Journal of Oral Microbiology

ISSN: 2000-2297 (Online) Journal homepage: www.tandfonline.com/journals/zjom20

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To cite this article: Luigi Santacroce, Emilio Jirillo, Lucrezia Bottalico, Skender Topi, Pier Carmine Passarelli, Antonio Mancini, Antonio D'Addona , Franklin Garcia Godoy, Veronica Folliero & Marica Colella (2025) Does a link exist between oral microbiota and oral squamous cell carcinoma? A review of current insights, Journal of Oral Microbiology, 17:1, 2569934, DOI: 10.1080/20002297.2025.2569934

To link to this article: https://doi.org/10.1080/20002297.2025.2569934

Published online: 23 Oct 2025.

JOURNAL OF ORAL MICROBIOLOGY
2025, VOL. 17, NO. 1, 2569934
https://doi.org/10.1080/20002297.2025.2569934

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REVIEW ARTICLE

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Does a link exist between oral microbiota and oral squamous cell carcinoma? A review of current insights

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ABSTRACT

Background: Oral squamous cell carcinoma (OSCC) represents more than 90% of all oral cancers. Among the known risk factors, periodontal diseases are a significant contributor to OSCC development. The balance between the various components of the oral microbial community contributes to oral and systemic health, while an altered balance leads to dysbiosis, with an excessive growth of pathogens. The OSCC microbiota is characterized by increased expression of genes related to bacterial chemotaxis, flagellar assembly, lipopolysaccharide biosynthesis and the metabolism of cofactors and vitamins.

Objective: The production of carcinogens, induction of an immune-mediated inflammatory response or immune suppression, cell proliferation and anti-apoptotic activity represent the mechanisms of oral microbe-mediated carcinogenesis. Interventions aimed at modifying the oral microbiota for inhibiting the development of OSCC should be performed; polyphenols and probiotics have demonstrated promising opportunities in cancer models and patients.

Design: We performed an extensive search on the link between OSCC and the oral microbiota accessing the main scientific databases.

Results: The aim of the present review is to describe the role of the oral microbiota in health and disease, including OSCC development, and its relationship with oral bacteria. Emphasis should also be placed on antibiotics, which may represent an additional risk factor for oral cancers. Interventions with natural products will be illustrated.

Conclusions: Current literature show a clear role of the oral microbiota in determining and control the evolution of OSCC. Specific interventions on the oral microbiota will help the prevention and management of OSCC in the next future.

KEY MESSAGES

- Oral microbiota is a complex biological niche, and its dysbiosis contributes to the pathogenesis of many diseases by promoting chronic inflammation, epithelial dysregulation and immune evasion, also creating a microenvironment where occurs production of carcinogenic metabolites (i.e. acetaldehyde from ethanol metabolism), leading to DNA damage and genomic instability in oral epithelial cells, increasing the risk of tumor initiation and progression.
- Specific bacterial species such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum* have been implicated in the development of oral squamous cell carcinoma (OSCC) through their ability to modulate host cell signaling pathways, including those involved in cell proliferation, apoptosis inhibition and metastasis.

ARTICLE HISTORY
Received 31 May 2025
Revised 12 September 2025
Accepted 29 September 2025

KEYWORDS
Oral microbiota; immunity; oral squamous cell carcinoma; periodontal disease; polyphenols; probiotics

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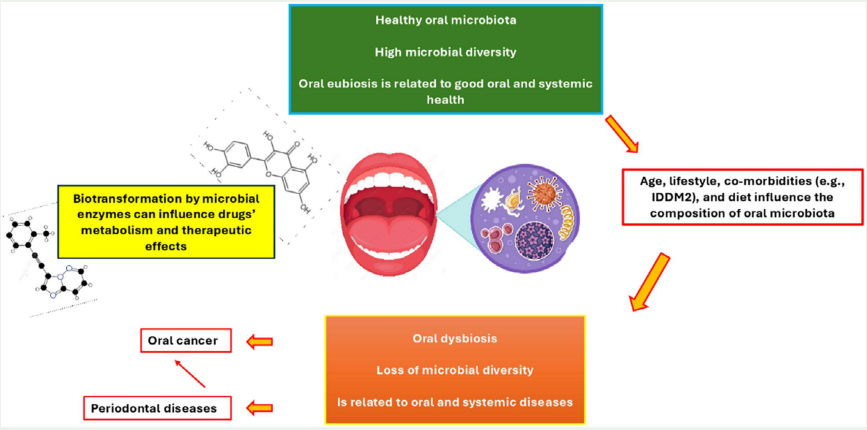
- Some specific microbial signatures in oral microbiota have been identified in both saliva and tumor tissues of OSCC patients, suggesting that they may serve as non-invasive biomarkers for early detection and diagnosis of OSCC. In addition, emerging research data show that nutraceuticals and probiotics may help restore microbial balance, reduce inflammation and inhibit carcinogenic pathways, indicating their potential role in the prevention and supportive therapy of OSCC.



Introduction

Oral cancers rank 16th among malignant tumors, with oral squamous cell carcinoma (OSCC) representing more than 90% of oral cancers [1].

Genetics, microbes, alcoholism, smoking and chewing betel are major etiologic factors accounting for the development of OSCC [2–4]. In this context, much emphasis has been placed on periodontal diseases as an important risk factor for OSCC development [5].

Under homeostatic conditions, the complex of buccal bacteria constitutes the so-called oral microbiota, which contributes to local health and protects the host from external and internal invaders [6]. The oral mucosa harbors various bacterial species, and among them, *Streptococcus, Actinomyces, Neisseria, Porphyromonas, Prevotella, Capnocytophaga, Fusobacterium* and *Veillonella* are the major ones [7]. Oral bacteria are not uniformly distributed in the mouth. For instance, on the tongue, the main commensals are *Streptococcus salivarius, Rothia mucilaginosa* and *Eubacterium* [8]. On the hard palate, *S. mitis, S. infantis, Granulicatella elegans, Gemella hemolysans* and *Neisseria subflava* are the main bacterial species [9].

A correct balance between the various oral microbial populations contributes to oral health, while an altered equilibrium leads to dysbiosis. Dysbiosis can be defined as an excessive growth of pathogenic microorganisms, which can lead to various diseases, including periodontal disease, especially when specific genetic polymorphisms are expressed [10]. Periodontal disease is a chronic inflammatory pathology characterized by a functionally proinflammatory bacteriome of the oral cavity, which may lead to oral cancer development [11]. In this respect, the microbiota of OSCC is mainly composed of *Porphyromonas gingivalis, Fusobacterium nucleatum, F. periodontium, Pseudomonas aeruginosa, Campylobacter rectus, C. showae, Peptostreptococcus stomatis, P. micros* and *Catonella morbi,* while *Streptococcus, Veillonella* and *Rothia* are less abundant in cancer tissue [12–14]. Interestingly, 16S rDNA sequencing on OSCC microbiota revealed an increase in genes related to bacterial chemotaxis, flagellar assembly, lipopolysaccharide (LPS) biosynthesis, and the metabolism of cofactors and vitamins [15].

The mechanisms of oral microbial-mediated carcinogenesis can be attributed to (I) the production of carcinogens (i.e. nitrosamines, sulfides, oxides and acetaldehyde); (II) the bacterial-induced inflammatory immune response, as well as immune suppression; and (III) cell proliferation and antiapoptotic activity [16].

Interventions aimed at modifying the OSCC microbiota are in the initial phase. In general, lactic acid bacteria have been shown to promote apoptosis, increase the numbers of cytotoxic T cells and improve tumor-suppressing gene expression [17]. Given their beneficial effects, such as antioxidants, anti-inflammatory and antibacterial activities, polyphenols represent promising opportunities for the treatment of oral diseases, including cancer [18]. Other potential therapies for OSCC are based on bacteria-mediated therapy, which more easily reaches and infiltrates the tumor tissue [19].

The aims of the present review are to describe the oral microbiota function and mechanisms of dysbiosis, which may account for the development of OSCC. Finally, emphasis should be placed on potential new treatment of OSCC based on the modification of the altered oral microbiota by natural products and the enhancement of the antitumor immune responsiveness.

Oral microbiota dysbiosis

Oral dysbiosis has been associated with the development and progression of OSCC [20]. In this context, genetic factors, scarce oral hygiene, tobacco smoking, psychological stresses and chewing betel strongly favor the association between oral pathogens and OSCC [21]. Periodontitis-correlated taxa is significantly increased in the OSCC microbiota [22]. In particular, the major components of the OSCC microbiota are *P. gingivalis, F. nucleatum, F. periodonticum, F. mortiferum* (formerly *C. rectum*), *P. aeruginosa, C. showae, P. stomatis, P. micros* and *C. morbi,* with a decrease in *Streptococcus, Veillonella* and *Rothia* [23–25]. Furthermore, *F. nucleatum* can clot with *P. gingivalis*, contributing to the growth of the latter through the generation of a reduced capnophilic environment [23]. Additionally, cooperation between *F. periodonticum* and *F. nucleatum* has been documented in tumor progression [22].

Notably, recent phylogenetic studies on *F. nucleatum* showed that it should be subdivided into five subspecies (i.e. *F. nucleatum* subsp. *animalis, F. nucleatum* subsp. *fusiforme, F. nucleatum* subsp. *nucleatum, F. nucleatum* subsp. *polymorphum* and *F. nucleatum* subsp. *vincentii*), of which the species involved in OSCC appears to be *F. nucleatum* subsp. *polymorphum*, clade 2 [26].

Moreover, hydrogen sulfide-producing bacteria, i.e. *F. naviforme, N. flavescens* and *Solobacterium moorei* can promote invasion in OSCC via the production of reactive oxygen species (ROS) and degradation of type 4 collagen [27].

The location of OSCC influences the composition of the respective oral microbiota, in particular *Capnocytophaga gingivalis, R. mucilaginosa* and *Prevotella intermedia,* which are very abundant in the lining mucosa, tongue and gingiva [28,29]. These bacteria secrete proteases, degrade the extracellular matrix as well as physical barriers, downregulate the immune response and ultimately promote the onset and progression of cancer [30].

The 16S rRNA gene amplicon sequencing techniques have contributed to a better understanding of microbiota dysbiosis in OSCC [31].

Saccharolytic and acid-tolerant bacteria, such as *Prevotella melaninogenica, Staphylococcus (S.) aureus, Veillonella parvula* and *Micrococcus* have been detected in OSCC [32]. In another study, the 16S rRNA gene sequencing of the V1–V3 regions from OSCC tissue specimens revealed the presence of an inflammatory bacteriome composed of *F. nucleatum, P. aeruginosa* and *C. concisus* [33]. In addition, a single-cell-based RNA sequencing method named INVADE reported an intratumoral microbial heterogeneity in OSCC patients, with *Fusobacterium* and *Treponema* spp. both involved in cancer progression [34]. Finally, a machine learning-based study revealed the presence of the bacterial genera *Prevotella, Stomatobaculum* and *Bifidobacterium* in OSCC patients, which correlated with the metastatic involvement of regional lymph nodes [35].

The oral microbiota dysbiosis in patients with OSCC is outlined in Table 1.

Pathogenesis and outcome of the oral dysbiosis-mediated OSCC

Oral potentially malignant disorders (OPMDs) are involved in the development of more than 80% of oral cancers [36]. Among OPMDs, oral leukoplakia (OLK), erythroplasia and lichen planus are major precancerous lesions [37]. In OLK, the oral microbiota is enriched in *Fusobacterium* spp., Bacteroidota and Bacillota phyla, which are also detected in OSCC patients [38]. Moreover, certain periodontal

Table 1. Oral microbiota composition in patients with OSCC.

- High numbers of *Capnocytophaga gingivalis, Rothia mucilaginosa* and *Prevotella. intermedia* in the lining mucosa, tongue and gingiva. These data are derived from Yang et al. (2021), who examined 65 samples from 23 OSCC patients via DNA extraction, PCR and 16S rRNA [29].
- Identification through the 16S rRNA gene amplicon sequencing techniques of *Prevotella melaninogenica, Staphylococcus aureus, Veillonella parvula,* and *Micrococcus,* as well as detection of an inflammatory bacteriome composed by *Fusobacterium nucleatum, Pseudomonas aeruginosa,* and *Campylobacter concisus.* These data are derived from Perera et al. (2006) and Hooper et al. (2018), who examined 20 OSCC patients via DNA extraction [12,33].
- Identification of *Fusobacterium nucleatum,* and *Treponema* sp. through a single-cell-based RNA sequencing method (INVADEseq), both accounting for cancer progression. Such data are derived from those of Galeano Niño et al. (2022), who examined 44 tissue samples from 11 individuals with OSCC [34].
- Involvement of *Prevotella, Stomatobaculum,* and *Bifidobacterium* in the metastatic spreading to regional lymph nodes. Such data are derived from Eun et al. (2021), who studied 54 OSCC patients via LEfSe analysis at the genus level [35].

pathogens, such as *F. nucleatum, P. intermedia* and *P. gingivalis,* have been detected in both OLK and oral cancers, with *R. mucilaginosa* less abundant in OSCC [39]. Despite the above data, more research is needed to confirm the relationship between the oral microbiota and the risk of OSCC outcome.

From a pathogenetic point of view, different mechanisms have been invoked to clarify the role of oral bacteria in the development of oral cancers.

Oral microbes produce carcinogens, i.e. nitrosamines, sulfides, oxides and acetaldehyde, which can interfere with DNA replication via binding to chemical bonds in the DNA, ultimately leading to tumorigenesis [40]. The activation of specific signaling pathways, such as the NF-kB, NrF2 and TLRs takes place in the above pathogenic mechanisms. This last feature has mostly been observed in oral *Candida albicans* infections, characterized by the presence of *Candida* in precancerous lesions. Furthermore, certain oral organisms, e.g. *Streptococcus, Rothia, P. gingivalis, Neisseria, Candida* and other yeasts can metabolize ethanol to acetaldehyde, which, in turn, generates DNA protein adducts that are linked with point mutations, chromosomal aberrations, and impaired normal DNA replication [41]. Moreover, some oral bacteria (*P. gingivalis, P. intermedia* and *F. nucleatum*) generate ROS, as well as volatile sulfide compounds, which contribute to tumor invasion, angiogenesis and metastasis [42,43].

The oral microbiota can promote cancer development via cell proliferation and anti-apoptotic activities.

For instance, *P. gingivalis* facilitates OSCC proliferation, upregulating cyclin D1 expression, thus accelerating the G1 phase of the cell cycle [44]. This effect is achieved through the miR-21/PDCD4/AP-1 negative signaling pathway. Furthermore, *F. nucleatum* causes DNA damage and promotes cell proliferation through the Ku70/p53 pathway in oral cancers [45]. Additionally, *F. nucleatum* generates elevated levels of putrescine, which promotes the malignant proliferation of esophageal squamous cell carcinoma [46]. Additionally, *F. nucleatum* quenches the cytotoxic activity of NK cells via Siglec-7 signaling, facilitating immune evasion [47]. Oral dysbiosis contributes to the OSCC pathogenesis through the production of pro-inflammatory cytokines and ROS. In a dysbiotic milieu, several pathogens contribute to oral damage, ultimately leading to OSCC development [48].

With special reference to *P. gingivalis*, this bacterium reduces host cell apoptosis by targeting heat-shock protein 27 [49]. Additionally, *P. gingivalis* can abrogate the pro-apoptotic protein BAD through Akt in primary gingival epithelial cells [50]. Another study reported that *Fusobacterium* promotes oral cancer progression by overexpressing MYC and the JAK1/AKT/STAT3 pathway [51]. Other authors reported that *Treponema denticola* facilitates OSCC development through the transforming growth factor-β (TGF-β) signaling pathway [52].

Another important pathogenetic mechanism elicited by oral microbiota dysbiosis is the subversion of the buccal immune system. First, the altered oral microbiota triggers a robust inflammatory response either locally or systemically. In this context, bacterial LPS or endotoxins, which are among the main components of the outer membrane of the cell wall of Gram-negative bacteria, bind to the TLR-4 on the surface of macrophages, with the release of pro-inflammatory cytokines, chemokines, phospholipase A2, prostaglandins and acute phase proteins [53,54]. For instance, the release of interleukin (IL)-1β induces angiogenesis and cancer progression by activating endothelial cells, with the release of vascular endothelial growth factor (VEGF) and tumor necrosis factor (TNF)-α as proangiogenic substances [55]. Furthermore, IL-1β promotes tumor invasiveness and aggression, decreasing E-cadherin expression while enhancing matrix-metalloproteinase (MMP)-9. Additionally, IL-6 exerts pro-tumorigenic activities, inducing oxidative stress and mitochondrial damage.

Several oral anaerobes form slimes (i.e. *Prevotella* spp., *Treponema* spp. and *Capnocytophaga* spp.) that are capable of driving chronic inflammation and impairing immune clearance [56]. Recently, it has been reported that these microorganisms can suppress both antigen presentation and phagocytosis, polarizing macrophages toward the M2 phenotype and recruiting suppressor cells via IL-6, CXCL2 and CCL5 signaling [57,58].

Oral bacteria can also favor tumor escape from immunosurveillance. *P. gingivalis* suppresses the cytolytic function of CD8 + T cells, upregulating PD-L1 expression in dendritic cells DCS through Akt-STAT3 signaling [59]. In addition, outer membrane vesicles and peptidoglycans from *P. gingivalis* induces PD-L1/PD-L2 expression on tumor and immune cells through RIP2-mediated pathways, fostering T-cell exhaustion and Treg expansion [58]. Additionally, *P. gingivalis* increases Foxp3 + T regulatory (TRG) cells, with the release of IL-10, which, in turn, suppresses antineoplastic T-cell function and transforms monocytes into suppressor DCs [60]. In the same direction, *P. gingivalis* upregulates the immune checkpoint B7H-4 and lysine demethylation 5B, thus favoring tumor immune escape [61]. On the other hand, *F. nucleatum* exerts immune suppression in diverse ways, interacting with TIGIT, an inhibitory receptor on natural killer (NK) cells, while promoting M2 polarization of macrophages, a suppressive cellular subset [62–64].

Regarding the oral microbiota-mediated immune enhancement, evidence has shown that *P. gingivalis* could activate IL17 + gamma-delta T cells through the STAT3 pathway, thus leading to infiltration of M2-tumor-associated macrophages into OSCC [65].

In addition, *F. nucleatum* promoted OSCC progression through M2 polarization because of the crosstalk between OSCC cells and macrophages [66].

Studies on the intra-tumoral microbiota in oral cancers have demonstrated an immunosuppressive profile, which may favor tumor immune escape [67].

The major pathogenetic events during OSCC progression are depicted in Figure 1.

Impact of the oral microbiota on the cancer therapy

The role of the oral microbiota in cancer therapy outcomes has been poorly investigated. Instead, a body of evidence suggests the role of the gut microbiota in the efficacy of cancer therapy, which will be discussed in the next paragraphs.

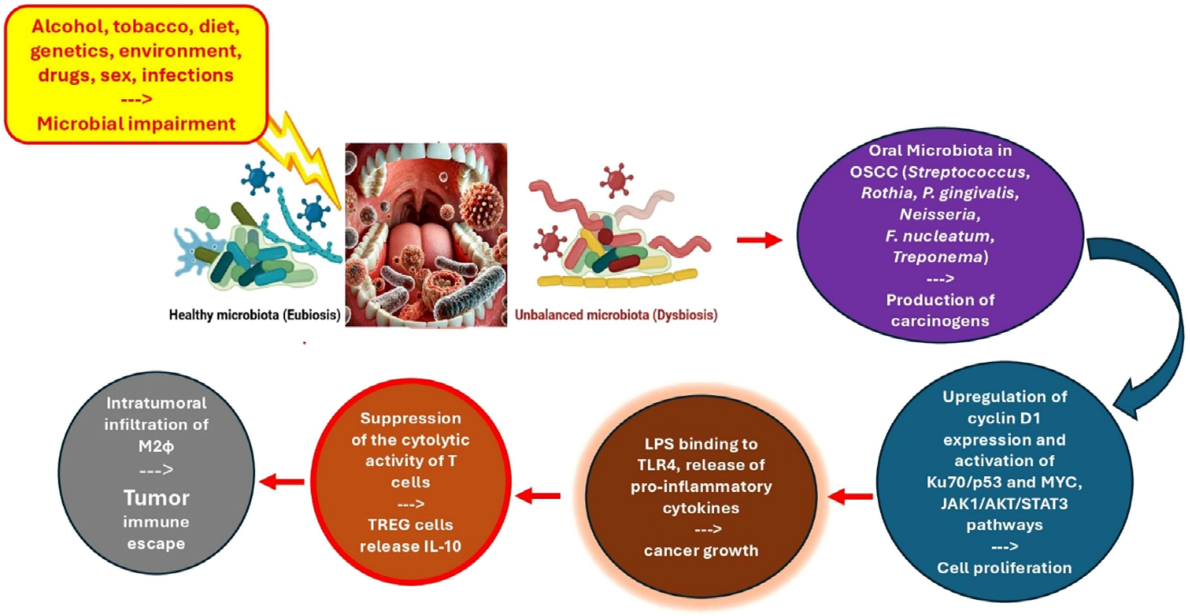


Figure 1. Bacterial pathogenesis of OSCC development. The oral microbiota promotes OSCC progression by producing carcinogens, promoting cell proliferation, inflammation and suppressing the antitumor immune response.

Pan-cancer analyses showed how oral microorganisms can amplify TLR/NF-κB/STAT3 signaling, stimulating the process of epithelial–mesenchymal transition and angiogenesis, also generating immunomodulatory metabolites that increase regulatory T-cell activity [68]. According to recent literature, the clinical relevance of these mechanisms correlates with a poor immune infiltration of tumors as well as with the failure of therapies based on immune checkpoint inhibitors [69].

A report documented that oral *F. nucleatum, Bacteroides fragilis* and *Escherichia coli* improved the adoptive cell therapy in colorectal cancer patients, increasing the T cytotoxic cell immune response [70]. Furthermore, Heshiki and coll. [71] demonstrated that *B. xilanisolvens* and *B. ovatus*, as components of the gut microbiota, improved the efficacy of chemotherapy in a heterogeneous cohort of cancer patients. In the same paper, it was reported that the administration by gavage of *B. xilanisolvens* and *B. ovatus* to mice under erlotinib therapy induced the expression of CXCL9 and interferon-γ, reducing the tumor volume by 46% in comparison with controls. Additionally, gut microbes could enhance the cyclophosphamide effects in cancer [72]. Accordingly, cyclophosphamide administration was shown to mediate the translocation of Gram-positive bacteria to secondary lymphoid organs, with the expansion of T helper(h) 17 and memory Th1 cells, contributing to cancer cell destruction. However, abrogation of these T cell subsets by antibiotic treatment induced resistance of cancer cells to cyclophosphamide in mice, which was partially restored by the adoptive transfer of Th17 cells.

A special reference is cancer radiotherapy; indeed, it generates harmful effects on the host, especially on nearby cells and immune cells. Notably, researchers have speculated that the gut microbiota may enhance the immune response in cancer patients under radiotherapy [73,74].

Immune checkpoint blockers are monoclonal antibodies for human use that act against molecules, i.e. PD-1, PD-L1 or CTLA-4, which inhibit the antitumor immune responsiveness [75,76]. Various gut bacteria have been shown to potentiate checkpoint inhibitor immunotherapy, such as *Bifidobacterium* spp., *Enterococcus hirae* and *Akkermansia muciniphila,* whose fecal levels were very high in cancer patients who respond well to such treatment [77,78]. In lung cancer patients treated with anti-PD-1 monoclonal antibodies, *Segatella copri* (formerly *Prevotella copri), B. longum* and *Alistipes putredinis* were the major bacteria in responders, along with a greater number of NK cells and memory CD8 + cytotoxic T cells in the periphery [79]. Furthermore, *A. muciniphila* and *Bifidobacterium* spp. or fecal microbiota transplantation reinforced the PD-1-based immunotherapy in cancer patients and improved antigenic presentation by DCs and, consequently, the T cytotoxic response [80]. Moreover, in melanoma patients treated with ipilimumab, the gut levels of *Barnasiellaceae, Bacteroidaceae* and *Rikenellaceae* were associated with resistance to colitis, while intestinal level of *Faecalibacterium* was related to a more beneficial outcome [81,82].

In recent years, bacteria-mediated tumor therapy has started, using non-pathogenic obligate anaerobes and facultative anaerobes, which can infiltrate and selectively replicate in the context of solid tumors, transport and amplify genes encoding pro-drug converting enzymes, toxins, angiogenesis inhibitors and cytokines [83,84]. Clinically, in a phase I trial, *Salmonella typhimurium* expressing cytosine deaminase was intratumorally administered in combination with 5-fluorocytosine (5-FC) to patients with advanced or metastatic cancer, followed by oral administration for 15 days; then, the determination of bacterial persistence and 5-FC levels in the tumor was measured [85,86].

Until now, no evidence of bacteria-mediated tumor therapy in OSCC patients has been reported, even if this tumor is very accessible to treatment at the site. Therefore, more research is needed in this specific field.

Attempts to normalize oral dysbiosis with natural products

In recent years, efforts have been made to prevent and treat oral diseases with nutrients. Among them, polyphenols have been found to promote human oral health [87–89]. Dietary polyphenols are commonly found in fruits, vegetables, cereals and beverages, such as red wine, tea, coffee and cocoa [90,91]. Polyphenols are classified as flavonoids and non-flavonoids, with the former categorized into flavanols, flavanones, flavonols, flavones, isoflavones, anthocyanins and proanthocyanidins, and the latter subgrouped into caffeic acid, lignans, and stilbenes (resveratrol) [92,93]. Polyphenols are endowed with a series of beneficial effects on the host, including antioxidant, anti-allergic, anti-inflammatory, antitumoral,

antihypertensive and antimicrobial effects [94,95]. In detail, red wine polyphenols have been shown to act *in vitro* on human monocytes with the release of NO, which seems to protect people from cardiovascular risk [96]. In terms of infectious events, *in vitro* experiments have demonstrated that polyphenols inhibit the binding of LPS to TLR-4 on human monocytes by steric hindrance, thus reducing cellular activation, and ultimately the release of inflammatory mediators [97].

Furthermore, *in vitro* polyphenols inhibit the LPS-mediated expression of NF-kB in human monocytes, thus reducing the production of pro-inflammatory cytokines [97]. Notably, polyphenols can induce the *in vitro* expansion of Foxp3 + TREG cells, with the production of the anti-inflammatory cytokine, IL-10, as also demonstrated in patients with nickel-mediated contact dermatitis [98,99]. In view of their anti-inflammatory, antioxidant, and immunomodulating properties, polyphenols have the potential to correct oral dysbiosis. In this respect, there is evidence that certain molecules, i.e. chlorogenic acid, prenylated flavonoids, theaflavins, baicalein and proanthocyanidins, exert antimicrobial activity against periodontal pathogens, e.g. *P. gingivalis, S. aureus, S. mitis, F. nucleatum* and *Aggregatibacter actinomycetemcomitans* [100,101]. In detail, Orophenol®, which is composed of polyphenols derived from berries could suppress the production of ROS by oral keratinocytes stimulated by *P. gingivalis,* thus reducing the damage provoked by this pathogen [102]. Additionally, polyphenols extracted from the pomace of the Croatina grape variety, as well as from *Lonicera caerulea* berries, *in vitro* exhibited antioxidant activity, reduced macrophage activation, intracellular glutathione depletion, and lipid peroxidation in LPS-treated cells [103,104]. Furthermore, the impact of polyphenols on the inflammatory reaction in periodontitis has been the subject of intensive research. *In vitro,* cranberry PACs mitigated inflammation, reducing the levels of IL-1 beta, IL-6, IL-8 and TNF-α through downregulation of the MAPK-A1 pathway, NF-kB expression and the secretion of MMP-3, MMP-8 and MMP-9 [105,106]. The combination of resveratrol and silymarin also decreased the release of IL-6, IL-8 and TNF-α from human-cultured fibroblasts [107]. Red wine polyphenols reduce the inflammatory process and bone resorption in rat apical periodontitis, modifying the expression of osteoprotegerin, IL-10 and tartrate-resistant acid phosphatase [108].

Clinically, mouthwash with fermented lingonberry juice for one year reduces inflammation in the oral mucosa and the loss of bone and periodontal tissues in patients with periodontitis [109]. PAC administration in patients with stage III-IV periodontitis resulted in an improvement in mild pockets and an increase in salivary MMP-3 [110]. Additionally, oligomeric PACs are effective in preventing human gingivitis [111].

In agreement with the aims of the present review, several effects of polyphenols against OSCC development have been reported [112]. Green and black tea polyphenols decreased tumor incidence and tumor bulk in experimental models of OSCC [113–115]. The administration of PACs reduced the proliferation of OSCC cells after transfection with human papillomavirus (HPV)-16 [116]. In terms of mechanisms of action, anthocyanins from black rice inhibited the metastasis of human oral cancer cells, CAL 27 cells, through reduced expression of MMP-2, MMP-9 and NF-kB p65 [117]. Additionally, epigallocatechin-3-gallate (EGCG) stopped the invasion of human oral cancer cells, inhibiting the expression of MMP-2, as did urokinase-plasminogen activator [118]. EGCG also inhibited the *in vivo* tumor growth of SCC-9 cells in a murine model [119]. A randomized placebo-controlled phase 1 trial based on the administration of APG-157, enriched in polyphenols, even including curcumin, to oral cancer patients demonstrated that polyphenols were absorbed, with a drastic reduction of IL-1β, IL-6 and IL-8 in the saliva, and of *Bacteroides* species [120].

The above-cited data suggest that polyphenols may exert chemopreventive and therapeutic activities against OSCC; however, further studies are needed to develop effective delivery systems, given the unfavorable physicochemical properties of polyphenols.

Recently, encapsulation has been a novel technique to coat polyphenols, enhancing their bioavailability and functions. In particular, liposomes and nanoparticles have been used to encapsulate polyphenols, showing an enhanced ability to enter cells and perform their biological activities [121,122].

Other natural products with antineoplastic effects against OSCC are probiotics.

Probiotics are defined as live organisms that offer protection to the host when they are administered in adequate amounts [123].

Among the various activities displayed by probiotics, the most important are the modulation of gut microbiota components, elimination of pathogens, immunomodulation, epithelial cell proliferation and differentiation of the epithelial barrier [124,125].

The impact of probiotics on the oral cavity has been investigated. Importantly, to manipulate the periodontal microbiota, probiotics should adhere to and colonize the oral mucosa, where they participate in the oral biofilm formation [126,127]. In detail, the synbiotic *Lacticaseibacillus rhamnosus* GG/L-arginine inhibited the growth of *S. mutans* while allowing longer survival and adherence of LGG in the oral cavity [128]. Additionally, a combination of prebiotics (xylitol, arabinose and xylose) with probiotics (*Limosilactobacillus fermentum, Lactiplantibacillus plantarum* and *Lacticaseibacillus paracasei)* could reduce the formation of oral biofilms composed of *C. albicans, S. mutans* and *P. gingivalis* [129].

Few studies have been conducted on the effects of probiotics on oral cancer. In this respect, the *in vitro* effects of *Lacticaseibacillus rhamnosus* GG (LGG) on the HSG-3 OSCC cell line have been investigated [130]. In detail, LGG could enhance the anti-cancer effects of the drug geniposide (obtained from *Gardenia jasminoides),* thus supporting the use of this combination therapy in patients with OSCC. Furthermore, *L. plantarum* induced the apoptosis of oral cancer KB cells, upregulating PTEN and downregulating MAPK signaling pathways [131]. Another probiotic, *Acetobacter syrygii,* has been shown to exert cytotoxic effects on KB human oral cancer cells similar to those of cisplatin [132]. *Ligilactobacillus salivarius* REN suppressed rat oral cancer induced by 4-nitroquinoline 1-oxide, protecting it from oxidative DNA damage [133].

Taken together, the above data suggest the role of probiotics in oral cancer prevention, even if more clinical trials are needed to confirm such a contention.

In this framework, emphasis should be placed on the role of antibiotics in cancer development. Oral antibiotic abuse and misuse may lead to resistance to certain bacterial strains, causing gut dysbiosis and increasing the risk of cancer [134–137]. However, the impact of antibiotic use on OSCC development has been poorly investigated. The possible interference of antibiotics with the gut microbiota composition and development of OSCC should be considered, including supporting therapy with probiotics [138].

The effects of natural products on oral microbiota pathologies are indicated in Table 2.

Discussion and conclusions

The oral microbiota has been demonstrated to account for OSCC development through various mechanisms, including carcinogen production, suppression of cell death and the immune response, and an increase in angiogenesis. The development of OSCC can be attributed to several classical pathogens, even if contradictory results have been obtained owing to different detection methodologies and techniques. For example, the use of 16S rRNA sequencing to detect the oral microbiota may be restrictive because of its small sample size. Therefore, alternative methods for quantitative detection are needed, such as LDA effect size analysis, fluorescent quantitative PCR, and flow cytometry.

Two hypotheses have been formulated from a pathogenic point of view: bacteria are the first trigger of OSCC development, or oral lesions attract bacteria. Therefore, an *in vitro* approach using cultured cell lines or long-term cohort studies is needed to clarify such a controversy, offering a more complete view of both the microbiological and clinical features of OSCC.

Notably, certain viruses are considered key factors in oral cancer, but their role remains unclear and is not discussed in this review. Certain viral genomes (e.g. those of HPV-16 and Epstein-Barr virus (EBV))

Table 2. Effects of natural products on oral microbiota and related pathologies.

POLYPHENOLS:
- Antibacterial activity against *P. gingivalis, S. aureus, S. mitis, F. nucleatum,* and *Aggregatibacter actinomycetemcomitans* by chlorogenic acid, prenylated flavonoids, theaflavins, baicalein, and proanthocyanidins (PACs).
- *In vitro* reduction of ROS production, antioxidant activity, macrophage activation, and LPS-mediated lipid peroxidation by Orophenol®, a mixture of polyphenols from the pomace of Croatina grape, and *L. caerulea* berries.
- Mitigation of periodontitis *in vitro* models by PACs, resveratrol plus silymarin, and red wine polyphenols.
- In patients with periodontitis, a reduction in the inflammatory process with fermented lingonberry juice mouthwash or PAC administration.
- In experimental models of OSCC, a reduction in tumor bulk, cancer cell proliferation, and metastatic spread by PACS and EGCG.
- In a phase I trial in patients with oral cancer, a reduction in proinflammatory cytokines and *Bacteroides* spp.

PROBIOTICS:
- Prevention of oral biofilm formation, and periodontal disease with reduced risk of cancer by synbiotics *L. rhamnosus* GG plus arginine, *L. fermentum, L. plantarum,* and *L. paracasei* plus xylitol, arabinose, and xylose.
- *L. rhamnosus* GG-mediated enhancement of the drug geniposide.
- *L. plantarum* and *Aerobacter syringae* mediated the apoptosis of oral cancer KB cells.
- *L. salivarius* REN-mediated suppression of rat oral carcinogenesis induced by 4-nitroquinoline 1-oxide.

have been repeatedly detected in OSCC tissues and were considered oncogenic factors because of their potential ability to induce oncogenic transformation.

However, the causal relationship between these viruses and oral carcinogenesis remains unclear because OSCC has a multifactorial etiology, and epidemiological data are inconsistent. Furthermore, the molecular events linking viral infection to malignant transformation in oral tissues are not fully defined.

For these reasons, the potential role of viruses in oral cancer has been acknowledged by many researchers but is often excluded because stronger evidence is needed to confirm their involvement.

Polyphenols, probiotics and bacteria-mediated cancer therapy exhibit some beneficial effects *in vitro* and *in vivo* in experimental models, while clinical trials are still scarce to understand the effectiveness of these interventions in OSCC patients. In this regard, these novel therapeutic interventions may enhance traditional treatments and/or reduce side effects for a better comprehension of the theme; these important aspects should be explored.

Author contributions

Concept and design: L. S., E. J. and L. B. Acquisition, analysis and interpretation of data: L. B., S. T., A. M., P. C. P., A. D., F. G. G. and V. F. Drafting of the manuscript: E. J. and L. S. Critical revision of the manuscript for important intellectual content: all the authors. Administrative, technical, or material support: A.M. and L.S. Supervision: M. C. Project administration: L. S. and E. J. All the authors have read and agreed to the published version of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

No funds available for this paper.

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Data availability statement

All data for this manuscript have been reported in the paper.

Institutional review board statement

Not applicable.

Informed consent statement

Not applicable.

References

[1] Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol. 2009;45(4-5):309–316. doi: 10.1016/j.oraloncology.2008.06.002

[2] Hoes L, Dok R, Verstrepen K, et al. Ethanol-induced cell damage can result in the development of oral tumors. Cancers. 2021;13(15):3846. doi: 10.3390/cancers13153846
[3] Ford P, Rich A. Tobacco use and oral health. Addiction. 2021;116(12):3531–3540. doi: 10.1111/add.15513
[4] Wang W, Chiu Y, Wang Y, et al. Effects of *DSM-5* betel-quid-related symptoms, pathological behaviors, and use disorder on oral squamous cell carcinoma risk. Cancers. 2022;14(16):3974. doi: 10.3390/cancers14163974
[5] Karpiński T. Role of oral microbiota in cancer development. Microorganisms. 2019;7(1):20. doi: 10.3390/microorganisms7010020
[6] Santacroce L, Sardaro N, Topi S, et al. The pivotal role of oral microbiota in health and disease. J Biol Regul Homeost Agents. 2020;34(2):733–737. doi: 10.23812/20-127-L-45
[7] Aas J, Paster B, Stokes L, et al. Defining the normal bacterial flora of the oral cavity. J Clin Microbiol. 2005;43(11):5721–5732. doi: 10.1128/JCM.43.11.5721-5732.2005
[8] Kazor C, Mitchell P, Lee A, et al. Diversity of bacterial populations on the tongue dorsa of patients with halitosis and healthy patients. J Clin Microbiol. 2003;41(2):558–563. doi: 10.1128/JCM.41.2.558-563.2003
[9] Abusleme L, Dupuy A, Dutzan N, et al. The subgingival microbiome in health and periodontitis and its relationship with community biomass and inflammation. ISME J. 2013;7(5):1016–1025. doi: 10.1038/ismej.2012.174
[10] Cafiero C, Grippaudo C, Dell'Aquila M, et al. Association between vitamin D receptor gene polymorphisms and periodontal bacteria: a clinical pilot study. Biomolecules. 2022;12(6):833. doi: 10.3390/biom12060833
[11] Perera M, Al-Hebshi N, Perera I, et al. Inflammatory bacteriome and oral squamous cell carcinoma. J Dent Res. 2018;97(6):725–732. doi: 10.1177/0022034518767118
[12] Hooper S, Crean S, Lewis M, et al. Viable bacteria present within oral squamous cell carcinoma tissue. J Clin Microbiol. 2006;44(5):1719–1725. doi: 10.1128/JCM.44.5.1719-1725.2006
[13] Luo Z, Lv S, Lou F, et al. Roles of intralesional bacteria in the initiation and progression of oral squamous cell carcinoma. Cancer Med. 2024;13(18):e70209. doi: 10.1002/cam4.70209
[14] Talapko J, Erić S, Meštrović T, et al. The impact of oral microbiome dysbiosis on the aetiology, pathogenesis, and development of oral cancer. Cancers. 2024;16(17):2997. doi: 10.3390/cancers16172997
[15] Zhang L, Liu Y, Zheng H, et al. The oral microbiota may have influence on oral cancer. Front Cell Infect Microbiol. 2020;9:476. doi: 10.3389/fcimb.2019.00476
[16] Wang J, Gao B. Mechanisms and potential clinical implications of oral microbiome in oral squamous cell carcinoma. Curr Oncol. 2023;31(1):168–182. doi: 10.3390/curroncol31010011
[17] Zhong L, Zhang X, Covasa M. Eemerging roles of lactic acid bacteria in protection against colorectal cancer. World J Gastroenterol. 2014;20(24):7878–7886. doi: 10.3748/wjg.v20.i24.7878
[18] Guo Y, Li Z, Chen F, et al. Polyphenols in oral health: homeostasis maintenance, disease prevention, and therapeutic applications. Nutrients. 2023;15(20):4384. doi: 10.3390/nu15204384
[19] Irfan M, Delgado R, Frias-Lopez J. The oral microbiome and cancer. Front Immunol. 2020;11:591088. doi: 10.3389/fimmu.2020.591088
[20] Pignatelli P, Romei F, Bondi D, et al. Microbiota and oral cancer as a complex and dynamic microenvironment: a narrative review from etiology to prognosis. Int J Mol Sci. 2022;23(15):8323. doi: 10.3390/ijms23158323
[21] Hsiao J, Chang C, Lee W, et al. The interplay between oral microbiome, lifestyle factors and genetic polymorphisms in the risk of oral squamous cell carcinoma. Carcinogenesis. 2018;39(6):778–787. doi: 10.1093/carcin/bgy053
[22] Zhao H, Chu M, Huang Z, et al. Variations in oral microbiota associated with oral cancer. Sci Rep. 2017;7(1):11773. doi: 10.1038/s41598-017-11779-9
[23] Santacroce L, Passarelli P, Azzolino D, et al. Oral microbiota in human health and disease: a perspective. Exp Biol Med. 2023;248(15):1288–1301. doi: 10.1177/15353702231187645
[24] Sukmana B, Saleh R, Najim M, et al. Oral microbiota and oral squamous cell carcinoma: a review of their relation and carcinogenic mechanisms. Front Oncol. 2024;14:1319777. doi: 10.3389/fonc.2024.1319777
[25] Karpiński T. Role of oral microbiota in cancer development. Microorganisms. 2019;7(1):20. doi: 10.3390/microorganisms7010020
[26] Wolf M, Steinberg T, Scholz K, et al. The rise and evolving role of Fusobacterium nucleatum subspecies. Curr Res Microb Sci. 2025;9:100414. doi: 10.1016/j.crmicr.2025.100414
[27] Diaz P, Zilm P, Rogers A. Fusobacterium nucleatum supports the growth of porphyromonas gingivalis in oxygenated and carbon-dioxide-depleted environments. Microbiology. 2002;148(Pt 2):467–472. doi: 10.1099/00221287-148-2-467
[28] Yaegaki K. Oral malodorous compounds are periodontally pathogenic and carcinogenic. Jpn Dent Sci Rev. 2008;44:100–108. doi: 10.1016/j.jdsr.2008.06.003
[29] Yang K, Wang Y, Zhang S, et al. Oral microbiota analysis of tissue pairs and saliva samples from patients with oral squamous cell carcinoma – a pilot study. Front Microbiol. 2021;12:12719601. doi: 10.3389/fmicb.2021.719601
[30] Gopinath D, Menon R, Wie C, et al. Differences in the bacteriome of swab, saliva, and tissue biopsies in oral cancer. Sci Rep. 2021;11(1):1181. doi: 10.1038/s41598-020-80859-0
[31] Santacroce L, Muzio E, Bottalico L, et al. Subversion of the oral microbiota and induction of immune-mediated systemic inflammation with special reference to periodontitis: current knowledge and perspectives. Endocr Metab Immune Disord Drug Targets. 2023;23(4):470–484. doi: 10.2174/1871530322666220629101357

[32] Gopinath D, Menon R, Banerjee M, et al. Culture-independent studies on bacterial dysbiosis in oral and oropharyngeal squamous cell carcinoma: a systematic review. Crit Rev Oncol Hematol. 2019;139:31–40. doi: 10.1016/j.critrevonc.2019.04.018
[33] Perera M, Al-Hebshi N, Perera I, et al. Inflammatory bacteriome and oral squamous cell carcinoma. J Dent Res. 2018;97(6):725–732. doi: 10.1177/0022034518767118
[34] Galeano Niño J, Wu H, LaCourse K, et al. Effect of the intratumoral microbiota on spatial and cellular heterogeneity in cancer. Nature. 2022;611(7937):810–817. doi: 10.1038/s41586-022-05435-0
[35] Eun Y, Lee J, Kim S, et al. Oral microbiome associated with lymph node metastasis in oral squamous cell carcinoma. Sci Rep. 2021;11(1):23176. doi: 10.1038/s41598-021-02638-9
[36] Kumari P, Debta P, Dixit A. Oral potentially malignant disorders: etiology, pathogenesis, and transformation into oral cancer. Front Pharmacol. 2022;13:825266. doi: 10.3389/fphar.2022.825266
[37] Hashimoto K, Shimizu D, Ueda S, et al. Feasibility of oral microbiome profiles associated with oral squamous cell carcinoma. J Oral Microbiol. 2022;14(1):2105574. doi: 10.1080/20002297.2022.2105574
[38] Pietrobon G, Tagliabue M, Stringa L, et al. Leukoplakia in the oral cavity and oral microbiota: a comprehensive review. Cancers. 2021;13(17):4439. doi: 10.3390/cancers13174439
[39] Halboub E, Al-Ak'hali M, Alamir A, et al. Tongue microbiome of smokeless tobacco users. BMC Microbiol. 2020;20(1):201. doi: 10.1186/s12866-020-01883-8
[40] Krogh P. The role of yeasts in oral cancer by means of endogenous nitrosation. Acta Odontol Scand. 1990;48(1):85–88. doi: 10.3109/00016359009012738
[41] Ayuningtyas N, Mahdani F, Pasaribu T, et al. Role of *Candida albicans* in oral carcinogenesis. Pathophysiology. 2022;29(4):650–662. doi: 10.3390/pathophysiology29040051
[42] Sami A, Elimairi I, Stanton C, et al. The role of the microbiome in oral squamous cell carcinoma with insight into the microbiome-treatment axis. Int J Mol Sci. 2020;21(21):8061. doi: 10.3390/ijms21218061
[43] Yaegaki K, Qian W, Murata T, et al. Oral malodorous compound causes apoptosis and genomic DNA damage in human gingival fibroblasts. J Periodontal Res. 2008;43(4):391–399. doi: 10.1111/j.1600-0765.2007.01052.x
[44] Chang C, Wang H, Liu J, et al. *Porphyromonas gingivalis* infection promoted the proliferation of oral squamous cell carcinoma cells through the miR-21/PDCD4/AP-1 negative signaling Pathway. ACS Infect Dis. 2019;5(8):1336–1347. doi: 10.1021/acsinfecdis.9b00032
[45] Geng F, Zhang Y, Lu Z, et al. *Fusobacterium nucleatum* caused DNA damage and promoted cell proliferation by the ku70/p53 pathway in oral cancer cells. DNA Cell Biol. 2020;39(1):144–151. doi: 10.1089/dna.2019.5064
[46] Galaski J, Rishiq A, Liu M, et al. Fusobacterium nucleatum subsp. nucleatum RadD binds siglec-7 and inhibits NK cell-mediated cancer cell killing. iScience. 2024;27(6):110157. doi: 10.1016/j.isci.2024.110157
[47] Cabral L, Martins I, Paulo E, et al. Molecular mechanisms in the carcinogenesis of oral squamous cell carcinoma: a literature review. Biomolecules. 2025;15(5):621. doi: 10.3390/biom15050621
[48] Azzolino D, Carnevale-Schianca M, Santacroce L, et al. The oral-gut microbiota axis across the lifespan: new insights on a forgotten interaction. Nutrients. 2025;17(15):2538. doi: 10.3390/nu17152538
[49] Lee J, Mir A, Edraki A, et al. Potent Cas9 inhibition in bacterial and human cells by AcrIIC4 and AcrIIC5 anti-CRISPR proteins. mBio. 2018;9(6):e02321-18. doi: 10.1128/mBio.02321-18
[50] Yao L, Jermanus C, Barbetta B, et al. Porphyromonas gingivalis infection sequesters pro-apoptotic bad through Akt in primary gingival epithelial cells. Mol Oral Microbiol. 2010;25(2):89–101. doi: 10.1111/j.2041-1014.2010.00569.x
[51] Harrandah A, Chukkapalli S, Bhattacharyya I, et al. Fusobacteria modulate oral carcinogenesis and promote cancer progression. J Oral Microbiol. 2020;13(1):1849493. doi: 10.1080/20002297.2020.1849493
[52] Peng R, Sun Y, Zhou X, et al. *Treponema denticola* promotes OSCC development via the TGF-β signaling pathway. J Dent Res. 2022;101(6):704–713. doi: 10.1177/00220345211067401
[53] Topi S, Bottalico L, Charitos I, et al. Biomolecular mechanisms of autoimmune diseases and their relationship with the resident microbiota: friend or foe? Pathophysiology. 2022;29(3):507–536. doi: 10.3390/pathophysiology29030041
[54] Akbari E, Epstein J, Samim F. Unveiling the hidden links: periodontal disease, fusobacterium nucleatum, and cancers. Curr Oncol Rep. 2024;26:1388–1397. doi: 10.1007/s11912-024-01591-w
[55] Coussens L, Werb Z. Inflammation and cancer. Nature. 2002;420(6917):860–867. doi: 10.1038/nature01322
[56] Wei K, Ma Y, Xu J, et al. Oral and intratumoral microbiota influence tumor immunity and patient survival. Front Immunol. 2025;16:1572152. doi: 10.3389/fimmu.2025.1572152
[57] Liu S, Zhou X, Peng X, et al. Porphyromonas gingivalis promotes immunoevasion of oral cancer by protecting cancer from macrophage attack. J Immunol. 2020;205(1):282–289. doi: 10.4049/jimmunol.1901138
[58] Wen L, Mu W, Lu H, et al. Porphyromonas gingivalis promotes oral squamous cell carcinoma progression in an immune microenvironment. J Dent Res. 2020;99(6):666–675. doi: 10.1177/0022034520909312
[59] Ren J, Han X, Lohner H, et al. P. gingivalis Infection upregulates PD-L1 expression on dendritic cells, suppresses CD8+ T-cell responses, and aggravates oral cancer. Cancer Immunol Res. 2023;11(3):290–305. doi: 10.1158/2326-6066.CIR-22-0541
[60] Arjunan P, Meghil M, Pi W, et al. Oral pathobiont activates anti-apoptotic pathway, promoting both immune suppression and oncogenic cell proliferation. Sci Rep. 2018;8(1):16607. doi: 10.1038/s41598-018-35126-8

[61] Yuan X, Liu Y, Li G, et al. Blockade of immune-checkpoint B7-H4 and lysine demethylase 5B in esophageal squamous cell carcinoma confers protective immunity against *P. gingivalis* infection. Cancer Immunol Res. 2019;7(9):1440–1456. doi: 10.1158/2326-6066.CIR-18-0709
[62] Gur C, Ibrahim Y, Isaacson B, et al. Binding of the Fap2 protein of fusobacterium nucleatum to human inhibitory receptor TIGIT protects tumors from immune cell attack. Immunity. 2015;42(2):344–355. doi: 10.1016/j.immuni.2015.01.010
[63] Nigam M, Mishra A, Deb V, et al. Evaluation of the association of chronic inflammation and cancer: insights and implications. Biomed Pharmacother. 2023;164:115015. doi: 10.1016/j.biopha.2023.115015
[64] Sun J, Tang Q, Yu S, et al. F. nucleatum facilitates oral squamous cell carcinoma progression via GLUT1-driven lactate production. EBioMedicine. 2023;88:104444. doi: 10.1016/j.ebiom.2023.104444
[65] Xu S, Wei M, Li G, et al. Comprehensive analysis of the nocardia cyriacigeorgica complex reveals five species-level clades with different evolutionary and pathogenicity characteristics. mSystems. 2022;7(3):e0140621. doi: 10.1128/msystems.01406-21
[66] Nie F, Zhang J, Tian H, et al. The role of CXCL2-mediated crosstalk between tumor cells and macrophages in Fusobacterium nucleatum-promoted oral squamous cell carcinoma progression. Cell Death Dis. 2024;15(4):277. doi: 10.1038/s41419-024-06640-7
[67] Pratap Singh R, Kumari N, Gupta S, et al. Intratumoral microbiota changes with tumor stage and influences the immune signature of oral squamous cell carcinoma. Microbiol Spectr. 2023;11(4):e0459622. doi: 10.1128/spectrum.04596-22
[68] Zhou Y, Meyle J, Groeger S. Periodontal pathogens and cancer development. Periodontol 2000. 2024;96(1):112–149. doi: 10.1111/prd.12590
[69] Gunjur A, Shao Y, Rozday T, et al. A gut microbial signature for combination immune checkpoint blockade across cancer types. Nat Med. 2024;30(3):797–809. doi: 10.1038/s41591-024-02823-z
[70] Azzolino D, Felicetti A, Santacroce L, et al. The emerging role of oral microbiota: a key driver of oral and systemic health. Am J Dent. 2025;38(3):111–116.
[71] Heshiki Y, Vazquez-Uribe R, Li J, et al. Predictable modulation of cancer treatment outcomes by the gut microbiota. Microbiome. 2020;8(1):28. doi: 10.1186/s40168-020-00811-2
[72] Viaud S, Saccheri F, Mignot G, et al. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. Science. 2013;342(6161):971–976. doi: 10.1126/science.1240537
[73] Roy S, Trinchieri G. Microbiota: a key orchestrator of cancer therapy. Nat Rev Cancer. 2017;17(5):271–285. doi: 10.1038/nrc.2017.13
[74] Kroemer G, Galluzzi L, Kepp O, et al. Immunogenic cell death in cancer therapy. Annu Rev Immunol. 2013;31:51–72. doi: 10.1146/annurev-immunol-032712-100008
[75] Magrone T, Jirillo E. Update on mechanisms of adaptive resistance to immune check point blockers in malignancies: a short commentary. Curr Pharm Des. 2018;24(45):5349–5351. doi: 10.2174/1381612824459041615491 7
[76] Schirinzi A, Cazzolla A, Lovero R, et al. New insights in laboratory testing for COVID-19 patients: looking for the role and predictive value of *Human epididymis secretory protein 4* (HE4) and the innate immunity of the oral cavity and respiratory tract. Microorganisms. 2020;8(11):1718. doi: 10.3390/microorganisms8111718
[77] Wilky B. Immune checkpoint inhibitors: the linchpins of modern immunotherapy. Immunol Rev. 2019;290(1):6–23. doi: 10.1111/imr.12766
[78] York A. Microbiome: gut microbiota sways response to cancer immunotherapy. Nat Rev Microbiol. 2018;16(3):121–121. doi: 10.1038/nrmicro.2018.12
[79] Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science. 2018;359(6371):91–97. doi: 10.1126/science.aan3706
[80] Naidoo J, Page D, Li B, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol. 2015;26(12):2375–2391. doi: 10.1093/annonc/mdv383. Erratum in: Ann Oncol. 2016 Jul;27(7):1362. doi: 10.1093/annonc/mdw141
[81] Gopalakrishnan V, Helmink B, Spencer C, et al. The Influence of the gut microbiome on cancer, immunity, and cancer immunotherapy. Cancer Cell. 2018;33(4):570–580. doi: 10.1016/j.ccell.2018.03.015
[82] Dubin K, Callahan M, Ren B, et al. Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis. Nat Commun. 2016;7:10391. doi: 10.1038/ncomms10391
[83] Chaput N, Lepage P, Coutzac C, et al. Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. Ann Oncol. 2017;28(6):1368–1379. doi: 10.1093/annonc/mdx108. Erratum in: Ann Oncol. 2019 Dec 1;30(12):2012. doi: 10.1093/annonc/mdz224
[84] Pawelek J, Low K, Bermudes D. Bacteria as tumour-targeting vectors. Lancet Oncol. 2003;4(9):548–556. doi: 10.1016/s1470-2045(03)01194-x. Erratum in: Lancet Oncol. 2003 Nov;4(11):658.
[85] Nallar S, Xu D, Kalvakolanu D. Bacteria and genetically modified bacteria as cancer therapeutics: current advances and challenges. Cytokine. 2017;89:160–172. doi: 10.1016/j.cyto.2016.01.002
[86] Cunningham C, Nemunaitis J. A phase I trial of genetically modified salmonella typhimurium expressing cytosine deaminase (TAPET-CD, VNP20029) administered by intratumoral injection in combination with 5-fluorocytosine for patients with advanced or metastatic cancer. protocol no: CL-017. version: april 9, 2001. Hum Gene Ther. 2001;12(12):1594–1596.

[87] Kováč J, Slobodníková L, Trajčíková E, et al. Therapeutic potential of flavonoids and tannins in management of oral infectious diseases-a review. Molecules. 2022;28(1):158. doi: 10.3390/molecules28010158
[88] Guo Y, Li Z, Chen F, et al. Polyphenols in oral health: homeostasis maintenance, disease prevention, and therapeutic applications. Nutrients. 2023;15(20):4384. doi: 10.3390/nu15204384
[89] Arrigoni R, Ballini A, Santacroce L, et al. Another look at dietary polyphenols: challenges in cancer prevention and treatment. Curr Med Chem. 2022;29(6):1061–1082. doi: 10.2174/0929867328666210810154732
[90] Esquivel-Chirino C, Bolaños-Carrillo M, Carmona-Ruiz D, et al. The protective role of cranberries and blueberries in oral cancer. Plants. 2023;12(12):2330. doi: 10.3390/plants12122330
[91] Magrone T, Magrone M, Russo M, et al. Recent advances on the anti-inflammatory and antioxidant properties of red grape polyphenols: in vitro and in vivo studies. Antioxidants. 2019;9(1):35. doi: 10.3390/antiox9010035
[92] Flemming J, Meyer-Probst C, Speer K, et al. Preventive applications of polyphenols in dentistry – a review. Int J Mol Sci. 2021;22(9):4892. doi: 10.3390/ijms22094892
[93] Watson RR, Preedy V, Zibaldi S, editors. Polyphenols in human health and disease. 2nd ed. Vol. 2.London, UK: Elsevier; 2018; p. 1–467. ISBN978-0-12-813008-7.
[94] Singla R, Dubey A, Garg A, et al. Natural polyphenols: chemical classification, definition of classes, subcategories, and structures. J AOAC Int. 2019;102(5):1397–1400. doi: 10.5740/jaoacint.19-0133
[95] Magrone T, Candore G, Caruso C, et al. Polyphenols from red wine modulate immune responsiveness: biological and clinical significance. Curr Pharm Des. 2008;14(26):2733–2748. doi: 10.2174/138161208786264098
[96] Ding Y, Yao H, Yao Y, et al. Protection of dietary polyphenols against oral cancer. Nutrients. 2013;5(6):2173–2191. doi: 10.3390/nu5062173
[97] Magrone T, Jirillo E. The new era of nutraceuticals: beneficial effects of polyphenols in various experimental and clinical settings. Curr Pharm Des. 2018;24(44):5229–5231. doi: 10.2174/1381612824441903291544 18
[98] Direito R, Barbalho S, Sepodes B, et al. Plant-derived bioactive compounds: exploring neuroprotective, metabolic, and hepatoprotective effects for health promotion and disease prevention. Pharmaceutics. 2024;16(5):577. doi: 10.3390/pharmaceutics16050577
[99] Marzulli G, Magrone T, Vonghia L, et al. Immunomodulating and anti-allergic effects of Negroamaro and Koshu Vitis vinifera fermented grape marc (FGM). Curr Pharm Des. 2014;20(6):864–868. doi: 10.2174/13816128200614022012 0640
[100] Santacroce L, Bottalico L, Charitos I, et al. Exploitation of natural by-products for the promotion of healthy outcomes in humans: special focus on antioxidant and anti-inflammatory mechanisms and modulation of the gut microbiota. Antioxidants. 2024;13(7):796. doi: 10.3390/antiox13070796
[101] Ullah H, Minno A, Filippis A, et al. In vitro antimicrobial and antibiofilm properties and bioaccessibility after oral digestion of chemically characterized extracts obtained from *Cistus* × *incanus* L., *Scutellaria lateriflora* L., and their combination. Foods. 2023;12(9):1826. doi: 10.3390/foods12091826
[102] Ben Lagha A, Howell A, Grenier D. Highbush blueberry proanthocyanidins alleviate porphyromonas gingivalis-induced deleterious effects on oral mucosal cells. Anaerobe. 2020;65:102266. doi: 10.1016/j.anaerobe.2020.102266
[103] Vaillancourt K, Ben Lagha A, Grenier D. Effects of a berry polyphenolic fraction on the pathogenic properties of *Porphyromonas gingivalis*. Front Oral Health. 2022;3:923663. doi: 10.3389/froh.2022.923663
[104] Iviglia G, Torre E, Cassinelli C, et al. Functionalization with a polyphenol-rich pomace extract empowers a ceramic bone filler with in vitro antioxidant, anti-inflammatory, and pro-osteogenic properties. J Funct Biomater. 2021;12(2):31. doi: 10.3390/jfb12020031
[105] Zdarilová A, Svobodová R, Chytilová A, et al. J. Polyphenolic fraction of Lonicera caerulea L. fruits reduces oxidative stress and inflammatory markers induced by lipopolysaccharide in gingival fibroblasts. Food Chem Toxicol. 2010;48(6):1555–1561. doi: 10.1016/j.fct.2010.03.024
[106] Galarraga-Vinueza M, Dohle E, Ramanauskaite A, et al. Anti-inflammatory and macrophage polarization effects of cranberry proanthocyanidins (PACs) for periodontal and peri-implant disease therapy. J Periodontal Res. 2020;55(6):821–829. doi: 10.1111/jre.12773
[107] Tipton D, Hatten A, Babu J, et al. Effect of glycated albumin and cranberry components on interleukin-6 and matrix metalloproteinase-3 production by human gingival fibroblasts. J Periodontal Res. 2016;51(2):228–236. doi: 10.1111/jre.12302
[108] Farzanegan A, Shokuhian M, Jafari S, et al. Anti-histaminic effects of resveratrol and silymarin on human gingival fibroblasts. Inflammation. 2019;42(5):1622–1629. doi: 10.1007/s10753-019-01023-z
[109] Dal-Fabbro R, Cosme-Silva L, Rezende Silva Martins de Oliveira F, et al. Effect of red wine or its polyphenols on induced apical periodontitis in rats. Int Endod J. 2021;54(12):2276–2289. doi: 10.1111/iej.13633
[110] Pärnänen P, Lomu S, Räisänen I, et al. Antimicrobial and anti-inflammatory oral effects of fermented lingonberry juice-a one-year prospective human intervention study. Eur J Dent. 2023;17(4):1235–1240. doi: 10.1055/s-0042-1759619
[111] Alkimavičienė E, Pušinskaitė R, Basevičienė N, et al. Efficacy of proanthocyanidins in nonsurgical periodontal therapy. Int Dent J. 2023;73(2):195–204. doi: 10.1016/j.identj.2022.08.006
[112] Díaz Sánchez R, Castillo-Dalí G, Fernández-Olavarría A, et al. A prospective, double-blind, randomized, controlled clinical trial in the gingivitis prevention with an oligomeric proanthocyanidin nutritional supplement. Mediators Inflamm. 2017;2017:7460780. doi: 10.1155/2017/7460780

[113] Trisha A, Shakil M, Talukdar S, et al. Tea polyphenols and their preventive measures against cancer: current trends and directions. Foods. 2022;11(21):3349. doi: 10.3390/foods11213349
[114] Mohan K, Gunasekaran P, Varalakshmi E, et al. In vitro evaluation of the anticancer effect of lactoferrin and tea polyphenol combination on oral carcinoma cells. Cell Biol Int. 2007;31(6):599–608. doi: 10.1016/j.cellbi.2006.11.034
[115] Letchoumy P, Mohan K, Prathiba D, et al. Comparative evaluation of antiproliferative, antiangiogenic and apoptosis inducing potential of black tea polyphenols in the hamster buccal pouch carcinogenesis model. J Carcinog. 2007;6:19. doi: 10.1186/1477-3163-6-19
[116] Srinivasan P, Suchalatha S, Babu P, et al. Chemopreventive and therapeutic modulation of green tea polyphenols on drug metabolizing enzymes in 4-Nitroquinoline 1-oxide induced oral cancer. Chem Biol Interact. 2008;172(3):224–234. doi: 10.1016/j.cbi.2008.01.010
[117] Gil da Costa R, Aragão S, Moutinho M, et al. HPV16 induces a wasting syndrome in transgenic mice: amelioration by dietary polyphenols via NF-κB inhibition. Life Sci. 2017;169:11–19. doi: 10.1016/j.lfs.2016.10.031
[118] Fan M, Wang I, Hsiao Y, et al. Anthocyanins from black rice (Oryza sativa L.) demonstrate antimetastatic properties by reducing MMPs and NF-κB expressions in human oral cancer CAL 27 cells. Nutr Cancer. 2015;67(2):327–338. doi: 10.1080/01635581.2015.990576
[119] Li Y, Cheng L, Li M. Effects of green tea extract epigallocatechin-3-gallate on oral diseases: a narrative review. Pathogens. 2024;13(8):634. doi: 10.3390/pathogens13080634
[120] Belobrov S, Seers C, Reynolds E, et al. Functional and molecular effects of a green tea constituent on oral cancer cells. J Oral Pathol Med. 2019;48(7):604–610. doi: 10.1111/jop.12914
[121] Coşkun N, Sarıtaş S, Bechelany M, et al. Polyphenols in foods and their use in the food industry: enhancing the quality and nutritional value of functional foods. Int J Mol Sci. 2025;26(12):5803. doi: 10.3390/ijms26125803
[122] Kalita P, Chakrabarti S, Bhattacharjee B, et al. Recent progress in improving delivery, bioavailability and bioactivity of polyphenolic compounds through encapsulation: a comprehensive review. Food Chem. 2025;490:145087. doi: 10.1016/j.foodchem.2025.145087
[123] Basak S, Bera A, Yoon A, et al. A randomized, phase 1, placebo-controlled trial of APG-157 in oral cancer demonstrates systemic absorption and an inhibitory effect on cytokines and tumor-associated microbes. Cancer. 2020;126(8):1668–1682. doi: 10.1002/cncr.32644
[124] Rossi M, Mirbagheri S, Keshavarzian A, Bishehsari F. Nutraceuticals in colorectal cancer: a mechanistic approach. Eur J Pharmacol. 2018;833:396–402. doi: 10.1016/j.ejphar.2018.06.027
[125] Sánchez B, Delgado S, Blanco-Míguez A, et al. Probiotics, gut microbiota, and their influence on host health and disease. Mol Nutr Food Res. 2017;61(1):doi: 10.1002/mnfr.201600240
[126] Santacroce L, Topi S, Bottalico L, et al. Current knowledge about gastric microbiota with special emphasis on *Helicobacter pylori*-related gastric conditions. Curr Issues Mol Biol. 2024;46(5):4991–5009. doi: 10.3390/cimb46050299
[127] Zhang Y, Ding Y, Guo Q. Probiotic species in the management of periodontal diseases: an overview. Front Cell Infect Microbiol. 2022;12:806463. doi: 10.3389/fcimb.2022.806463
[128] Siddiqui R, Badran Z, Boghossian A, et al. The increasing importance of the oral microbiome in periodontal health and disease. Future Sci OA. 2023;9(8):FSO856. doi: 10.2144/fsoa-2023-0062
[129] Bijle M, Neelakantan P, Ekambaram M, et al. Effect of a novel synbiotic on Streptococcus mutans. Sci Rep. 2020;10(1):7951. doi: 10.1038/s41598-020-64956-8
[130] Mohd Fuad A, Amran N, Nasruddin N, et al. The mechanisms of probiotics, prebiotics, synbiotics, and postbiotics in oral cancer management. Probiotics Antimicrob Proteins. 2023;15(5):1298–1311. doi: 10.1007/s12602-022-09985-7
[131] Cheng Z, Xu H, Wang X, et al. *Lactobacillus* raises *in vitro* anticancer effect of geniposide in HSC-3 human oral squamous cell carcinoma cells. Exp Ther Med. 2017;14(5):4586–4594. doi: 10.3892/etm.2017.5105 114. Asoudeh-Fard A et al. Bioimpacts 7: 193-98, 2017.
[132] Aghazadeh Z, Pouralibaba F, Yari Khosroushahi A. The prophylactic effect of *Acetobacter syzygii* probiotic species against squamous cell carcinoma. J Dent Res Dent Clin Dent Prospects. 2017;11(4):208–214. doi: 10.15171/joddd.2017.037
[133] Zhang M, Wang F, Jiang L, et al. Lactobacillus salivarius REN inhibits rat oral cancer induced by 4-nitroquioline 1-oxide. Cancer Prev Res. 2013;6(7):686–694. doi: 10.1158/1940-6207.CAPR-12-0427
[134] Wang G, He X, Wang Q. Intratumoral bacteria are an important "accomplice" in tumor development and metastasis. Biochim Biophys Acta Rev Cancer. 2023;1878(1):188846. doi: 10.1016/j.bbcan.2022.188846
[135] Santacroce L, Spirito F, Bottalico L, et al. Current Issues and perspectives in antimicrobials use in dental practice. Curr Pharm Des. 2022;28(35):2879–2889. doi: 10.2174/1381612828666220920114723
[136] Santacroce L, Di Domenico M, Montagnani M, et al. Antibiotic resistance and microbiota response. Curr Pharm Des. 2023;29(5):356–364. doi: 10.2174/1381612829666221219093450
[137] Arrigoni R, Ballini A, Jirillo E, et al. Current view on major natural compounds endowed with antibacterial and antiviral effects. Antibiotics. 2024;13(7):603. doi: 10.3390/antibiotics13070603
[138] Wei W, Li J, Liu F, et al. Alteration of intestinal microecology by oral antibiotics promotes oral squamous cell carcinoma development. Mol Immunol. 2022;149:94–106. doi: 10.1016/j.molimm.2022.06.013