Optimalisasi Produk Bakteri sebagai Strategi Antikanker dalam Imunoterapi Kanker Mulut: Review

(Optimizing Bacterial Products as The Anticancer Strategy in Oral Cancer Immunotherapy: Review)

Hilmy Irsyadi Hanif[1,2], Alma Linggar Jonarta[3]
[1]Department or Oral Biology, Master's program of Dental Science, Faculty of Dentistry, Universitas Gadjah Mada. Yogyakarta, Indonesia
[2]Department of Oral and Maxillofacial Pathology, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia
[3]Department of Oral Biology, Faculty of Dentistry, Universitas Gadjah Mada, Yogyakarta, Indonesia

Abstrak

Mikrobiota di rongga mulut terlibat sebagai faktor penyebab infeksi dan peradangan, terutama memperburuk prognosis pada kanker. Beberapa mikroorganisme yang diketahui dapat menunjukkan aktivitas onkolitik terhadap tumor tertentu. Penelitian ini bertujuan untuk menyusun dan merangkum publikasi yang membahas dampak produk bakteri pada kanker mulut sebagai terapi potensial. Tema fokus diturunkan melalui mesin pencari ilmiah, merangkum data dari ulasan yang merujuk pada kata kunci yang berkaitan dengan penyelidikan efek sitotoksik bakteri juga telah terlihat pada tumor padat, menghambat perkembangannya. Kami mengantisipasi bahwa pemberian judul ini dapat menghadirkan peluang baru mengenai produk bakteri sebagai sumber daya untuk wawasan dalam mengembangkan terapi untuk kanker mulut.

Kata kunci: Antikanker, Bioproduk, Kanker mulut, Produk bakteri, Terapi kanker

Abstract

The microbiota in the mouth cavity is implicated as a causal factor in infection and inflammation, particularly exacerbating prognosis in cancer. Several known microorganisms have can exhibit oncolytic activity against specific tumors. This study aims to compile and summarize publications discussing the impact of bacterial products on oral cancer as potential therapeutics. The focus themes were derived via a scientific search engine, summarizing data from reviews that referenced the keywords pertinent to the investigation the cytotoxic effects of the bacteria have also been seen in solid tumors, inhibiting their progression. We anticipate that giving this title may present new opportunities concerning bacterial products as resources for insights into developing therapy for oral cancer.

Keywords: Anticancer, Bacterial products, Bioproduct, Cancer therapy, Oral cancer

Korespondensi (*Correspondence*): Hilmy Irsyadi Hanif, Department or Oral Biology, Master's program of Dental Science, Faculty of Dentistry, Universitas Gadjah Mada. Yogyakarta, Indonesia. Email: hilmyhanief@gmail.com

Advancements in technology within the health sector have enabled the attenuation of germs, presenting a possible therapeutic approach for treating carcinogenesis. Understanding bacterial strains can be employed to combat cancer through molecular biology, leveraging the natural responses elicited by bacterial features[1]. Chemoproducts derived from cancer microorganisms have been demonstrated to be effective interventions for cancer progression[2]. Busch and Colley identified the bacteria in a viable state that effectively influences tumor regression. Bacterial growth is regarded as a component of the tumor microenvironment union [3]. Microorganisms have been previously studied and cultured for their potential role in tumor progression. Furthermore, various renowned scientists have successfully isolated microorganisms exhibiting pleomorphism from tumor tissue. The various stages of microorganisms have been identified as significant in carcinogenesis[4].

The concept of bacteria-based cancer immunotherapy has been recognized for use in inoperable cancers, specifically utilizing live forms of *Streptococcus pyogenes*. Facultative and obligate anaerobes have been developed to engineer drug modalities for cancer targeting. [5]Bacillus Calmette-Guerin is an FDA-approved bacterial agent for the treatment of non-muscle invasive bladder cancer. *Mycobacterium bovis* was attenuated for BCG therapy at the Pasteur Institute in the 1900s[6]. Bacterial-based carriers are well-developed for tumor targeting, utilizing the autonomous movement of bacteria to enhance permeability into tumor tissue. Bacteria are examined as both passive and active mechanisms for tissue penetration. Bacteria serve dual functions as carriers for autonomous insertion and as oncolytic agents with immunomodulatory activity[7].

Oral cancer ranks sixteenth in global prevalence among cancers. The complications arising from chemotherapy and conventional surgical approaches include side effects that harm healthy cells[8]. The microbiome's involvement may result in direct or indirect clinical manifestations. A paradigm of the microbiome involved in oral cancer, proposed by Chocolatewala et al. in 2010, describes how microorganisms suppress apoptotic mechanisms in neoplasia through the modulation of Bcl and pRB protein expression, leading to uncontrolled growth in oral tissue. Secondly, it was suggested that certain substances induce carcinogenic effects by modifying acetaldehyde synthesis, leading to DNA damage and hyperproliferation of epithelial cells[9]. Other bacterial species are strongly correlated with oral squamous cell carcinoma (OSCC), including *Porphyromonas gingivalis, Prevotella* sp., and *Streptococcus* sp. Additionally, *Fusobacterium, Clostridium*, and *Actinomyces* are identified as precursors of epithelial involvement in oral cancer. These are pathogenic bacteria implicated in oral cancer, with certain species, such as *Fusobacterium nucleatum* and *Porphyromonas gingivalis*, also playing a crucial role in colorectal

development. [10]. *Kingella* and *Corynebacterium* have been identified as factors that may reduce the risk of head and neck cancer development, acting protectively against various harmful substances through biodegradation mechanisms of xenobiotics. Lactic acid from bacterial products induces apoptotic mechanisms and exhibits anticancer properties [11].

Active and passive immunotherapies are utilized in the treatment of oral cancer. The prevalent active immunotherapy method involves culturing immune cells from blood and injecting them into tumor cells, utilizing active NK cells, cytotoxic T cells, and additional NK cells. Passive immunotherapy has been enhanced through the promotion of antibody-dependent cell-mediated cytotoxicity[12]. Recent studies have introduced the term immunotherapy-related adverse effects (irAEs), which affect 90% of patients undergoing anti-CTLA-4 and anti-PD-1/PD-L1 treatments[13].

In Indonesia, the manufacturing of beneficial bacterial products has seen improvements in recent years. The microbial diversity in Indonesia presents opportunities for the exploration of novel resources relevant to the study of natural compounds. The study conducted by Handayani et al. in 2021 identified various strains of Actinomycetes sp. that were cultivated for the production of valuable bioproducts, including desferrioxamine, amicetin, echinomycin, tirandamycin, and naphthyridinomycin[14]. The microbial products derived from the enriched biodiversity of the Indonesian environment have the potential to yield new beneficial compounds that may serve as anticancer agents for oral cancer immunotherapy. This review summarizes data on microbiome products as anticancer agents, highlighting the limited research on the potential of natural bioproducts from microorganisms for cancer immunotherapy. It emphasizes the need to explore undiscovered proteins for novel approaches in oral cancer treatment.

METHOD:

Our review study was performed with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) steps for following the checklist (Fig. 1). This review identified within 10-years publication from three electronic databases (Google Scholar, PubMed, and ScienceDirect). The selection of the criteria must contain all information related to "bacterial products", "anticancer", and "oral cancer," as the keywords were obtained from articles in publishing search engines written in full-free access English with any type of the study (table 1). However, those keywords are primarily combined and structured in the searching method using the Boolean technique and Medical Subheading (MeSH) term input. Any relevant topic and chapter of discussion in any research type will be included due to the to the need to be elucidated through comprehensive reading and synthesis reviewing the articles. The quality assessment is performed using the Database of Abstract of Reviews of Effects (DARE) technique [15] which consists of five variable questions with each question's interpretation of among three answers (yes, partial, and no) then scoring with consensus of authors according to level of agreement and Kappa coefficient index [16].

Table 1. The Search Strategy

Database	Keywords
Google Scholars PubMed	"bacterial products" [All field] AND, ("bacterial products" [MeSH Subheading] OR "bioproduct" [All field]), AND ("anticancer" [All field] OR "cancer therapy" [All field]), AND "oral cancer" [All field],
ScienceDirect	"bacterial products" OR "bioproduct" AND "anticancer" OR "cancer therapy" AND "oral cancer"

Table 2. The DARE Assesment

No	Author	Inclusion and Exclusion	Search coverage	Assessment of Quality	Study Description	Synthesis of Study	Kappa Index	Level of Agreement
1.	Gharbavi *et al*.	Y	Y	Y	Y	Y	1.00	Almost perfect
2.	Thakker and Narayanan	Y	Y	Y	Y	Y	1.00	Almost perfect
3.	Gupta *et al*	Y	Y	Y	Y	Y	1.00	Almost perfect
4.	Bachran *et al*	Y	Y	Y	Y	Y	1.00	Almost perfect
5.	Trivanovic *et al*	Y	Y	Y	Y	Y	1.00	Almost perfect
6.	Taj and Chattopadhyay	Y	Y	Y	Y	Y	1.00	Almost perfect
7.	Yaghoubi *et al*	Y	Y	Y	Y	Y	1.00	Almost perfect
8.	Choi *et al*	Y	Y	Y	Y	Y	1.00	Almost perfect

Y: Yes, N: Partial; N: No

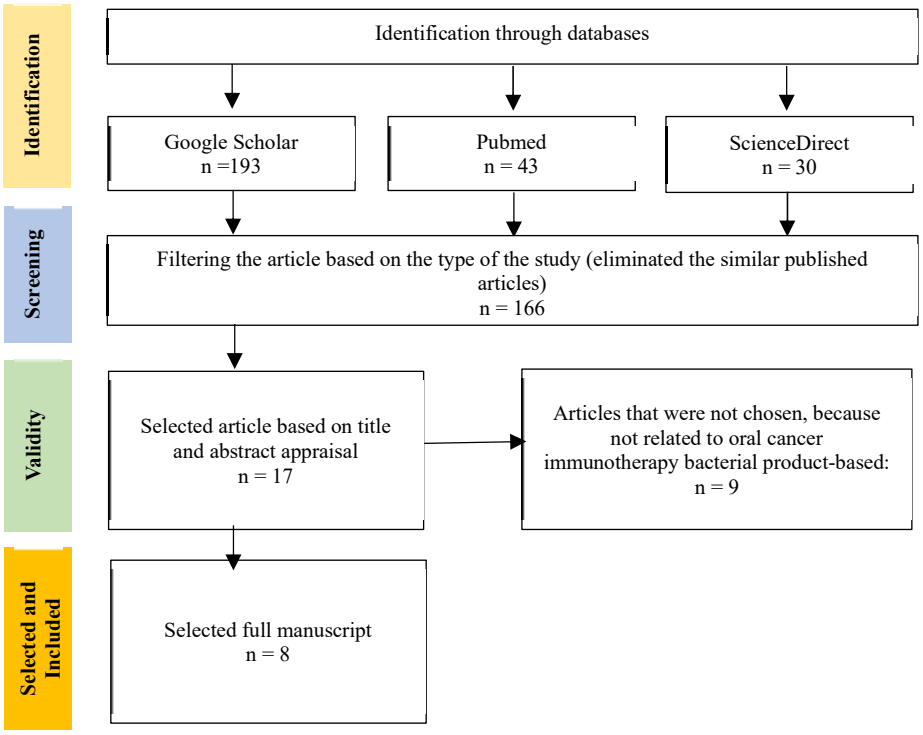

Figure 1. PRISMA flow diagram

RESULT

Table 3. Bacteria species and the product for cancer therapy

No	Author	Bacteria Species	Bacteria specific product	Clinical Outcome as cancer therapy
1	Gharbavi *et al*. [17]	*Salmonella sp.*	Outer membrane cell and Type III secretion System (T3SS)	Trigger and Zipper processes in nonphagocytic of cancer therapy. Rck protein throug Zipper process, initiating GTPase Cdc42 for actin polymerization. Trigger processes by *Salmonella sp* allowing entry mechanism using effectors for host cell cytoskeleton remodelling.
		Salmonella typhimurium VNP20009	Removed mshB gene for lipopolysaccharide synthesis	VNP20009 engineered for able to converting 5-fluorocystein to 5-fluorouracil
		Clostridium histolytic		Lysis in tumor cells of murine models
		Clostridium tetani		Shrinking tumor cells
		Clostridium novyi	Liposomase	As cytotoxic enzyme for cancer cells by deletion gene NT toxin
2	Thakker and Narayanan[18]	*Lactobacillus casei*		*In vitro* proven to decreased the papilloma virus cancer and promoting caspase expression for trigger the apoptosis mechanism
		Lactobacillus reuter I		Destroying plasma membrane of carcinoma cell
		Lactobacillus rahmnosus	Beclin-1	Inihibiting cancer cell proliferation and enhancing apoptotic gene BCL2
		Lactobacillus acidophilus		Along with *L. casei* combined with 5-FU to inhibit cancer cell proliferation
		Lactococcus lactis	Nisin A	Inhibit cancer cell proliferation and interrupt cell cycle
		Streptococcus bovis		together with *L. lactis*destroy carcinoma cell
3	Gupta *et al.*[1]	*Listeria monocytogenes*	Hyl gene deletion and mutation actA	Resistance in cancer cell phagolysosome
		Clostridium spp.	actin-specific ADP-ribosyltransferase, hemolysins, phospholipases	Interfering intracellular cancer cell function

		Bifidobacterium spp.	enterolactone	Able to convert fatty acids into pectin oligosaccharides
			spectinomycin-resistant gene	
		Magnetococcus spp.	magnetotatic and nanoliposome binding ability	as a drug delivery agent *in vitro* tumor research
4	Bachran *et al.*[19]	*Bacillus anthracis*	cytolethal distending toxin (Cdt)	Fused with *Haemophilus ducreyi* design novel tumor therapy using anthraz toxin for kill human tumor cell
		Bifidobacterium adolescentis	for vector expression	By expressing endostatin, supporting in angiogenesis inhibition of the tumor
		Bifidobacterium longum	for vector expression	
		Clostridium butyricum	for delivery vectors	induce drug delivery withour severe immune response
5	Trivanovic *et al.*[20]	*Clostridium spp.*	cystosine deaminase and nitroreducatse	Bacterial enzyme for cancer cell inhibition
		Clostridium perfringens	enterotoxin	activating immune system by binding to the antigens in cancer cell surface
		Pseudomonas spp.	enterotoxin	
		Corynebacterium diphteria	Diptheria toxin	Bind heparing-pbind epidermal growth factor percusor in cell surface, causing cell metabolism disruption and death of the cell
		Clostridium botulinum	Botulinum neurotxin	
6	Taj and Chattopadhyay[21]	*Actinobacteria spp.*	Actinosporin	Work as therapeutic of OSCC with gingivitis by *Porphyromonas gingivalis*
7	Yaghoubi *et al*[22]	*Pseudomonas aeruginosa*	Azurin	Binding p23 for modulating p53 and decrease endothelial cell motility and migration
8	Choi *et al*[23]			

REVIEW

Salmonella spp.

Salmonella is a facultative anaerobic microorganism that colonizes tumor regions, regardless of whether the environment is hypoxic or highly vascularized. *Salmonella* functions as an anticancer agent. The dissemination of *Salmonella* occurs via the Trigger and Zipper mechanisms of entry. The trigger mechanism involves the effectors SipA, SipC, SopE, and SopE2 from the *Salmonella* type III secretion system (T3SS), which are subsequently injected into host cells. Actin will bind with SipA and SipC. The remodeling of the cytoskeleton by Rho GTPases is modulated by the binding of SopE, SopE2, and SopB effectors. The Zipper mechanism in *Salmonella* occurs in the cell membrane through the expression of the Rck protein. This will regulate Akt/PI-3 activation and the actin polymerization mediated by GTPase Cdc42 [17].

Salmonella enterica serovar *Typhimurium* VNP20009 attenuated for delivering the detectable vector in solid tumor. This strain is constructed with *pur*I gene deletion, that this gene used for synthesis of purine. Another gene, *msb*B gene also been deleted inducing lipopolysaccharide (LPS) truncation [24]. The engineered VNP20009 strain expresses cytosine deiminase, facilitating the conversion of 5-fluorocytosine (5-FC) into the pharmaceutical cytotoxin 5-fluorouracil (5-FU). This cytoxin can inhibit cell proliferation in a mouse model. Modifying *Salmonella* strains can lead to the degradation of cancer cells through their toxic byproducts [18].

The mobility of *Salmonella* has been extensively studied due to its ability to migrate into tumor regions. Salmonella can specifically target and destroy tumor cells through its accumulation in the internal regions of the tumor. *Salmonella*'s chemotaxis and motility are facilitated by its flagella, enabling it to penetrate the tumor microenvironment. Several receptors facilitate the binding of *Salmonella*'s flagella, including aspartate and ribose/galactose receptors. This will facilitate the regulation of tumor accumulation and enhance the detection of immune system clearance protection. Salmonella interacts with pattern-recognition receptors (PRRs), enabling the immune system to respond. Activation of Nuclear Factor Kappa B-Light Chain (NF-κB) and signaling of Mitogen Activated Protein Kinase (MAPK) are critical for the induction of the adaptive immune response. This may serve as a potent vector for combating tumor cells by preventing dendritic cell activity through Bafilomycin A1 (Baf A1) and modulating macrophage function via the pyropyroptosis mechanism. *Salmonella* can induce the ubiquitination process of the major histocompatibility class II complex (MHC-II) to modulate dendritic cells (DC). In the B-lymphocyte cell system, *Salmonella* is regulated by modulating its distribution through the B-cell receptor (BCR). *Salmonella* employs T cells to inhibit tumor growth by activating T cells through the stimulation of connexin-43 protein on Salmonella LPS[17].

The mechanism of action in utilizing *Salmonella* as cancer therapy can act as tumor targeting and direct colonizing within the tissue with hypoxic and necrotic condition, modulating the myeloid cell to enhance innate and adaptive immune response, and combining with interferon will act as a good carrier as antitumor by induce CD8+ T cell immunity in tumor microenvironment[25–27]. Attenuating the *Salmonella* as the carriers and immunomodulators is now being studied by observing the outer membrane vesicle which can be safe for the host cell. The current research also focusing with genetic engineering in *Salmonella*

with combination of regiments to sustain the immune detection in combatting tumor tissues[28–30].

Clostridium spp.

Clostridium histolyticum is employed in the treatment for lysing tumor cells. Tumor cells have also been shown to shrink with *Clostridium tetani* treatment. Other species within *Clostridium* indicate that *Clostridium novyi* lacks pathogenic characteristics due to the deletion of the NT toxin gene. This gene is engineered to improve liposome-encapsulated anticancer drug efficacy[18]. *Clostridium acetobutyicum* can secrete TNF-a and interleukin-2 (IL-2), which promote T cell secretion. The engineered NT toxin strain of *Clostridium novyi* (NCT01925689) can induce inflammation by secreting cytokines such as TIMP-1, IL-6, MIP-2, and G-CSF at the infection site, thereby facilitating adaptive immunity for antitumor responses. Clostridium difficile toxin B (TcdB) has been evaluated for its potential in cancer treatment, demonstrating a tumor-specific immune response. High specificity antibodies induced by *Clostridium*-directed antibody therapy (CDAT) have been developed through gene engineering. *C. novyi*-NT toxin is also a component of Combination Bacteriolytic Therapy (COBALT) for the treatment of solid tumors in cancer therapy. *C. acetobutylicum* and *C. beijerinckii* were studied and engineered for the secretion of TNF-a and IL-2[1,20]. *C. perfringens'* enterotoxin interacts with tumor cell receptors CLDN3 and CLDN4, potentially inhibiting tumor progression. *C. botulinum* produces eight subtypes of botulinum neurotoxin type 8, which may influence the immunological response in cancer therapy[20].

The potential of *Clostridium* in oral cancer is utilized for its oncolytic activity, gene delivery and immunomodulation towards oral cancer. *Clostridium* can infiltrate into the hypoxic tumors and targeting inside without affecting normal tissue. The *Clostridium*-Directed Enzyme Prodrug Therapy (CDEPT), a strategy engineered-*Clostridium* for expressing the antitumor prodrugs for reducing the systemic toxicity and better therapeutic efficacy enhancement [31,32]. The safety in *Clostridium* application shown the potential in preclinical models. An IV injection $1x10^{10}$ *C. butyricum* spores M-55 stain shown oncolysis in tumor tissue, especially in glioblastoma patient. The germination of *C. butyricum* will require the surgical debridement after the abscess formed with no recurrence rate[33,34]. To optimize the *Clostridium* strategy by genetic engineering via CRISPR-Cas9 modification for ensuring the stable therapeutic genes[35]. The strategy in OSCC by utilizing *Clostridium perfringens* enterotoxin suppressed the phosphorylation yes-associated protein-1 (YAP1) and damaging the claudin-4 and -3 (CDLN4 and CDLN3) gene in epithelial malignant tumors[36].

Lactobacillus spp

Lactobacillus casei BL23 has been shown to inhibit the proliferation of cancer cells induced by human papillomavirus. In vitro testing demonstrated that *Lactobacillus reuteri BCRC14652* effectively disrupted the plasma membrane of HT29 colon cancer cells and inhibited proliferation through a mechanism of cell death. The proliferation of HT29 cancer cells is being investigated for inhibition by *Lactobacillus acidophilus* and *Lactobacillus rhamnosus*, which directly target the autophagy protein Beclin-1 and the endoplasmic reticulum chaperone GRP78, while also activating B-cell lymphoma 2 to facilitate apoptosis mechanisms. The use of two *Lactobacillus species, L. acidophilus* and *L. casei*, in conjunction with the 5-FU agent, serves as an adjunct in the treatment of colorectal cancer. L. acidophilus is also utilized for its extracellular polysaccharide (EPS) in the treatment of Ehrlich ascites carcinoma. L. plantarum NCU116 and its EPS116 product inhibit the growth of colon carcinoma cells. Another type of *L. casei* Shirota strain was investigated for its potential to inhibit colon cancer growth through the blockade of IL-6/STAT3 signaling[18].

Lactobacillus acidophilus shown to suppress the tumor growth and viability of OSCC by inducing high expression TRAIL gene which involved in apoptosis[37]. While the *Lactobacillus* strain Y33 *Lactiplantibacillus plantarum* induced apoptosis in OSCC cell lines reducing cell growth without deteriorating the normal cells. Probiotic with *lactobacillus*-based also proven to module immune system which contributing the anti-cancer properties[38]. Extracellular vesicles of *Lactobacillus reuteri* exhibiting the anti-tumor effects orally administrated, thus enhancing apoptosis in cancer cells[39]. *Lactobacillus salivarius* REN in *in vivo* study also proven to suppress the 4-nitroquioline 1 oxide (4NQO) in oral carcinogenesis by protecting the DNA and cyclooxygenase-2 downregulation prohibit the oxidative damage in nucleus with dose of colony $5x10^{10}$ CFU/kg body weight[40]. To enhance the safety in *Lactobacillus* as the treatment, it is required to combination with conventional cancer therapy such as phototermal regiments for showing the synergistic by enhancing in tumor ablation and immunogenic cell death.

Streptococcus spp.

The initial cancer vaccine developed using live *Streptococcus pyogenes* aims to induce TNF upregulation to combat neoplasms through inflammation regulation. *S. bovis* produced nisin A and bovicin HC5, which are effective in targeting carcinoma cells. *S. thermophilus'* DNA fragments have demonstrated anti-tumor potential through the enhancement of immune responses[18]. Taj *et al*, through in their *in vitro* study, proving that antimicrobial peptide (AMP) derived from *Streptococcus* reducing cancer cell survival in OSCC with its high binding affinity towards the tumor proteins. Those peptides are highly potential for mitigating cancer by inhibiting pathogenic bacteria inducing carcinogenesis in OSCC[41]. Probiotic based of *S. salivarius* had been studied in preclinical models for enhancing anti-PD-1 therapy, inducing the immune cell infiltration and reducing the tumor growth in oropharyngeal carcinoma[42]. *Streptoccus anginosus* are shown to induce the autophagy and promoting apoptosis in cancer cell, inhibiting the proliferation, migration,

and invasion in OSCC *in vitro*[43]. This bacterium also influences the tumor microenvironment by eliciting proinflammatory response in macrophages which may affect the human papilloma virus-infected oral carcinogenesis[44].

Listeria spp.

Modification of genes in *Listeria monocytogenes* is possible to eliminate cytotoxic properties which potential for the oral cancer therapy. The deletion of the hyl gene will impair the release process of the phagolysosome. Other genes that modified actA gene is responsible for inhibition in the process of intracellular diffusion. An in vivo study using a murine model of fibrosarcoma demonstrated that immunization with the p60 peptide of *L. monocytogenes* provided protection to healthy cells. *L. monocytogenes* interacts with various molecules, such as tumor-associated antigens (TAAs). Melanoma antigen gene-B/ MAGE-B serves as a tumor-associated antigen (TAA) delivered with *L. monocytogenes*, facilitating the reduction of metastasis and the induction of apoptosis in tumor cells. *Listeria* product, listeriolysin (LLO), has been utilized as an adjuvant and a delivery modality for drugs targeting tumor cells, potentially enhancing immune responses by increasing MHC-1 peptide expression on cell surfaces and stimulating cytotoxic T cells. LLO facilitates the transport of DNA molecules into the cytoplasm as cargo, while delivering cancer drugs to target specific tumor cell receptors [1].

Listeria monocytogenes as facultative intracellular bacterium can be a promising vector for delivering cancer immunotherapy. The immune activation by *Listeria monocytogenes* can robust the cytotoxic T lymphocyte which can employ the immune response for activating the necroptosis and pyroptosis in cancer cells. This bacterium can reform the TME by induced activated-T cell to eliminate the immunosuppressive cells for enhance the efficacy in combatting in tumor eradication[45]. The preclinical and clinical trials in use of this bacterium shown the efficacy in HPV-associated cancer[46]. The *Listeria*-based vaccine such as ADXS NEO personalized immunotherapy, designed to target neoantigen of specific mutation in tumor cells[47]. The safety strategy to use *Listeria*-based therapy to modify with encapsulation in red blood cell membranes to avoid the side effects[48].

Bifidobacterium spp.

Bifidobacterium has been engineered for use as carriers, exemplified by *Bifidobacterium adolescentis*, due to its non-pathogenic characteristics that facilitate endostatin expression within tumors. This will impede tumor growth and angiogenesis in tumor tissue. *Bifidobacterium longum* is employed for enhanced safety and stability in the delivery of endostatin for cancer gene therapy[20]. As the probiotic genus bacteria, *Bifidobacterium* shown potential as a therapeutic agent by modulate the immune system and alter the TME formation. Modulating the tumor-associated macrophages into M1 phenotype is *Bifidobacterium*-based therapy strategy. Shifting the macrophages may enhance the immune response towards the tumor cells, allowing the tumor growth suppression by oral administration of *Bifidobacterium breve*[49]. The composition of pathogenic of oral microbiome which induced carcinogenesis can be altered by administrating the *Bifidobacterium* to help the reducing the cancer risk. *Bifidobacterium* also can be utilized as an adjunct to immune checkpoint inhibitors (ICIs) which has been done in mouse model renal cell carcinoma. This study led by Ueki *et al*, proven the *Bifidobacterium longum* enhanced the efficacy of ICIs[50], which can be a next potential treatment for oral cancer.

Pseudomonas spp.

The protein azurin, secreted by *Pseudomonas aeruginosa*, is an amphipathic molecule characterized by a structure comprising 28 a-helical amino acids and a total of 128 amino acids. This copper-containing redox protein is utilized in tumor therapy. Azurin has been demonstrated to possess the capability of penetrating through the protein transduction domain. A peptide of p28 azurin may serve as an effective inhibitor of cancer cell proliferation. The mechanisms by which p28 penetrates intracellularly are mediated by caveolin-1, the Golgi complex, and GM-1 ganglioside[22]. The cell viability of the OSCC cell line YD-9 was reduced when treated with a combination of 5-FU and Azurin. The sensitivity for tumor suppression was enhanced through DNA damage, which promoted the activation of p53 and cyclin B1[23].

Pseudomonas aeruginosa mannose-sensitive hemmaglutinin (PA-MHSA) strain shown potential in inhibition of cancer cell growth by inducing the apoptosis. This specific strain activating pro-apoptotic pathway inclusing caspase-9, caspase-3, and causing cell cycle arrest in cancer. *Pseudomonas* shown in activating the immune system through NF-κB/TLR5 pathway which modulating for natural ability to eradicate the cancer cells[51]. The clinical use already arose in China of PA-MHSA strain, which effectively eliminated the various cancer cells and showing synergistic approach with chemotherapy[51,52]. The safety of *Pseudomonas aeruginosa* use with inactive form one has been used into clinical trials. It requires the pre-test tolerance of PA-MHSA to stimulate the immune tolerance towards this bacterium. Genetical engineering is also required to activate tumor specific CD8+ T cells for inducing the specificity mechanism and long-lasting tumor immune response. *Pseudomonas* exotoxin A is currently used for great antitumor in both *in vitro* and *in vivo* studies[53]. However, it requires the high specificity modification of this immunotoxin to overcome the clinical applications.

Actinobacteria spp.

Taj and Chattopadhyay conducted an in-silico study in which they identified 179 bioactive compounds from *Actinobacteria*. The compounds were identified through molecular docking processes, with Actinosporin G exhibiting a high binding affinity and being recognized as targeted

for OSCC. Actinosporin can bind to bacterial gingipain secreted by *P. gingivalis*, which is induced in patients with OSCC. Actinosporin, also known as AM-158, exhibits an affinity for binding to MMP-9, indicating a molecular interaction with another entity[21].

As the gram-positive type bacteria, *Actinobacteria* can produce bioactive compounds which has anticancer functions. Other genus belongs to *Actinobacteria*, such as *Streptomyces* and *Haliclona* produced metabolites which used in antibiotic compounds tetracenoquicine and 5-iminoaranciamycin. Those 2 compounds exhibit highest cytotoxic activities in HeLa cells and acute myelogenous leukemia LH-60 cells. Other bioactive compounds derived *Actinobacteria* within its genus is aureolic acids. This compound exhibitied antitumor activities in many cancer cells *in vitro,* which now modified into new aureolic acid chromomycin B, chromomycin A2, and chromomycin A3. Other bioactive compounds which it is found in this bacterium is *actinomycin D*, isolated from *actinomycete* streain $AUBN_{10}/2$, can be utilized for inhibit gastric adenocarcinoma and hepatic carcinoma cell viability *in vitro*[54].

Actinobacteria is found prominent in oral buccal mucosa in OSCC patients in China, yet none of the discovery mention the role of this bacterium towards the cancer. It is suggested the bioactive compounds of this bacterium may affect and alter the microbiome of the OSCC[55,56]. *Actinobacteria* can adapt into extreme environments which has the ability to survive in the complex and hostile of TME. The bioengineering technologies is currently used to modify the *actinobacteria* use for therapeutic efficiency for reducing the side effects[57].

Corynebacterium spp.

Corynobacterium diphteria secretes diphtheria toxin (DT), which was the first immunotoxin and is now referred to as denileukin diftitox (ONTAK). The two fragments, DTA and DTB, consist of 535 amino acids and are capable of binding to heparin-binding epidermal growth factor precursor (HB-EGF) on the surface of cancer cells. The toxicity of DT has been mitigated through the modification that involves the removal of the receptor binding domain of the toxin. The recombinant DT385 may exhibit cytotoxic activity against cancer cells, effectively reducing angiogenesis and minimizing tumor mass[20].

Corynebacterium matruchotii has specific effects in OSCC by use it as the therapeutic agent. It regulates the genome stability and immune response. The use of this bacterium through the mechanism in DNA damage response (DDR) pathway in OSCC, which upregulating via the gamma histone family member X /γ-H2AX, phosphorylated- human ataxia telangiectasia mutated and Rad3-mutated/ p-ATR, and phosphorylated-check point kinase 1/ p-CHK1. By upregulating via those pathways, it includes the suppression of proliferation and tumor growth in OSCC. This bacterium will modulate immune response and inflammatory activation via nucleotide-binding leucine-rich-containing family pyrin domain-domain-containing-3/NLRP3 inflammasome pathway[58].

The clinical use is still remained undergoing research and required combination with chemotherapy and modified with bacterial nanomedicine-photodynamic immunotherapy for enhancing the OSCC anticancer strategy. The safety of *Corynebacterium's* use as monotherapy still remained no evidence which mostly requiring the encapsulation method for ensuring the stability and avoiding the side effects[59].

Conclusion and potential for future cause

The oral microbiome has emerging various significant factor in oral carcinogenesis. The potential implication, complex interactions among bacteria and chemoterapies, altering the TME, and influencing the host cell responses can be specifically observed in each species. As the microbiome plays a crucial role in the body, serving as an important indicator of overall health. Over the years, advancements in oral cancer biology, oral microbiology, bioinformatics, biochemistry, biotechnology, and bioengineering have elucidated the roles of microbiology in oral cancer therapy. The benefits of bacterial bioproducts have been demonstrated and researched for their ability to act as carriers, targeting cancer cells and inhibiting tumor growth. Clinical trials examining bioproducts are currently being conducted by numerous esteemed scientists globally, providing an opportunity to enhance our understanding of microbiological potential. Exploring the potential engineering of harmful agents for application in future oral cancer immunotherapy.

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