (P.g)* and *Fusobacterium nucleatum (F.n)* in the progression of non-alcoholic steatohepatitis (NASH)-related HCC. The study included analyses of medical and periodontal records as well as saliva and blood samples from 40 patients with NASH and 20 individuals with NASH-related HCC.

While clinical periodontal parameters were similar between groups, patients with NASH-HCC were significantly older and exhibited higher levels of serum endotoxin and total bilirubin levels than those with NASH alone.[23] Microbiological and immunological analyses revealed that individuals in the NASH-HCC group had significantly lower salivary mi-

crobial diversity and a higher abundance of *F.n* compared with the NASH group (Table 2). Furthermore, serum immunoglobulin G (IgG) antibody titers against both *P.g* and *F.n* were significantly elevated in NASH-HCC patients *versus* controls.[21] Notably, the NASH-HCC group demonstrated significantly reduced salivary IgA concentrations and flow rates, which were negatively correlated with the abundance of *F.n,* suggesting a decline in salivary immunity may facilitate oral microbiome dysbiosis with enrichment of specific periodontopathic bacteria, potentially contributing to the pathogenesis of NASH-related HCC.[23]

Matsui *et al.*,[24] investigated the relationship between key pathogens involved in the oral-gut-liver axis and metabolic dysfunction-associated steatohepatitis-related HCC (MASH-HCC). The authors compared 41 patients with MASH and 19 individuals with MASH-HCC using periodontal examinations and 16S rRNA gene sequencing of saliva and fecal samples. MASH-HCC patients were significantly older and presented higher serum endotoxin and total bilirubin levels, along with lower salivary immunoglobulin A (IgA) levels than their MASH counterparts, suggesting impaired oral immune responses (Table 2).

The MASH-HCC group also exhibited reduced microbial diversity and marked dysbiosis in both saliva and fecal microbiota, including: (i) higher abundance of salivary *F.n* and lower occupancy of *Treponema denticola (T.d)*; and (ii) increased occupancy of fecal *Fusobacterium* and reduced *Butyricicoccus, Roseburia* and *Faecalibacterium* genera.[24] Statistical analyses showed that HCC directly influenced the salivary composition of key periodontal pathogens (*P.g, Tannerella forsythia, F.n* and *Prevotella intermedia*), as well as several gut genera, suggesting a role for HCC in periodontal and gut dysbiosis.

Notably, salivary *P.g* was found to directly affect fecal *Lactobacillus* and *Streptococcus* species, which in turn seemed to decrease other gut microbes. These findings point to a specific oral-gut-liver microbial pathway in which MASH-HCC may exacerbate oral and gut dysbiosis, impair immune responses, and potentially worsen liver damage.[24]

Periodontitis, oxidative stress, and HCC Severity

Tamaki *et al.*,[21] investigated the relationship between periodontitis, HCC severity, and systemic oxidative stress by comparing serum samples from HCC patients with (n=31) and without periodontitis (n=33) and 15 healthy controls. The Japan Integrated Stage (JIS) score was used to assess HCC severity, while systemic oxidative stress was measured by quantifying serum reactive oxygen metabolites (ROMs), which serve as circulating markers of reactive oxygen species (ROS). Additional serum determinations included total bilirubin, albumin, and total antioxidant capacity.[21]

The study showed that HCC patients with periodontitis had significantly higher JIS scores and total bilirubin levels than periodontally healthy HCC individuals, indicating more advanced liver damage in HCC individuals with periodontal inflammation.[21] While both HCC groups had significantly higher levels of reactive oxygen metabolites (ROM) levels and reduced antioxidant capacity compared to healthy controls, the HCC group with periodontitis showed a substantial 25.8% increase in ROM levels than the periodontally healthy HCC group, suggesting periodontitis may significantly contribute to circulating reactive oxygen species (ROS) (Table 2).

Multivariate analysis demonstrated that increased JIS scores were significantly and independently associated with periodontal probing depths and tobacco exposure,[21] supporting a prospective role for periodon-

Table 2 Summary of included studies

Ref.	Objectives	Results	Conclusion
et al.,[24]	To analyze the involvement of periodontal bacteria as well as the oral and intestinal bacterial flora in MASH-related HCC (MASH-HCC).	Patients with MASH-HCC were significantly older than MASH individuals (p<0.0004) and exhibited significantly higher serum endotoxin levels (p<0.0001) and total bilirubin levels (p=0.014). Salivary IgA concentrations were significantly lower in MASH-HCC individuals compared to HCC patients (p>0.001). The MASH-HCC group showed asignificant occupancy rate of *F.n* (p=0.002) and lower rates of *Butyricicoccus* (p=0.022) and R*oseburia* (p<0.05) compared to the MASH group. Salivary bacterial diversity was significantly lower in MASH-HCC patients (p=0.03), with a higher abundance of *F.n* (p=0.014). Periodontal pathogens and enteric bacteria did not affect HCC. However, HCC directly affected the salivary presence of *P.g, T.f, F.n,* and *P.i,* as well as several intestinal genera (*Lactobacillus, Roseburia, Fusobacterium, Prevotella, Clostridium, Ruminococcus, Trabulsiella,* and SMB53). Salivary *P.g* directly affected the intestinal genera *Lactobacillus* and *Streptococcus*.	HCC directly influences the periodontal and intestinal pathogens, and salivary *P.g* could play a role in modulating the intestinal microbiome associated with gastrointestinal cancer.
et al.,[26]	To evaluate the relationship between the oral bacterial microbiome and HCC.	The oral microbiome of HCC cases showed significantly reduced alpha diversity compared with controls (Shannon p = 0.002; Simpson p=0.049), and beta diversity differed significantly (weighted UniFrac p = 0.004). The relative abundance of 30 taxa varied significantly, including cyanobacteria, which were enriched in HCC cases compared to controls (p = 0.018). Cyanobacteria were positively associated with HCC (OR 8.71; 95% CI: 1.22–62.00, p = 0.031) after adjustment for confounders.	Oral cyanobacteria may represent a novel independent risk factor for HCC.
et al.,[23]	To analyze the involvement of periodontopathogenic bacteria in NASH-related HCC.	The NASH-HCC group was significantly older than the NASH group (p<0.001). However, both groups showed similar periodontal parameters (p >0.05). NASH-HCC patients had significantly higher serum endotoxin levels, blood glucose and total bilirubin than NASH controls (p <0.001). Immunoglobulin (Ig) G antibody titers against P.g (p = 0.031) and F.n (p = 0.003) were significantly higher in the NASH-HCC group compared with the NASH group.	Oral P.g and F. n are possibly associated with the pathogenesis of NASH-related HCC. Furthermore, F.n was negatively correlated with salivary IgA levels.

Table 2 continues on the next page →

Table 2 Summary of included studies

Ref.	Objectives	Results	Conclusion
et al.,[23]	To analyze the involvement of periodontopathogenic bacteria in NASH-related HCC.	NASH-HCC patients had significantly higher serum endotoxin levels, blood glucose and total bilirubin than NASH controls (p<0.001).	Oral *P.g* and *F.n* are possibly associated with the pathogenesis of NASH-related HCC. Furthermore, F.n was negatively correlated with salivary IgA levels.
		Immunoglobulin (Ig) G antibody titers against P.g (p = 0.031) and *F.n* (p = 0.003) were significantly higher in the NASH-HCC group compared with the NASH group.	
		The proportions of *P.g* and *F.n* were higher in the NASH-HCC group than in the NASH group; however, only the proportion of *F.n* reached statistical significance (p = 0.009). Conversely, the proportion of *T.d* was significantly lower in NASH-HCC patients *versus* NASH individuals (p = 0.013).	
		The Shannon index of salivary bacterial flora was significantly lower in the NASH-HCC group compared with the NASH group (p< 0.001). The NASH-HCC group also exhibited a significantly lower salivary IgA concentration (p= 0.007) and a slower salivary IgA flow rate (p= 0.003). Across all participants, the salivary IgA flow rate and the proportion of *F. nucleatum* showed a significant negative correlation (p= 0.02).	
et al.,[22]	To investigate the association between self-reported poor oral health and the risk of various gastrointestinal cancers.	No significant association was found between self-reported poor oral health and overall gastrointestinal cancer risk (HR: 0.97; 95% CI: 0.88–1.07).	Self-reported poor oral health was associated with an increased risk of HCC.
		In contrast, adjusted site-specific analyses showed a significant association between poor oral health and HCC (HR: 1.75; 95% CI: 1.04–2.92), along with a non-significant trend toward increased hepatobiliary cancer risk (HR: 1.32; 95% CI: 0.95–1.80).	
		The association between poor oral health and HCC was particularly robust among smokers.	
et al.,[25]	To examine whether periodontal disease is associated with incident cancer among postmenopausal women in the Women's Health Initiative Observational Study.	Periodontal disease history was associated with overall cancer risk (HR: 1.14; 95% CI: 1.01-1.23), findings were similar in analyses limited to never-smokers (HR: 1.12; 95% CI: 1.04-1.22).	
		Positive associations were observed for breast (HR, 1.13; 95% CI, 1.03–1.23), lung (HR, 1.31; 95% CI, 1.14– 1.51), esophagus (HR, 3.28; 95% CI, 1.64–6.53), gallbladder (HR, 1.73; 95% CI, 1.01–2.95), and melanoma skin (HR, 1.23; 95% CI, 1.02–1.48) cancers. Stomach cancer was borderline (HR, 1.58; 95% CI, 0.94 – 2.67) and HCC was null (HR not reported as there were fewer than 20 reported cases).	Periodontal disease history increases risk of total cancer among postmenopausal women, irrespective of smoking. Specific risk regarding HCC cannot be reported due to limited number cases within this cohort.

Table 2 continues on the next page →

Table 2 Summary of included studies

Ref.	Objectives	Results	Conclusion
et al.,[21]	To investigate JIS scores in patients with HCC with and without periodontitis.	The HCC+periodontitis and HCC+periodontally healthy groups had similar body mass index, habitual alcohol consumption, and tobacco exposure ($p< 0.05$). The HCC+periodontitis group showed higher JIS scores and total bilirubin levels compared with the HCC+periodontally healthy group ($p< 0.027$). Both probing depth (OR=3.38) and tobacco exposure (OR=4.11) were identified as independent risk factors for advanced JIS scores. While both HCC groups had significantly higher serum ROM levels and reduced total antioxidant capacity than healthy controls ($p<0.01$), the HCC+periodontitis group showed a 25.8% higher circulating ROM levels than HCC+periodontally healthy group ($p< 0.001$).	Patients with HCC and periodontitis exhibited higher JIS scores and circulating ROS levels compared to HCC patients without periodontitis.

HCC: hepatocellular carcinoma. **HR:** Hazard Ratio. **Pg:** Porphyromonas gingivalis. **T.f:** Tannerella forsythia. **F.n:** Fusobacterium nucleatum. **P.i:** Prevotella intermedia. **HFD:** high-fat diet. **HCV:** hepatitis C virus. **HBV:** hepatitis B virus. **NASH:** non-alcoholic steatohepatitis. **MASH:** metabolic dysfunction-associated steatohepatitis. **ROS:** reactive oxygen species. **JIS:** Japan Integrated Staging. **ROM:** reactive oxygen metabolites.

titis-induced systemic oxidative stress as a pathogenic mechanism linking oral inflammation and liver carcinogenesis.

DISCUSSION

This scoping review systemically mapped and synthesized the available human evidence regarding the association between periodontitis and HCC. Although the current evidence is limited and heterogenous, it increasingly supports a potential association between these two diseases.

However, the biological mechanisms un-derlying this association remain poorly understood, highlighting the need for mechanistic research to assess causality and clarify the exact role of periodontitis in HCC carcinogenesis.

Epidemiological and Genetic Evidence

At the epidemiological level, existing evidence is conflicting. Jordao's study demonstrated that self-reported poor oral health was a significant site-specific risk factor for HCC. This association persisted after adjusting for confounders and was particularly pronounced among smokers, suggesting that periodontal inflammation may potentially amplify the carcinogenic effects of other known exposures.[22] This synergistic pattern, where periodontitis adds to systemic disease risk, has also been reported in other chronic inflammatory conditions and cancers.[27,28]

In contrast, Nwizu's study reported no substantial association between self-reported history of periodontal disease and incident HCC among postmenopausal women.[25] We believe discrepancies between these two studies could stem from substantial methodological differences —particularly in participant demographics and how periodontitis and HCC were defined—, highlighting the need for additional rigorous, large-scale prospective research using standardized clinical examinations.

Recent mendelian randomization analyses by Sergeeva *et al.*,[29] found no significant genetic evidence supporting a causal relationship between periodontitis and HCC risk, further fueling the ongoing debate. The authors proposed that human gastric acidity may act as a natural barrier to bacterial translocation from the oral cavity to the gut-liver, as experimental data show P.g has minimal activity below pH 2.5.[29] However, these results should be interpreted with caution since:

(i) the analysis was limited to populations of European ancestry, reducing generalizability;

and (ii) Mendelian randomization captures only inherited genetic risk, overlooking environmental exposures such as oral or gut dysbiosis, which may still contribute to hepatocarcinogenesis independently of host genetic susceptibility.

Clinical and Experimental Insights into HCC progression and severity

Beyond incidence risk, clinical data from Tamaki *et al.*,[21] study indicate that periodontitis may exacerbate HCC severity. Periodontal probing depth —an indicator for periodontal disease severity— was significantly and independently associated with more advanced JIS scores and higher levels of circulating ROS in HCC patients.[21]

These findings suggest that while periodontitis may not be a universal contributor to hepatocarcinogenesis, it may function as a site-specific modulator of HCC severity and progression in certain vulnerable populations.

Animal models further support this biological plausibility. Sakamoto *et al.*,[30] found that odontogenic infection with *P.g* in high-fat

diet mice significantly increased neoplastic nodule formation (p=0.0188) and HCC incidence (33.3% *versus* 8.3%) compared to low-fat diet controls. Moreover, immunohistochemistry confirmed the translocation of *P.g* from the oral cavity to both non-neoplastic and HCC liver tissues, with activation of oncogenic signaling pathways.[30]

Based on their observations, the authors proposed two biological mechanisms linking periodontitis and HCC:

(i) *P.g* infection activates the integrin β1-FAK/AKT signaling pathway in hepatocytes, promoting cell survival, proliferation and migration while inhibiting apoptosis;

and (ii) *P.g* infection increases the production of TNF-α-mediated inflammation, fostering a ROS-rich microenvironment that promotes liver DNA oxidation enabling carcinogenesis. This was supported by significantly increased levels of 8-OHdG in *P.g*-infected mice (p=0.0029), a genotoxic marker linked to G:C to T:A mutations in cancer.[30]

Similarly, the Stelic Animal Model (STAM) by Ohno *et al.*,[31] showed that STAM mice with induced periodontitis developed more aggressive forms of NASH-related HCC than periodontally healthy counterparts, exhibiting more advanced vacuolar degeneration and a greater number of visible liver tumors. Histological and molecular analyses further revealed that the periodontitis group had significant upregulation of key inflammatory and tumor-promoting mediators, including TNA-α and angiopoietin-like protein 2 (ANGPTL2).[31]

Notably, ANGPTL2 levels were elevated in both the periodontal tissues and serum of periodontitis-induced mice, supporting the notion that inflammatory mediators produced from chronically inflamed periodontal tissues can enter the circulation, reach the liver, and contribute to a pro-inflammatory microenvironment that promotes HCC.

Microbial dysbiosis and the Oral-Gut-Liver Axis

Alterations in the gut microbiome have been implicated in the onset of chronic liver diseases and HCC, while emerging evidence suggests that oral microbiome dysbiosis—often driven by periodontitis—plays an important upstream role.[31,32] Periodontitis disrupts the healthy oral ecosystem, replacing it with pathogenic anaerobes that trigger chronic inflammation and periodontal tissue destruction.[33] This dysbiosis is coupled with ulceration of the gingival epithelium, enabling oral bacteria and their byproducts to enter the bloodstream and promote sustained low-grade systemic inflammation.[6]

Furthermore, oral bacteria can be transferred enterally through salivary transplants, potentially contributing to gut dysbiosis and increased intestinal permeability.[34] This now "leaky gut" enables bacterial translocation through the portal vein into the liver, where they may interact with hepatocytes triggering inflammation.[34] Building on this mechanistic framework, three of the included studies used 16S rRNA sequencing to characterize microbial shifts in HCC and NASH/MASH-related HCC patients.[23,24,26] All reported significantly reduced salivary alpha diversity and enrichment of specific pathogens in HCC and NASH/MASH-related HCC individuals compared to controls, including Cyanobacteria, *F.n*, and *P.g*. Interestingly, oral *Cyanobacteria* emerged as an independent risk factor for HCC,[23,24,26] a finding most likely due to its ability to produce hepatotoxic and tumor-promoting microcystins.[35]

Significantly higher *F.n* levels were found in both saliva and feces of NASH/MASH-related HCC patients,[23,24] supporting its central role in the oral-gut-liver axis. Mechanistically, *F.n* may promote carcinogenesis by evading immune responses through the recruitment of myeloid-derived suppressor cells, which

impair the anti-tumor activity of cytotoxic T cells and natural killer cells.[36] It may further facilitate tumor progression and metastasis through its FadA adhesin, activating the E-cadherin/β-catenin pathway and upregulating methyltransferase-like protein 3 METTL3 expression.[36]

Beyond the included studies, additional mechanistic literature identifies specific microRNAs as shared regulatory hubs linking periodontitis and HCC. Fan *et al.*,[19] demonstrated through bioinformatic analysis and tissue validation that the non-coding RNA MIAT acts as a central mediator, as it was significantly upregulated in periodontitis and associated with increased HCC cell proliferation, invasion, and immune escape. This regulatory framework is further characterized by the lncRNA MIAT/hsa-miR-155-5p/CTHRC1 and MIAT/hsa-miR-205-5p axes, where high expression correlates with poor clinical HCC outcomes.[19]

Notably, *F.n* and *P.g* may influence these pathways favoring pro-carcinogenic environments. *F.n* has been shown to upregulate methyltransferase-like protein 3 (METTL3), interacting with hsa-miR-155-5p networks to promote colorectal cancer metastasis,[37] whereas *P.g* inhibits hsa-miR-205-5p expression, activating JAK/STAT signaling in periodontal and liver tissues, facilitating periodontal inflammation and tumor growth/invasion.[19,38]

In-vitro evidence supports the inflammatory and hepatosteatotic potential of *P.g.* Ding *et al.*,[39] demonstrated that human HepG2 hepatocytes exposed to *P.g*-derived lipopolysaccharides (LPS) accumulated significantly more intracellular lipids than hepatocytes treated with *Escherichia coli*–derived LPS or untreated controls.[39]

This was accompanied by increased secretion of pro-inflammatory cytokines (interleukin (IL) -1, IL-8, and TNF-α), and enhanced expression of MyD88 with phosphorylation of p65 and JNK. Notably, silencing p65 and JNK significantly reduced lipid accumulation,[39] suggesting that *P.g*-derived LPS may trigger steatotic and inflammatory changes in hepatocytes, mirroring key features of HCC and NASH/MASH-related HCC. Clinical relevance of elevated salivary *P.g* in NASH-related HCC patients in Takuma *et al.*,[23] research was further highlighted by significantly higher serum immunoglobulin G (IgG) antibody titers in this group compared to controls.

Authors found this to be consistent with a history of chronic infection, suggesting a plausible role of periodontitis as a chronic reservoir for the microbial and inflammatory drivers of hepatocarcinogenesis.[23] Functional oral-fecal microbial analyses showed that salivary *P.g* altered the gut microbiota composition, increasing *Lactobacillus* and *Streptococcus* abundance.[24]

This shift was accompanied by a reduction in short-chain fatty acid (SCFA)-producing bacteria, including *Bacteroides* and *Butyricicoccus*.[24] This is important as SCFA producers have strong anti-inflammatory[40] and anti-tumorigenic effects,[41] and their depletion may foster gut-liver axis dysfunction, exacerbating liver inflammation and carcinogenesis.

Oxidative Stress as a Shared Pathogenic Mechanism

Over 90% of HCC arise in the context of chronic liver inflammation, a condition characterized by sustained oxidative stress and excessive production of ROS.

Oxidative stress is a well-established driver of carcinogenesis, as it promotes genomic instability, induces DNA damage, and activates pro-tumorigenic signaling pathways.[42]

Periodontitis has similarly been shown to increase circulating levels of ROS and disrupt the systemic pro-oxidant/antioxidant balance. Importantly, periodontal treatment

has been associated with significant reductions in ROM levels and partial restoration of redox homeostasis, indicating that oxidative stress generated in periodontal tissues may have systemic effects, potentially damaging distant organs like the liver.[43]

Clinical evidence from Tamaki *et al.*,[21] supports this systemic link, demonstrating that HCC patients with periodontitis had significantly higher circulating levels of ROMs compared to periodontally healthy HCC individuals (Table 2). Conversely, the authors did not find significant intergroup differences in serum total antioxidant capacity, suggesting that periodontitis may contribute to hepatocarcinogenesis primarily by increasing the oxidative insult rather than by compromising the host's antioxidant capacity.[21]

These results partially align with prior animal and clinical evidence, in which periodontitis increased the circulatory levels of ROS, but also diminished hepatic glutathione (GSH) and other antioxidant enzymes.[44,47] Notably, some of these animal models have shown that periodontitis induces liver steatosis and fibrosis in rats,[47,48] which are hallmark features of fatty liver diseases (like NASH and MASH) and recognized risk factors for HCC.

Study Limitations

The findings of this review should be interpreted with caution due to several intrinsic limitations. As a scoping review, the goal was to map available human evidence on the association of periodontitis and HCC rather than establish definitive causality. Despite a comprehensive search, only a small number of studies met the inclusion criteria (n=6), and inconsistencies in outcome measures (e.g., self-reported oral health status vs objective clinical periodontal examinations) precluded meta-analysis.

Methodological and clinical heterogeneity across studies further limits generalizability, with populations ranging from specific demographics such as postmenopausal women in the United States, to broader adult cohorts in the United Kingdom and Japan. Microbiological analyses were also limited in scope, often focusing on a narrow range of oral and fecal bacteria. Finally, in line with the JBI's guidelines, no formal risk-of-bias assessment was performed.

CONCLUSIONS

This scoping review examined the available human evidence on the association of periodontitis and HCC. While epidemiological data on periodontitis as a risk factor for HCC remain inconsistent, growing clinical evidence suggests it may play a role in HCC progression and severity. This association appears biologically plausible and may be mediated by shared mechanisms such as chronic inflammation, oxidative stress, microbial dysbiosis, and the translocation of oral pathogens via the oral-gut-liver axis. Since causality has not been established, future research should prioritize robust, large-scale longitudinal studies and mechanistic investigations to further clarify the direction, strength, and underlying biological mechanisms driving this association.

REFERENCES

1. Meisel P, Heins G, Carlsson LE, Giebel J, John U, Schwahn C, Kocher T. Impact of genetic polymorphisms on the smoking-related risk of periodontal disease: the population-based study SHIP. Tob Induc Dis. 2003 Sep 15;1(3):197. https://doi.org/10.1186/1617-9625-1-3-197. PMID: 19570260; PMCID: PMC2671548.
2. Bascones Martínez A, Figuero Ruiz E. Las enfermedades periodontales como infecciones bacterianas. Avances en Periodoncia e Implantología Oral. 2005;17:147-56.
3. Carvajal P. Enfermedades periodontales como un problema de salud pública: el desafío del nivel primario de atención en salud. Rev Clin Periodoncia Implantol Rehabil Oral (PIRO). 2016;9:177-83.
4. Chapple ILC, Mealey BL, Van Dyke TE, Bartold PM, Dommisch H, Eickholz P, Geisinger ML, Genco RJ, Glogauer M, Goldstein M, Griffin TJ, Holmstrup P, Johnson GK, Kapila Y, Lang NP, Meyle J, Murakami S, Plemons J, Romito GA, Shapira L, Tatakis DN, Teughels W, Trombelli L, Walter C, Wimmer G, Xenoudi P, Yoshie H. Periodontal health and gingival diseases and conditions on an intact and a reduced periodontium: Consensus report of workgroup 1 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Periodontol. 2018;89 Suppl 1: S74-S84. https://doi.org/10.1002/JPER.17-0719. PMID: 29926944.
5. Papapanou PN, Sanz M, Buduneli N, Dietrich T, Feres M, Fine DH, Flemmig TF, Garcia R, Giannobile WV, Graziani F, Greenwell H, Herrera D, Kao RT, Kebschull M, Kinane DF, Kirkwood KL, Kocher T, Kornman KS, Kumar PS, Loos BG, Machtei E, Meng H, Mombelli A, Needleman I, Offenbacher S, Seymour GJ, Teles R, Tonetti MS. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Periodontol. 2018;89 Suppl 1:S173-S182. https://doi.org/10.1002/JPER.17-0721. PMID: 29926951.
6. Hajishengallis G, Chavakis T. Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities. Nat Rev Immunol. 2021;21(7):426-440. https://doi.org/10.1038/s41577-020-00488-6. Epub 2021 Jan 28. PMID: 33510490; PMCID: PMC7841384.
7. Michaud DS, Fu Z, Shi J, Chung M. Periodontal Disease, Tooth Loss, and Cancer Risk. Epidemiol Rev. 2017;39(1):49-58. https://doi.org/10.1093/epirev/mxx006. PMID: 28449041; PMCID: PMC5868279.
8. Tuominen H, Rautava J. Oral Microbita and Cancer Development. Pathobiology. 2021;8 (2):116-126. https://doi.org/10.1159/00510979. Epub 2020 Nov 11. PMID: 33176328.
9. Olsen I, Yilmaz Ö. Possible role of Porphyromonas gingivalis in orodigestive cancers. J Oral Microbiol. 2019;11(1):1563410. https://doi.org/10.1080/20002297.2018.1563410
10. Nagaraju GP, Dariya B, Kasa P, Peela S, El-Rayes BF. Epigenetics in hepatocellular carcinoma. Semin Cancer Biol. 2022;86(Pt 3): 622-632. https://doi.org/10.1016/j.semcancer.2021.07.017. Epub 2021 Jul 26. PMID: 343-24953.
11. Prieto Ortíz JE, Restrepo Gutiérrez JC. Epidemiología y factores de riesgo. Revista colombiana de Gastroenterología. 2013;28:7-11.
12. Kirstein MM, Vogel A. The pathogenesis of hepatocellular carcinoma. Dig Dis. 2014; 32(5): 545-53. https://doi.org/10.1159/000360499. Epub 2014 Jul 14. PMID: 25034287.
13. Tabrizian P, Jibara G, Shrager B, Schwartz M, Roayaie S. Recurrence of hepatocellular cancer after resection: patterns, treatments, and prognosis. Ann Surg. 2015;261(5):947-55. https://doi.org/10.1097/SLA.0000000000000710. PMID: 25010665.
14. Luan X, Zhou X, Fallah P, Pandya M, Lyu H, Foyle D, Burch D, Diekwisch TGH. MicroRNAs: Harbingers and shapers of periodontal inflammation. Semin Cell Dev Biol. 2022;124:85-98. https://doi.org/10.1016/j.semcdb.2021.05.030. Epub 2021 Jun 10. PMID: 34120836; PMCID: PMC9071582.
15. Luan X, Zhou X, Naqvi A, Francis M, Foyle D, Nares S, Diekwisch TGH. MicroRNAs and immunity in periodontal health and disease. Int J Oral Sci. 2018 Aug 6;10(3):24. https://doi.org/10.1038/s41368-018-0025-y. PMID: 30078842; PMCID: PMC6080405.

16. Polizzi A, Alibrandi A, Lo Giudice A, Distefano A, Orlando L, Analazi AM, Pizzo G, Volti GL, Isola G. Impact of periodontal microRNAs associated with alveolar bone remodeling during orthodontic tooth movement: a randomized clinical trial. J Transl Med. 2024;22(1):1155. https://doi.org/10.1186/s12967-024-05933-x. PMID: 39736760; PMCID: PMC11684316.
17. Polizzi A, Nibali L, Tartaglia GM, Isola G. Impact of nonsurgical periodontal treatment on arterial stiffness outcomes related to endothelial dysfunction: A systematic review and meta-analysis. J Periodontol. 2025;96(4): 330-345. https://doi.org/10.1002/JPER.24-0422. Epub 2024 Nov 16. PMID: 39549247; PMCID: PMC 12062727.
18. Singh V, Sen A, Saini S, Dwivedi S, Agrawal R, Bansal A, Shekhar S. MicroRNA Significance in Cancer: An Updated Review on Diagnostic, Prognostic, and Therapeutic Perspectives. EJIFCC. 2024;35(4):265-284. PMID: 39810890; PMCID: PMC11726331.
19. Fan X, Song Z, Qin W, Yu T, Peng B, Shen Y. Potential Common Molecular Mechanisms Between Periodontitis and Hepatocellular Carcinoma: A Bioinformatic Analysis and Validation. Cancer Genomics Proteomics. 2023;20(6):602-616. https://doi.org/10.21873/cgp.20409. PMID: 37889061; PMCID: PMC10614068.
20. Aromataris E, Lockwood C, Porritt K, Pilla B, Jordan Z, editors. JBI Manual for Evidence Synthesis. JBI; 2024. https://doi.org/10.46658/JBIMES-24-01
21. Tamaki N, Takaki A, Tomofuji T, Endo Y, Kasuyama K, Ekuni D, Yasunaka T, Yamamoto K, Morita M. Stage of hepatocellular carcinoma is associated with periodontitis. J Clin Periodontol. 2011;38(11):1015-20. https://doi.org/10.1111/j.1600-051X.2011.01777.x. Epub 2011 Sep 15. PMID: 22092473.
22. Jordao HW, McKenna G, McMenamin UC, Kunzmann AT, Murray LJ, Coleman HG. The association between self-reported poor oral health and gastrointestinal cancer risk in the UK Biobank: A large prospective cohort study. United European Gastroenterol J. 2019;7(9):1241-9.
23. Takuma R, Morozumi T, Yamamoto Y, Kobayashi T, Matsui T, Yoneda M, Kessoku T, Nogami A, Tamura M, Kamata Y, Sugihara S, Nomura Y, To M, Minabe M, Mitsudo K, Nakajima A, Komaki M. Association between Non-Alcoholic Steatohepatitis-Related Hepatocellular Car-cinoma and Periodontopathic Bacteria: A Cross-Sectional Pilot Study. Applied Sciences. 2023;13(6):3839. https://doi.org/10.3390/app13 063893
24. Matsui T, Morozumi T, Yamamoto Y, Kobayashi T, Takuma R, Yoneda M, Nogami A, Kessoku T, Tamura M, Nomura Y, Takahashi T, Kamata Y, Sugihara S, Arai K, Minabe M, Aoyama N, Mitsudo K, Nakajima A, Komaki M. Relationship of Metabolic Dysfunction-Associated Steato-hepatitis-Related Hepatocellular Carcinoma with Oral and Intestinal Microbiota: A Cross-Sectional Pilot Study. Medicina (Kaunas). 2024; 60(7):1150. https://doi.org/10.3390/medicina60071150. PM- ID: 39064580; PMCID: PMC 11279156.
25. Nwizu NN, Marshall JR, Moysich K, Genco RJ, Hovey KM, Mai X, LaMonte MJ, Freudenheim JL, Wactawski-Wende J. Periodontal Disease and Incident Cancer Risk among Postmenopausal Women: Results from the Women's Health Initiative Observational Cohort. Cancer Epidemiol Biomarkers Prev. 2017;26(8):1255-1265. https://doi.org/10.1158/1055-9965.EPI-17-0212. PMID: 28765338; PMCID: PMC5551444.
26. Hernandez BY, Zhu X, Risch HA, Lu L, Ma X, Irwin ML, Lim JK, Taddei TH, Pawlish KS, Stroup AM, Brown R, Wang Z, Wong LL, Yu H. Oral Cyanobacteria and Hepatocellular Carcinoma. Cancer Epidemiol Biomarkers Prev. 2022 Jan;31(1):221-229. https://doi.org/ 10.1158/1055-9965.EPI-21-0804. Epub 2021 Oct 25. PMID: 34697061; PMCID: PMC8755591.
27. Holmstrup P, Damgaard C, Olsen I, Klinge B, Flyvbjerg A, Nielsen CH, Hansen PR. Comorbidity of periodontal disease: two sides of the same coin? An introduction for the clinician. J Oral Microbiol. 2017;9(1):1332710. https://doi.org/10.1080/20002297.2017.1332710. PMID: 287480 36; PMCID: PMC5508374.
28. Hajishengallis G. Interconnection of periodontal disease and comorbidities: Evidence, mechanisms, and implications. Periodontol 2000. 2022;89(1):9-18. https://doi.org/10.1111/prd.12430. Epub 2022 Mar 4. PMID: 35244969; PMCID: PMC9018559.

29. Sergeeva I, Meng Z, Ma Y. Periodontitis and Hepatocellular Carcinoma: A Two-Sample Mendelian Randomisation Study. Int Dent J. 2025 Apr;75(2):605-612. https://doi.org/10.1016/j.identj.2024.09.015. Epub 2024 Oct 2. PMID: 39358171; PMCID: PMC11976544.
30. Sakamoto S, Nagasaki A, Shrestha M, Shintani T, Watanabe A, Furusho H, Chayama K, Takata T, Miyauchi M. Porphyromonas gingivalis-odontogenic infection is the potential risk for progression of nonalcoholic steatohepatitis-related neoplastic nodule formation. Sci Rep. 2023 Jun 8;13(1):9350. https://doi.org/10.1038/s41598-023-36553-y. PMID: 37291206; PMCID: PMC10250332.
31. Ohno T, Kikuchi T, Suzuki Y, Goto R, Takeuchi D, Hayashi JI, Nishida E, Yamamoto G, Kondo S, Ono K, Nomoto S, Mitani A. Periodontitis promotes hepatocellular carcinoma in Stelic Animal model (STAM) mice. Sci Rep. 2024;14(1):17560. https://doi.org/10.1038/s41598-024-68422-7. PMID: 39080409; PMCID: PMC11289391.
32. Kang Y, Cai Y, Yang Y. The Gut Microbiome and Hepatocellular Carcinoma: Implications for Early Diagnostic Biomarkers and Novel Therapies. Liver Cancer. 2021 Dec 21;11(2):113-125. https://doi.org/10.1159/000521358. PMID: 35634424; PMCID: PMC9109080.
33. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. Nat Rev Immunol. 2015;15(1):30-44. https://doi.org/10.1038/nri3785. PMID: 25534621; PMCID: PMC4276050.
34. Bao J, Li L, Zhang Y, Wang M, Chen F, Ge S, Chen B, Yan F. Periodontitis may induce gut microbiota dysbiosis via salivary microbiota. Int J Oral Sci. 2022;14(1):32. https://doi.org/10.1038/s41368-022-00183-3. PMID: 35732628; PMCID: PMC9217941.
35. Nishiwaki-Matsushima R, Ohta T, Nishiwaki S, Suganuma M, Kohyama K, Ishikawa T, Carmichael WW, Fujiki H. Liver tumor promo-tion by the cyanobacterial cyclic peptide toxin microcystin-LR. J Cancer Res Clin Oncol. 1992;118(6):420-4. https://doi.org/10.1007/BF01629424. PMID: 1618889; PMCID: PMC12200900.
36. Luo M, Li Q, Gu Q, Zhang C. Fusobacterium nucleatum: a novel regulator of antitumor immune checkpoint blockade therapy in colorectal cancer. Am J Cancer Res. 2024;14(8):3962-3975. https://doi.org/10.62347/MYZA2640. PMID: 39267665; PMCID: PMC11387864.
37. Chen S, Zhang L, Li M, Zhang Y, Sun M, Wang L, Lin J, Cui Y, Chen Q, Jin C, Li X, Wang B, Chen H, Zhou T, Wang L, Hsu CH, Zhuo W. Fusobacterium nucleatum reduces METTL3-mediated m6A modification and contributes to colorectal cancer metastasis. Nat Commun. 2022;13(1):1248. https://doi.org/10.1038/s41467-022-28913-5. PMID: 35273176; PMCID: PMC8913623.
38. Li J, Li L, Wang X, Xiao L. Porphyromonas gingivalis Inhibition of MicroRNA-205-5p Expression Modulates Proinflammatory Cytokines in Gingival Epithelial Cells. Biochem Genet. 2020;58(4):566-579. https://doi.org/10.1007/s10528-020-09957-y. Epub 2020 Apr 17. PMID: 32303947.
39. Ding LY, Liang LZ, Zhao YX, Yang YN, Liu F, Ding QR, Luo LJ. Porphyromonas gingivalis-derived lipopolysaccharide causes excessive hepatic lipid accumulation via activating NF-κB and JNK signaling pathways. Oral Dis. 2019;25(7):1789-1797. https://doi.org/10.1111/odi.13153. Epub 2019 Jul 28. PMID: 31283861.
40. Liu G, Tang J, Zhou J, Dong M. Short-chain fatty acids play a positive role in colorectal cancer. Discov Oncol. 2024 Sep 10;15(1):425. https://doi.org/10.1007/s12672-024-01313-5. PMID: 39256239; PMCID: PMC11387572.
41. Hou M, Yu QQ, Yang L, Zhao H, Jiang P, Qin L, Zhang Q. The role of short-chain fatty acid metabolism in the pathogenesis, diagnosis and treatment of cancer. Front Oncol. 2024;14:1451045. https://doi.org/10.3389/fonc.2024.1451045. PMID: 39435279; PMCID: PMC11 491288.
42. Fu Y, Chung FL. Oxidative stress and hepatocarcinogenesis. Hepatoma Res. 2018;4:39. https://doi.org/10.20517/2394-5079.2018.29. Epub 2018 Aug 1. PMID: 30761356; PMCID: PMC6370311.
43. Tomofuji T, Irie K, Sanbe T, Azuma T, Ekuni D, Tamaki N, Yamamoto T, Morita M. Periodontitis and increase in circulating oxidative stress. Japanese Dental Science Review. 2009;45(1):46-51. https://doi.org/10.1016/j.jdsr.2008.12.002
44. Ahmadi-Motamayel F, Goodarzi MT, Jamshidi Z, Kebriaei R. Evaluation of Salivary and Serum Antioxidant and Oxidative Stress Statuses in Patients with Chronic Periodontitis: A Case-

Control Study. Front Physiol. 2017 Mar 31;8:189. https://doi.org/10.3389/fphys.2017.00189. PMID: 28408887; PMCID: PMC5374205.

45. Sobaniec H, Sobaniec-Lotowska ME. Morphological examinations of hard tissues of periodontium and evaluation of selected processes of lipid peroxidation in blood serum of rats in the course of experimental periodontitis. Med Sci Monit. 2000;6(5):875-81. PMID: 11208425.
46. Bains VK, Bains R. The antioxidant master glutathione and periodontal health. Dent Res J (Isfahan). 2015 Sep-Oct;12(5):389-405. https://doi.org/10.4103/1735-3327.166169. PMID: 26604952; PMCID: PMC4630702.
47. Pessoa LS, Pereira-da Silva FR, Alves EH, França LF, di Lenardo D, Carvalho JS, Martins VB, Sousa FB, Drumond KO, Medeiros JV, de Oliveira JS, Vasconcelos DF. One or two ligatures inducing periodontitis are sufficient to cause fatty liver. Med Oral Patol Oral Cir Bucal. 2018 May 1;23(3):e269-e276. https://doi.org/10.4317/medoral.22204. PMID: 29680842; PMCID: PMC5945241.
48. Tomofuji T, Ekuni D, Yamanaka R, Kusano H, Azuma T, Sanbe T, Tamaki N, Yamamoto T, Watanabe T, Miyauchi M, Takata T. Chronic administration of lipopolysaccharide and proteases induces periodontal inflammation and hepatic steatosis in rats. J Periodontol. 2007;78(10):1999-2006. https://doi.org/10.1902./jop.2007.070056. PMID: 17916001.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

ETHICS APPROVAL

This study was approved by the ethical-scientific committee of the Faculty of Dentistry, Universidad Andrés Bello, Santiago (#PROPRGFO_2024_66).

FUNDING

This research was supported by a grant from Dirección General de Investigación de la Universidad Andrés Bello (DGI-UNAB, DI-36-18/CBC).

AUTHORS' CONTRIBUTIONS

Valentina Gallardo: Data acquisition and analysis, Visualization, Writing original draft.
Constanza Gómez: Data acquisition and analysis, Visualization, Writing original draft.
Dominga Rivera: Writing original draft, Writing review & Editing.
Karen Kasztan: Writing original draft, Writing review & Editing.
Alejandra Fernández: Funding acquisition, Methodology, Supervision.
Constanza Jiménez: Conceptualization, Data acquisition and analysis, Methodology, Project administration, Supervision, Visualization, Writing review & Editing.

ACKNOWLEDGEMENTS

The authors thank Universidad Andres Bello for providing access to the databases essential for this work, and the faculty of the Department of Oral Medicine & Pathology for their academic guidance and valuable feedback for this review.

ORCID

Valentina Gallardo
No Aplicate
Constanza Gómez
No Aplicate
Dominga Rivera
No Aplicate
Karen Kasztan
0009-0004-9093-7223
Alejandra Fernández
0000-0002-1970-7159
Constanza Jiménez
0000-0002-2363-4036

PUBLISHER'S NOTE

All statements expressed in this article are those of the authors alone and do not necessarily represent those of the publisher, editors, and reviewers.

COPYRIGHT

This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY 4.0). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms. ©2026.

PEER REVIEW

This manuscript was evaluated by the editors of the journal and reviewed by at least two peers in a double-blind process.

PLAGIARISM SOFTWARE

This manuscript was analyzed Compilatio plagiarism detector software. Analysis report of document ID. 0dd271f408ee7c4c71deec7e820662f8ca55c5d1

ISSN Print 0719-2460 - ISSN Online 0719-2479
https://joralres.com/index.php/JOralRes