Probiotics and Antimicrobial Proteins
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The Mechanisms of Probiotics, Prebiotics, Synbiotics, and Postbiotics in Oral Cancer Management

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Abstract

Oral carcinogenesis is preceded by oral diseases associated with inflammation such as periodontitis and oral candidiasis, which are contributed by chronic alcoholism, smoking, poor oral hygiene, and microbial infections. Dysbiosis is an imbalance of microbial composition due to oral infection, which has been reported to contribute to oral carcinogenesis. Therefore, in this review, we summarised the role of probiotics, prebiotics, synbiotics, and postbiotics in promoting a balanced oral microbiome, which may prevent oral carcinogenesis due to oral infections. Probiotics have been shown to produce biofilm, which possesses antibacterial activity against oral pathogens. Meanwhile, prebiotics can support growth and increase the benefit of probiotics. In addition, postbiotics possess antibacterial, anticariogenic, and anticancer properties that potentially aid in oral cancer prevention and treatment. The use of probiotics, prebiotics, synbiotics, and postbiotics for oral cancer management is still limited despite their vast potential, thus, discovering their prospects could herald a novel approach to disease prevention and treatment while participating in combating antimicrobial resistance.

Keywords Probiotic · Prebiotic · Synbiotic · Postbiotic · Oral cancer management

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Introduction

Oral cancer is the 16th most common cancer worldwide with men having a higher incidence and mortality rate compared to women. Asia continent makes up the majority of the total incident (65.8%) and mortality (74%) of lips and oral cancer worldwide, followed by Europe and North America. GLOBOCAN 2020 reported a total of 377,713 new cases and 177,757 mortalities of lip and oral cancer [1]. Tobacco smoking, alcohol drinking, areca nut (betel quid) consumption, and microbial infections such as Human Papilloma Virus and *Candida albicans* are among the contributing factors to oral carcinogenesis [2].

A study by Kleinstein et al. suggested a new concept in the prevention and treatment of oral diseases through manipulation of the oral microbiome by administering pro-resolving small lipids molecules to target specific immune-microbial markers [3]. Another study showed that a balanced oral microbiome may overcome oral diseases that are caused by dysbiosis, subsequently reducing the use of antimicrobial agents, which have been a continuous problem in oral cancer patients due to antimicrobial resistance [4]. Dysbiosis occurs when the equilibrium of an oral microbiome is disturbed. This condition changes the distribution and

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functional component of the oral microbiome, which may trigger the pathogenicity of opportunistic microorganisms such as *C. albicans* [5]. Sustained dysbiosis may lead to the colonisation of microbial-mediated inflammation such as *C. albicans* that have been reported to promote oral carcinogenesis [6]. Furthermore, several cancer-causing pathogens such as *Helicobacter* spp. can produce genotoxins and other cancer-causing metabolites that induce tumorigenesis [7].

In oral cancer, the association between dysbiosis and carcinogenesis remains unclear. Although oral cancer is commonly associated with alcohol and tobacco use, a study found that poor oral hygiene is among the important risk factor for non-smokers and non-drinkers [8]. Thus, oral carcinogenesis is also suggested to be associated with dysbiosis. Chronic inflammation is one of the hallmarks that contribute to the development of cancer [9]. In oral squamous cell carcinoma (OSCC), periodontitis has been indicated as the facilitating trait of oral cancer development as it is a common inflammatory ailment affecting the oral cavity [10]. Chronic periodontal inflammation is an established risk factor for oral cancer, as patients with chronic inflammation were shown to have a higher risk of developing malignancy compared to healthy individuals [11]. Furthermore, La Rosa et al. reported that stimulation of microorganisms during chronic inflammation increases the expression of inflammatory cytokines and mediators. This would then facilitate mutagenesis, angiogenesis, and uncontrolled cell proliferation, leading to oral cancer [12].

Chronic inflammation associated with periodontal inflammation is commonly caused by anaerobic bacteria such as *Fusobacterium*, *Porphyromonas*, and *Prevotella*. These bacteria release inflammatory mediator that interacts with several types of tissues to induce inflammation. The bacteria also stimulate the release of pro-inflammatory cytokines such as IL-1, IL-6, IL-17, IL-23, tumour-necrosis factor-α (TNF-α), and proteinases that can destroy the extracellular matrix. Some bacteria such as *Mycoplasma salivarium*, *Porphyromonas gingivalis*, and *Pseudomonas aeruginosa* are capable to shift cell proliferation through the initiation of NF-κB and inhibition of apoptosis [12, 13].

Hanahan reported in a study that the oral microbiome possesses the capability to modulate tumorigenesis through immunomodulation, secretion of toxin that contributes to DNA damages, and adhesion to the epithelial receptors to stimulate cell proliferation [14]. Furthermore, in the conditions where the intestinal barrier is disrupted due to dysbiosis, the pathogen can produce butyrate, which possesses pleiotropic and paradoxical effects on differentiated cells in the epithelium, affecting cellular energetics and metabolism, histone modification, cell-cycle progression, and (tumour-promoting) inflammation that is immunosuppressive of the adaptive immune response [15].

Thus, in this review, we summarised the role of a balanced oral microbiome utilising probiotics, prebiotics, synbiotics and postbiotics in the prevention and as a potential treatment for oral cancer.

Probiotics and Its Derivatives

Probiotics

According to the World Health Organization, probiotic is defined as "living microorganisms which when administered in adequate amounts confer a health benefit on the host" [16]. The seven core genera of microbial organisms used in probiotic-based products are *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus, Escherichia, and Bacillus* [17]. Probiotics have been utilised as a dietary supplement to improve individual health, specifically the gastrointestinal system. In intestinal microbiome, it promotes wellbeing by hindering potential pathogens, increasing barrier function, immunomodulation, and manufacturing neurotransmitters, and having varieties of host-target, ranging from the resident microbiome to the cellular components of the brain-gut axis [18]. In addition, *Lactobacillus rhamnosus, Lactobacillus helveticus, and Lactobacillus casei* have been shown to exhibit strong cytoprotective effects against cadmium-induced tissue injury, which could be due to their anti-inflammatory and antioxidant properties [19].

Furthermore, in the recent COVID-19 pandemic outbreak, several studies have also been reported on the ability of probiotics to increase immunity against SARS-CoV-2 infection [20]. According to Fernández-Ferreiro et al., probiotic *Loigolactobacillus cornyiforis* K8 CECT 5711 has been shown to improve immunity among vaccinated elderly [21].

Prebiotics

Prebiotics is the substance in food, mainly oligosaccharides that can stimulate the growth of beneficial bacteria or fungi as mentioned in Fig. 1 [22]. The concept was coined in 1995 by Gibson and Roberfroid, in which prebiotic was termed as a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and activity of one or a limited number of bacteria in the colon, thus improving the health of the host [23]. These dietary supplements are commonly indigestible, and it serves to improve the growth and development of advantageous bacteria while suppressing the detrimental bacteria [24]. Most prebiotics is a subset of carbohydrate groups such as fructo-oligosachharides (FOS), galacto-oligosaccharides (GOS), starch and glucose-derived oligosaccharides [25]. Prebiotic consumption has been shown to increase the population of protective microbiome thus improving immunity. A study observed that the humoral immune response to measles vaccine in infants

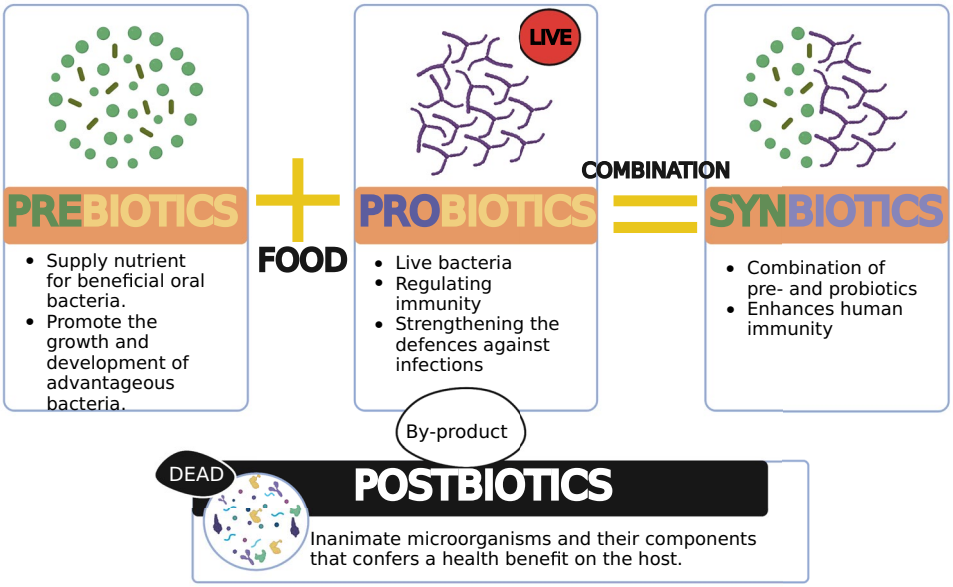

Fig. 1 Definition of prebiotics, probiotics, synbiotics, and postbiotics

has significantly improved after receiving infant cereal with fructo-oligosaccharides [26].

Prebiotics such as FOS and GOS could also elicit positive effects on the neural pathway through the involvement of gut hormones. The compounds were reported to trigger the increase of brain-derived neurotrophic factor (BDNF) and N-methyl-d-aspartate receptor (NMDAR) subunits, which help to repair failing brain cells and protect healthy brain cells [27].

Synbiotics

Synbiotic is defined as the synergistic combination of prebiotics and probiotics (Fig. 1). It is relatively a new concept that is introduced to improve oral health, even though the effects of prebiotics and probiotics for both gut and oral health are well established. Synbiotics were developed to increase the survival of probiotics in microhabitats such as the oral cavity. The rationale for synbiotics appears to be based on the observation demonstrating improved probiotics survival during passage through the upper intestinal tract. More efficient implantation in the colon, as well as the stimulating effect of probiotics and ubiquitous bacteria, contribute to the maintenance of intestinal homeostasis and a healthy body [28, 29]. Administration of synbiotics could also assist in maintaining the oral microbiome by retaining the survivability of beneficial oral bacteria in the oral cavity, subsequently preventing the colonisation of oral pathogens such as *Candida* spp. and *Streptococcus mutans* [30].

Postbiotics

Postbiotic is defined as the "preparation of inanimate microorganisms and their components that confers a health benefit on the host" (Fig. 1). Several consensuses have been reached such as 1) it is a purposely inactivated microbial cell that can benefit the host, with or without its' metabolites of cell components, 2) it does not have to be originated from a probiotic for the inactivated version to be recognised as a postbiotic, and 3) postbiotics must be administered at the host's surfaces and the target organ and is not limited to the gut [31]. Examples of postbiotic substances are short-chain fatty acids (SCFAs) and components such as microbial fractions, functional proteins, secreted polysaccharides, extracellular polysaccharides (EPS), cell lysates, teichoic acid, peptidoglycan-derived muropeptides, and pili-type structures [32].

Postbiotic *Lactobacillus paracasei* was shown to have a protective effect against Inflammatory Bowel Disease (IBD) caused by *Salmonella* [33]. It is suggested that postbiotics may have therapeutic and protective activities, similar to probiotics, with less risk, particularly to immunocompromised patients. Furthermore, the use of *Lact. casei* EPS as an adjuvant has also been reported to improve the efficacy of the foot-and-mouth disease vaccine, thus indicating the potential application of postbiotic in improving oral health [34].

Figure 1 summarises the definition of these terms graphically.

Promotion of Growth and Function of Oral Probiotics

A balanced oral microbiome plays a vital role in maintaining oral health. Prebiotics could assist immensely in promoting the growth of oral beneficial bacteria such as *Lactobacilli* spp. [35], *Streptococcus parasanguinis* and *Streptococcus gordonii* [36, 37]. This is important as

dysbiosis can contribute to unresolved inflammation, in addition to other independent cancer-driving mechanisms that lead to oral cancer.

Prebiotics promote the growth of oral-beneficial bacteria by being the nutrient source to aid in their colonisation in the oral cavity. Three potential prebiotics, which are N-acetyl-D-mannosamine, succinic acid and Met-Pro, possess the ability to stimulate the growth of oral probiotics including *Streptococcus salivarius* and *Streptococcus oralis*. Further treatment with prebiotics demonstrated that N-acetyl-D-mannosamine shows the most prominent changes in microbial composition, identifying it as the most promising oral prebiotic substrate [38]. Kojic Glucomannan hydrolysate (GMH) promotes the growth of probiotic bacteria such as lactic-acid bacteria and suppresses pathogens such as *Escherichia coli* and *Listeria monocytogenes* [39]. Furthermore, it is also capable of suppressing cariogenic bacteria residing in the oral cavity such as *Strep. mutans* [40].

Arabinose, xylose, and xylitol are the three saccharides that can potentially function as prebiotics [41]. They act by supporting the growth of *Lactobacilli* spp. and prevent the growth of common oral pathogens such as *Strep. mutans* and *C. albicans* [35]. Xylitol was also shown to have inhibitory effects on the development of *Strep. mutans* and *C. albicans* in the presence of glucose [42]. The similarity of the molecular structure of xylitol with arabinose and xylose is suggestive that arabinose and xylose might confer the same inhibitory effect as xylitol [43]. Arginine is used as a prebiotic to improve the growth of alkalogenic bacteria such as *Strep. parasanguinis* and *Strep. gordonii*, consequently suppressing the growth of cariogenic bacteria *Strep. mutans*. In combination with sodium fluoride (NaF), fluoride/arginine wards off the unwarranted alkalisation of biofilm, hence reversing the. *Strep. mutans*/*Strep. sanguinis* balance towards a more ecological ratio. It also sustained the predominance of these two bacteria over *P. gingivalis* in the biofilm [36, 37].

The Roles of Probiotics in Promoting a Balanced Oral Microbiome for Oral Cancer Management

There are a few prominent roles of probiotics in managing oral diseases including antimicrobial and anti-biofilm activity against carcinogenic pathogens, probiotics distribution as a tumour biomarker, their ability to secrete anticancer agents, immunomodulation effects leading to apoptosis and antimetastatic activity. Although these mechanisms have been studied to treat multitudes of oral diseases, reports have also shown the potential of probiotics, synbiotics, and postbiotics as treatment and/or prevention for oral cancer. Table 1 summarises each of their roles in detail.

Antimicrobial and Anti-Biofilm Activity Against Carcinogenic Pathogens

Probiotics commonly form biofilm as protective mechanisms against oral pathogens. They also fill the spaces where cariogenic bacteria might reside and compete with pathogens to colonise the cavity. Some probiotics were also shown to inhibit the growth of periodontitis-associated oral pathogens. Other mechanisms include competition for nutrients or adhesion sites with other pathogens, production of antimicrobial substances and toxin-degrading substances, and local or systemic immunomodulation [44]. Table 1 also describes several oral probiotics and their mechanisms of action against common oral pathogens that frequently contribute to chronic oral inflammation, preceding oral cancer.

The synbiotic combination of L-arginine and *Lactobacillus rhamnosus* GG possess a dose-dependent inhibitory effect against *Strep. mutans*. A concentration of 2% L-arginine and *L. rhamnosus* GG reduces the biofilm biomass and thickness, substantially inhibiting the growth of *Strep. mutans*. This synbiotic also allows longer survival and adherence to *Lact. rhamnonus* GG in the oral cavity, making up for the lack of long-term adaptation of the probiotic in the oral cavity [37].

Another study by Ohshima et al. also reported several prebiotics and probiotics suitable for synbiotic combinations against oral pathogens. Xylitol, arabinose, and xylose are the best prebiotic candidates, while *Lactobacillus fermentum*, *Lactobacillus plantarum Lactobacillus* spp., and *Lactobacillus paracasei* are identified as the best probiotic candidates. The combination of any of the aforementioned prebiotics and probiotics can reduce the biofilm formation of *C. albicans*, *Strep. mutans*, and *P. gingivalis* [43].

Postbiotics secreted by *Lactobacilli* spp. are known for their rich source of a bacteriostatic factor called bacteriocin [49]. A glycerol-derived compound produced by *Lactobacillus reuteri* called reuterin exhibited a potent antipathogenic activity as it is capable to inhibit a broad spectrum of microorganisms. Reuterin also maintains a healthy intestinal gut mucosa by averting the overgrowth of pathogenic and commensal bacteria. This mechanism might be employed in the oral mucosa [50]. *Lact. reuteri* is known to effectively reduce the severity of gingivitis, suggesting that its postbiotic might also have the same ability.

Postbiotics in the form of culture supernatant from *Lact. rhamnosus* GG were reported to successfully inhibit the growth of *P. gingivalis*, *C. albicans*, and *Strep. mutans* [41]. Spent-culture supernatant (SCS) of *Lactococcus lactis*

Table 1 Example of probiotics, synbiotics, and postbiotics and their mechanisms of action against oral diseases

Oral microbiome	Benefit(s)	Species/compounds involved	Mechanism of action	Prevention and/or treatment for oral cancer	Reference(s)
Probiotics	Antimicrobial and anti-biofilm activity against carcinogenic pathogens	*Lactobacillus reuteri*	Antimicrobial activity for gingivitis	Prevention	[45]
		Lactobacillus paracasei *Lactobacillus plantarum* *Lactobacillus rhamnosus* *Lactobacillus salivarius*	Antimicrobial activity for periodontitis	Prevention	[46]
		Weisella cibaria	Co-aggregation with *Fusobacteria nucleatum* for gingivitis treatment	Prevention	[47]
		Streptococcus salivarius K12	Reduce biofilm formation and inhibit dimorphism aggregation of *C. albicans* for oral candidiasis treatment	Prevention	[48]
	Probiotics distribution as a tumour biomarker	(Anaerobes) *Veillonella, Prevotella, Porphyromonas, Actinomyces, and Clostridium* (Aerobes) *Haemophilus, Enterobacteriaceae, and Streptococcus* subspecies	The hypoxic tumour microenvironment allows these bacterias to act as tumour markers	Treatment	[55]
		Capnocytophaga gingivalis *Prevotella melaninogenica* *Streptococcus mitis*	Found in high abundance in the saliva of OSCC patients	Treatment	[57] [58]
		Lactobacillus salivarius REN	Decompose 4NQO, protection against oxidative damage and decreasing the expression of cyclooxygenase 2 (COX-2), the expression of proliferating cell nuclear antigen and induce apoptosis	Treatment	[64]
	Immunomodulation leading to apoptosis	*Lactobacillus plantarum*	Reduce the mRNA expression of MAPK, a cancer-progressing pathway while increasing the mRNA expression of PTEN, a cancer-inhibiting pathway	Treatment	[66]
		Lactobacillus reuteri	Promote apoptosis via suppression of proteins involved in cell proliferation and anti-apoptosis	Treatment	[69]
		Lactobacillus debrueckii subsp. *Lactis*	Upregulation of E-cadherin levels in HeLa cells	Treatment	[77]
	Anti-metastasis activity	*Lactobacillus reuteri GMNL-89* and *Lactobacillus paracasei GMNL-133*	Lower the expression of EMT-related markers in pancreatic cancer mouse models	Treatment	[78]

Table 1 (continued)

Oral microbiome	Benefit(s)	Species/compounds involved	Mechanism of action	Prevention and/or treatment for oral cancer	Reference(s)
		L-arginine and *Lactobacillus rhamnosus* GG	• Reduces the biofilm biomass and thickness, inhibiting the growth of *Strep. mutants* • Allow longer survival and adherence of *Lact. rhamnonus* GG in the oral cavity	Prevention	[37]
Synbiotics	Antimicrobial and anti-biofilm activity against carcinogenic pathogens	Xylitol, arabinose, and xylose *Lactobacillus fermentum, Lactobacillus plantarum, Lactobacillus* spp. *and Lactobaciluus paracasei*	Reduce the biofilm formation of *C. albicans*, *Strep. mutans,* and *P. gingivalis*	Prevention	[29]
		Lactobacilli spp.	Rich source of a bacteriostatic factor called bacteriocin	Prevention	[49]
Postbiotics	Antimicrobial and anti-biofilm activity against carcinogenic pathogens	Glycerol-derived compound produced by *Lactobacillus reuteri* (reuterin)	• Reuterin exhibited a potent antipathogenic activity • Avert the overgrowth of pathogenic and commensal bacteria	Prevention	[50]
		Lactobacillus rhamnosus GG (culture supernatant)	Successfully inhibit the growth of *P. gingivalis, C. albicans*, and *Strep. mutans*	Prevention	[27]
		Lactococcus lactis MG5125 *Lactobacillus salivarius MG4265* (spent-culture supernatant)	• Inhibit the growth and preformed biofilm formation of *Strep. mutans* • Suggestive production of extracellular components and metabolites possessing anticariogenic activity	Prevention	[51]
		Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium longum (postbiotics)	Depicted a significant antitumour activity against an implantable and chemically induced tumour	Treatment	[61]
	Secretion of anticancer agent	*Propionibacterium freudenreichii* (fermented milk)	Increased the cytotoxicity of camptothecin	Treatment	[62]
		Lactobacillus brevis, *Lactobacillus paracasei* (fermented beetroot juice)	Offers protection against ACF formation in N-nitroso-N-methylurea tumour regression	Treatment	[62] [67]
		Streptococcus anginosus (postbiotics)	• Increase autophagosome activity and amplify the mRNA expression of Beclin1 and LC3 • Reduces cell proliferation and migration of SCC15 • Induces apoptosis	Treatment	
	Immunomodulation leading to apoptosis	*Acidobacter syzygii* (secreted metabolites)	Induces apoptosis	Treatment	[68]

Table 1 (continued)

Oral microbiome	Benefit(s)	Species/compounds involved	Mechanism of action	Prevention and/or treatment for oral cancer	Reference(s)
		Lactobacillus reuteri ATCC 6475 (supernatant)	• Combination of TNF with the supernatant also suppresses the COX-2 and cyclin D1 protein • Suppressed the production of Bcl-2 and Bcl-xL • Induces apoptosis	Treatment	[69]
		Streptococcus salivarius M18 (cell-free supernatant)	Exhibit an anticancer activity against the colon cancer line by triggering apoptosis	Treatment	[70]
		Lactobacillus casei and *Lactobacillus rhamnosus* GG (cell-free supernatants)	• Decreased the levels of matrix metalloproteinase-9 (MMP-9) • Increased the levels of tight junction protein ZO-1	Prevention	[79, 80]
	Anti-metastasis activity	Kefir water (Grain-free supernatant)	Induce the upregulation of tissue inhibitors of MMPs (TIMPs)	Prevention	[81]
		Lactobacillus plantarum YYC-3 (Cell-free supernatant)	Suppressed the vascular endothelial growth factor (VEGF)-MMP2/9 signalling pathway	Prevention	[82]

MG5125 and *Lact. salivarius* MG4265 exhibited inhibitory activity against the growth and preformed biofilm formation of *Strep. mutans*, suggestive of the production of extracellular components and metabolites possessing anticariogenic activity [51].

Probiotic Distribution as a Tumour Biomarker

While most tumour markers are biological markers that are produced by the tumour itself or by bodily response towards the tumour, the presence of bacteria in a precancerous lesion or tumour microenvironment can also contribute as a diagnostic or prognostic tumour biomarker [52]. Dysbiosis caused an inflammatory response that leads to changes in the oral microenvironment, preceding to amassing of oral pathogens. The condition of the tumour microenvironment (pH and O2 concentration) also only permits certain species of bacteria to thrive.

In OSCC, an association of precancerous lesion with *Actinomyces*, *Clostridium*, *Enterobacteriaceae*, *Fusobacterium*, *Haemophilus*, *Porphyromonas*, *Prevotella*, *Streptococcus*, and *Veillonella* has also been established. Furthermore, *P. gingivalis* and *Fus. nucleatum* were found 600 times more frequent in oral squamous cell carcinoma than in para-cancerous and normal tissues [53]. The hypoxic tumour microenvironment only permits the growth of facultative or obligate anaerobic microorganisms due to their low content (median O2 percentage at 1.9% in OSCC, 5.9% in the normal oral microbiome), hence allowing those bacteria to act as a tumour marker [54]. In OSCC, the bacterial taxa *Veillonella*, *Prevotella*, *Actinomyces*, and *Clostridium* belonging to anaerobes, and *Haemophilus*, *Enterobacteriaceae*, and *Streptococcus* subspecies belonging to aerobes, were highly abundant in the tumour. Remarkably, the assessment of Fusobacteria was propositioned as OSCC diagnostic criterium [55]. This is contributed by the increase in *Fusobacterium* sp. transcript in both pre-tumour and tumour tissue associated with OSCC in comparison to healthy samples. This finding is also suggestive that Fusobacteria virulence factors play a role in oral cancer pathogenesis [56].

Bacillus, *Enterococcus*, *Parvimonas*, *Peptostreptococcus*, and *Slackia* sp. abundance differed significantly between epithelial precursor lesions and OSCC. Changes in these microbial communities could be used as a predictor of the epithelial precursor lesion–OSCC transition. Both premalignant lesions and OSCC have been linked to *Prevotella*, *Porphyromonas*, *Veillonella*, *Actinomyces*, *Clostridium*, *Haemophilus*, *Streptococcus* subspecies, and *Enterobacteriaceae*. When compared to normal patients, *Cloacibacillus*, *Gemmiger*, *Oscillospira*, and *Roseburia* were abundant in patients with epithelial precursor lesions and OSCC. *Capnocytophaga gingivalis*, *Prevotella melaninogenica*, and *Streptococcus mitis* have been found in high abundance in the saliva of OSCC patients [57].

P. melaninogenica, *Strep. mitis*, and *C. gingivalis* were found in high concentrations in the saliva of OSCC patients and could be used as diagnostic markers for the disease. These probiotics have been found to act as diagnostic markers, predicting 80% of oral cancers. *Streptococcus* sp. may have the most promising OSCC tumour-targeting therapeutic effect as it is one of the genera most prevalent in the OSCC library and is used as an oral cancer diagnostic marker. *Candida* spp., which is commonly detected in oral cancer, has been reported to serve as a precancerous diagnostic marker [58].

Secretion of Anticancer Agent

Anticancer agents present in postbiotics can provide an alternative to conventional chemotherapy, which commonly comes with major side effects such as high blood pressure, bleeding, and kidney damage [59]. Components of postbiotics include short-chain fatty acids (SCFA), polysaccharides, metabolites, microbial cell fractions, functional proteins, EPS, and cell lysates [60]. Polysaccharides exhibited the most prominent anticancer activity among all compounds commonly present in postbiotics [59].

Postbiotics of *Lactobacillus acidophilus, Lactobacillus casei*, and *Bifidobacterium longum* depicted a significant antitumour activity against an implantable and chemically induced tumour. In an in vivo study, administration of cytoplasmic fraction of Lactic acid bacteria (LAB) increases the specific antitumour activity through modulation of cellular immunity. No direct killing of the tumour was reported [61]. Fermented milk containing *Propionibacterium freudenreichii* increased the cytotoxicity of camptothecin, a chemotherapeutic agent used to treat gastric cancer. Beetroot juice fermented by *Lactobacillus brevis* and *Lact. paracasei* offers protection against ACF formation in N-nitroso-N-methylurea tumour regression in advanced cancer during therapy with sterile filtrates from *Clostridium histolyticum* [62].

Although these studies are not specific to oral cancer, the effects of probiotics on other types of tumours offer an alternative as an adjuvant to treat oral-related diseases. Even though, the anticancer activity of postbiotic might not be as effective as the current chemotherapy as it only involves the indirect killing of the tumour cells through immunomodulatory action. However, it could be an adjunct therapy towards cancer, thus reducing the side effect of chemotherapy. Nevertheless, more studies are needed to support the hypothesis.

Immunomodulation Leading to Apoptosis

For over 3 decades, apoptosis is among the most sought-after method to effectively eliminate cancer. This programmed cell death is arbitrated by several intrinsic and extrinsic pathways that congregate to caspase-dependent proteolysis of the cell. Currently, there are limited FDA-approved drugs that target the Bcl-2 family of apoptosis regulator proteins. However, other emerging therapeutic approaches such as the production of agents that target the tumour-suppressor pathways or the tumour microenvironment or trigger the extrinsic apoptosis pathway provide an alternative to the current anticancer treatment [63].

A study by Zhang et al. reveals the potential of probiotic *Lact. salivarius* REN can suppress oral carcinogenesis in a dose-dependent manner. The mechanism of action includes protection against oxidative damage and decreasing the expression of cyclooxygenase 2 (COX-2) and the expression of proliferating cell nuclear antigen [64]. COX-2 has commonly overexpressed in cancer-inhibiting apoptosis, altering cell adhesion, and hijacking the normal cell signalling pathway [65]. An in vitro study on KB oral cancer cell line reveals the ability of probiotic *Lact. plantarum* to reduce the mRNA expression of MAPK, a cancer-progressing pathway, while increasing the mRNA expression of PTEN, a cancer-inhibiting pathway, within 24 h of treatment. The co-culture of *Lact. plantarum* with KB cancer cell line also elicits apoptosis, hindering the cancer progression [66]. These findings prove that probiotics possess anticancer properties through induction of apoptosis and immunomodulation of cancer signalling pathways (Fig. 2).

Postbiotic of *Streptococcus anginosus* treatment on oral tongue squamous cell carcinoma cells SCC15 showed the ability of the postbiotic to increase autophagosome activity, amplify the mRNA expression of Beclin1 and LC3, compared to the control groups ($p < 0.05$). The postbiotic also reduces cell proliferation and migration of SCC15, apart from inducing apoptosis [67]. Secreted metabolites of *Acidobacter syzygii* possess anticancer activity through induction of apoptosis. Upon treatment with the postbiotic for 24 h, the human oral cancer (KB) cell line exhibited apoptosis symptoms such as nucleus fragmentation or fragmentation, with minimal necrotic bodies observed. The postbiotic also induced 63.7% late apoptosis, 12% early apoptosis, and 0.0% necrosis in the 24 h. Meanwhile, secretion of *Lact. acidophilus* on KB cell lines exhibited 2.4% late apoptosis, 86.9% early apoptosis and 8.7% necrosis [68].

Oral administration of probiotic *Lact. salivarius* REN or its postbiotic can effectively suppress 4NQO-induced oral carcinogenesis in a dose-dependent manner. The in-vivo study revealed no formation of SCC or papilloma in rats fed with high-dose probiotics. The strain was able to decompose 4NQO to produce a less toxic compound, protect DNA against oxidative damage caused by the carcinogen, downregulate COX-2/PCNA expression, and induce

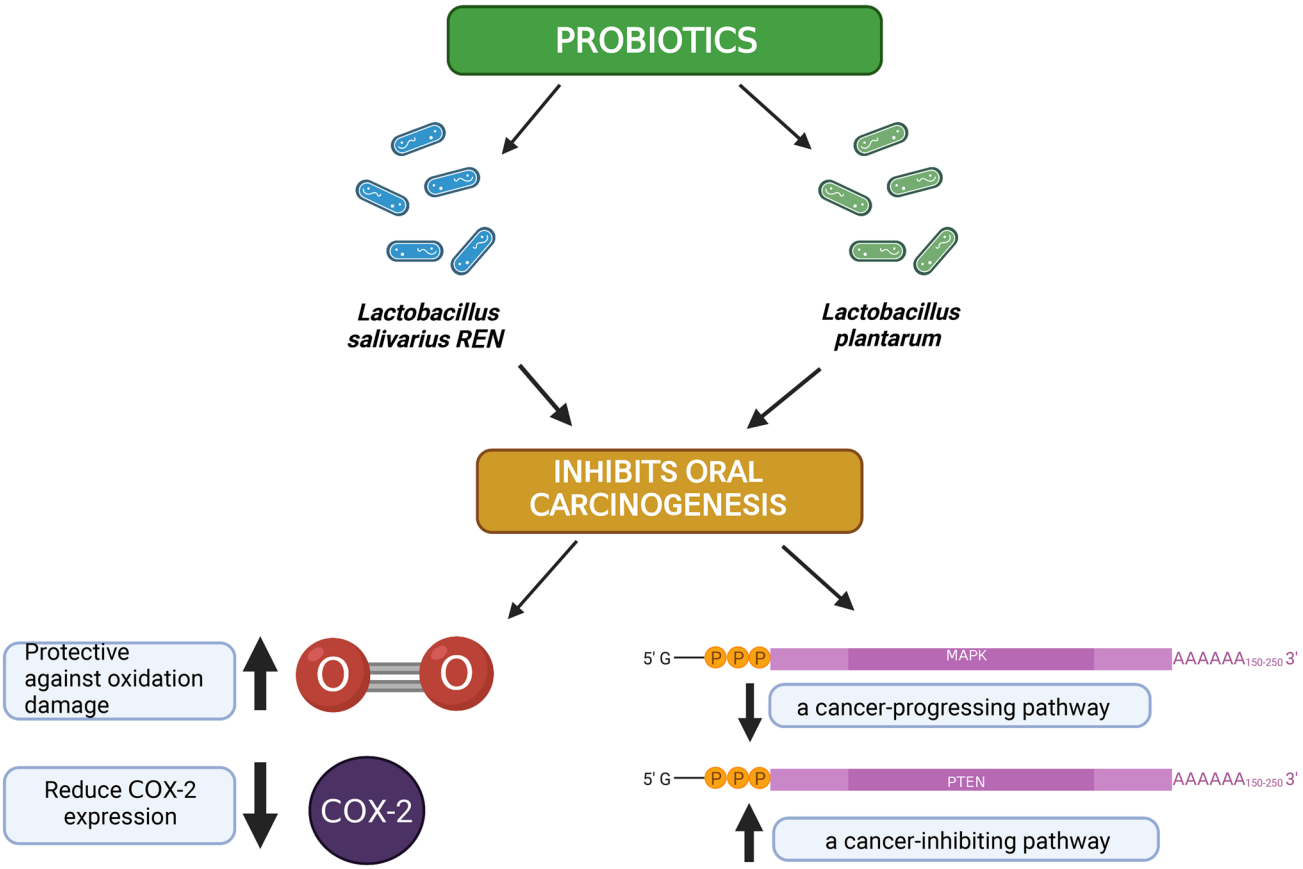

Fig. 2 Mechanism of action for probiotics to perform immunomodulation against oral cancer

apoptosis. The sequential decomposition of 4NQO to lesser or non-toxic compounds (4AQA and 4AQ) caused by the probiotic or its postbiotics proves their potential as a chemopreventive agent [64].

Promotion of apoptosis through NF-kB and MAPK pathways by probiotics *Lact. reuteri* ATCC 6475 supernatant (Lr-S 6475) in combination with tumour necrosis factor (TNF) was documented through an in vitro study on human myeloid cells. Its postbiotic promoted TNF-induced apoptosis as the cytotoxicity increases from 3 to 38% upon treatment on the cell with the presence of TNF. The NF-kB activation was also significantly inhibited through TNF. However, the probiotic alone does not exhibit any cytotoxic effects. The combination of TNF with the supernatant also suppressed the COX-2 and cyclin D1 protein. It also suppressed the production of Bcl-2 and Bcl-xL, the family of apoptosis-regulating proteins, in a time-dependent manner. Probiotic Lr-S6475 may promote apoptosis via the suppression of proteins involved in cell proliferation and anti-apoptosis. In Lr-S 6475-treated cells, NF-kB activation was significantly inhibited. Lr-S6475 alone did not activate NF-kB, but TNF-induced NF-kB activation was inhibited by Lr-S 6475 in a time-dependent manner [69]. Apart from that, the cell-free supernatant of *Strep. salivarius* M18 exhibited an anticancer activity against the colon cancer line by triggering apoptosis, and the effects are enhanced by inulin, a prebiotic [70].

Anti-Metastasis Activity

Metastasis could develop years after the diagnosis of the primary tumour and has become the main cause of death for more than 90% of cancer patients [71, 72]. It is defined as the spreading of cancer cells from the primary tumour to surrounding tissues and distant organs [73]. The primary reason for metastasis to develop is due to the epithelial-mesenchymal transition (EMT) of cancer cells [74]. EMT is a physiological process whereby the epithelial cells acquire the morphological and physiological characteristics of mesenchymal cells. The steps of metastasis formation can be referred to in Fig. 3 [75]. Even though the prevention of initial metastasis is important, additional metastases must

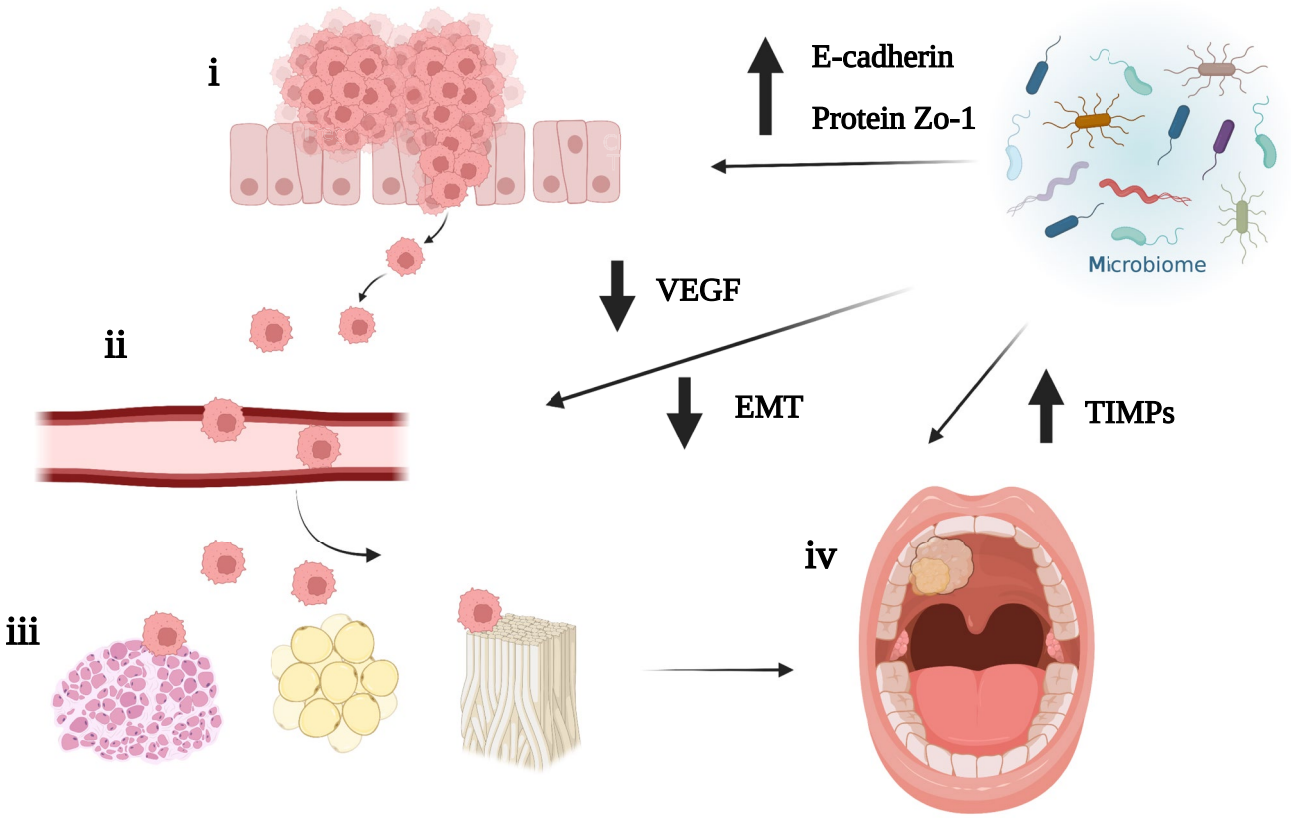

Fig. 3 A schematic representation of the mechanism underlying cancer metastasis and the antimetastatic potential of the oral microbiome. (**i**) Infiltration of cancer cells through the basement membrane. (**ii**) Intravasation into the surrounding vasculature or lymphatic system. (**iii**) Extravasation to secondary tissue. (**iv**) Colonisation as secondary tumours, an example is oral cancer

also be inhibited in patients with already occurring metastases to improve their prognosis [62, 76].

Lactobacillus debrueckii subsp. *Lactis* exhibited a significant upregulation of E-cadherin levels in human carcinoma of the uterine cervix cell lines (HeLa cells). E-cadherin is the most vital protein for cell–cell adhesion. Hence, the increased response of E-cadherin inhibited cancer cell migration [77]. Other than that, *Lact. reuteri GMNL-89* and *Lact. paracasei GMNL-133* treatment have proven to lower the expression of EMT-related markers in pancreatic cancer mouse models, which in turn decreases the risk of metastasis [78].

Postbiotics of *Lact. casei* and *Lact. rhamnosus* GG in the form of cell-free supernatants decreased the levels of matrix metalloproteinase-9 (MMP-9) and increased the levels of tight junction protein ZO-1. This resulted in a reduced incidence of colon cancer and thus, its metastatic effects as well [79, 80]. Kefir water, grain-free supernatant possessed antimetastatic and antiangiogenic effects when used in the treatment of murine breast cancer cells, due to its ability to induce the upregulation of tissue inhibitors of MMPs (TIMPs) [81].

Cell-free supernatant of *Lact. plantarum YYC-3* suppressed the vascular endothelial growth factor (VEGF)-MMP2/9 signalling pathway, which inhibited the metastasis of colon cancer cells [82]. The degradation of the basement membrane is the first step of metastasis, and it can be inhibited by suppressing the VEGF-MMP2/9 signalling pathway. This is because VEGF is a signalling protein that promotes the growth of new blood vessels, while matrix metalloproteinases (MMPs) degrade the extracellular matrix. Hence, postbiotic treatment was able to suppress (VEGF)-MMP2/9 signalling pathway, which in turn helped to reduce the metastasis risk of colon cancer cells [83]. These findings portray the ability of probiotics, and postbiotics in their antimetastatic ability against various types of cancer cells. However, their ability in suppressing oral cancer by metastasis prevention warrants further investigation.

These potential mechanisms of action on the role of a balanced microbiome that can contribute to oral cancer prevention and treatment are summarised in Fig. 4.

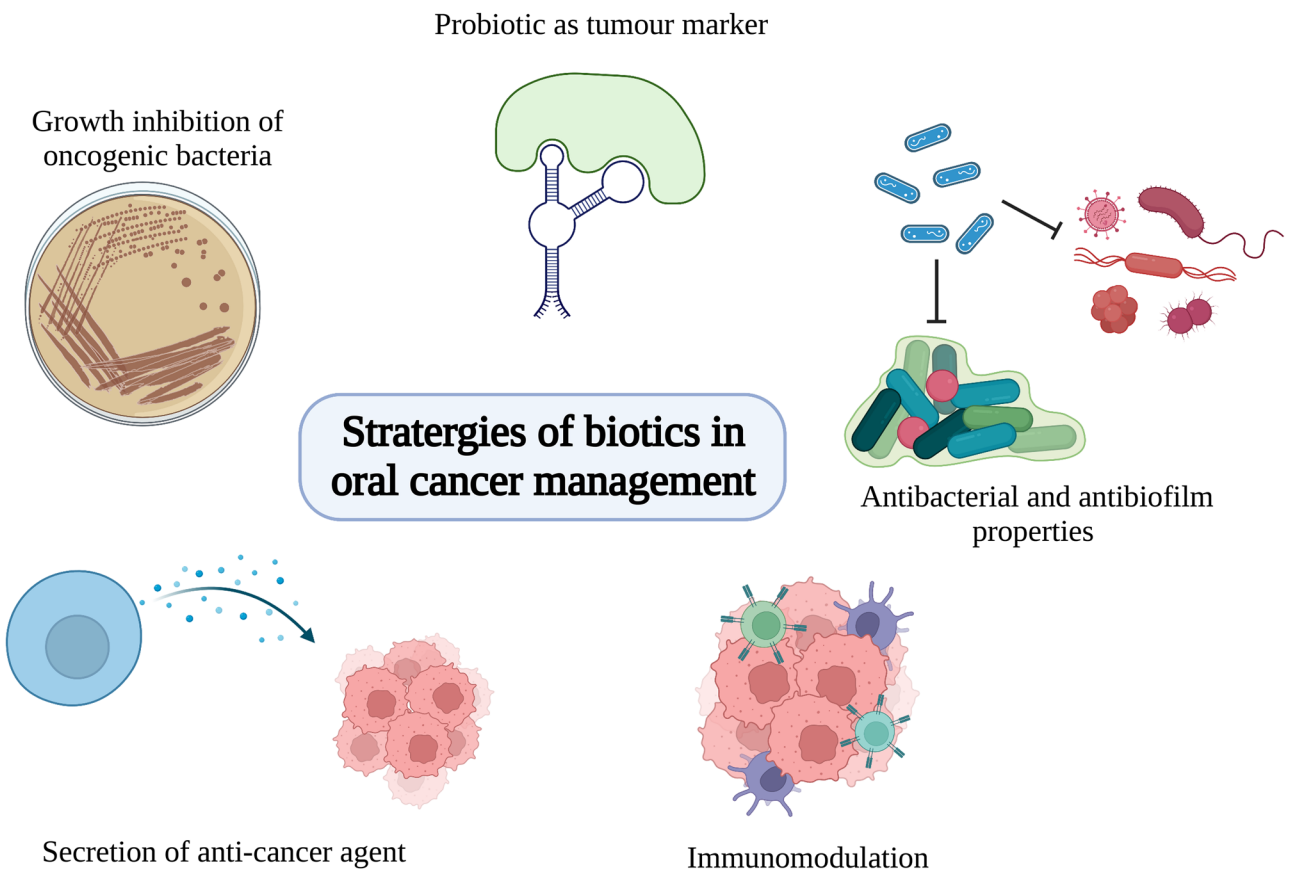

Fig. 4 Strategies for bacteria to manage cancer

Conclusion

The oral microbiome houses a plethora of microbial species that work synergistically to maintain a harmonious environment. This review highlights the potential of probiotics and their derivatives for oral cancer management. Sustained dysbiosis can cause amassing of pathogenic and cariogenic bacteria that lead to inflammation. Chronic inflammation may produce cancer-causing metabolites, in addition to genotoxins produced by the pathogens, leading to oral carcinogenesis. Probiotics can work individually or synergistically in preventing and managing oral cancer by balancing the oral microbiome and providing a targeted approach against oral diseases. Prebiotics or probiotics alone can protect from cariogenic and pathogenic oral bacteria. The synbiotic can provide enhanced protection, while the postbiotic allows protection against those pathogens without causing dysbiosis or harming the host, rendering it useful as a cancer-preventive modality.

The present review also highlights the lack of studies involving synbiotics and postbiotics in oral cancer management. Further studies on their role in cytotoxicity, immunomodulatory, and protective effects on cancer are well sought. In cancer treatment, probiotics, prebiotics, synbiotics, and postbiotics can be adjunctive therapy and aid to reduce the side effects caused by the treatment modalities. However, extensive studies are required to explore the efficacy and effectiveness of the substance. Overall, these new treatment modalities against infectious disease and cancer are worth exploring due to their vast potential.

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Declarations

Conflict of Interest The authors declare no competing interests.

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