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Review

Therapeutic and Adjuvant Effects of Probiotics in the Management of Oral Cancer: A Scoping Review of Preclinical and Clinical Evidence

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Abstract

Background/Objectives: Oral cancer remains a major global health challenge, with persistent limitations in treatment efficacy and significant therapy-related morbidity. Probiotics, owing to their immunomodulatory, anti-inflammatory, and microbiota-regulating properties, have emerged as potential therapeutic and adjuvant agents. This scoping review aimed to systematically map and critically appraise preclinical and clinical evidence regarding the therapeutic and supportive effects of probiotics in oral cancer. Methods: A comprehensive literature search was conducted across PubMed, Scopus, Web of Science, and Google Scholar without temporal restrictions, including studies published up to February 2026. Eligible studies comprised in vitro, in vivo, and clinical investigations evaluating the effects of live or non-viable probiotic interventions on oral cancer biology and related clinical outcomes. Results: Twenty-one studies were included: 13 in vitro, 3 in vivo, and 6 clinical studies. Preclinical evidence indicates that strains such as *Lactiplantibacillus plantarum*, *Lactobacillus acidophilus*, and *Lacticaseibacillus paracasei* exert selective antiproliferative effects (up to 85% inhibition) via apoptosis induction, modulation of PTEN/MAPK and NF-κB signaling, and reduction in pro-inflammatory mediators. In vivo models demonstrated tumor growth suppression and improved survival without significant toxicity. Clinically, probiotics reduced treatment-induced oral mucositis, improved salivary function, and enhanced microbiota stability and patient-reported outcomes. However, evidence on direct oncological endpoints remains limited. Conclusions: Probiotics demonstrate biologically plausible, strain-specific antitumor and supportive effects, with the strongest evidence supporting their role as adjunctive agents, particularly in managing treatment-related complications. Further well-designed in vivo and clinical studies are required to define optimal strains, dosing strategies, and integration with standard oncologic treatments.

Keywords: oral squamous cell carcinoma; probiotics; antitumor activity; treatment-related mucositis; microbiota modulation

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1. Introduction

Oral cancer, encompassing malignancies of the lip and oral cavity, represents a major and growing global public health challenge [1]. According to the Global Cancer Observatory (GLOBOCAN), an estimated 389,498 new cases and 188,230 deaths were recorded worldwide in 2022 [2]. Earlier GLOBOCAN iterations estimated 377,713 new cases and 177,757 deaths in 2020 [3], compared with 354,900 cases in 2018 [4]. Although derived

from successive GLOBOCAN updates, these estimates collectively suggest a sustained upward trend in the global burden of oral cancer. Globally, the disease ranks 16th in overall incidence [2], occupying the 12th position among men and the 18th among women, with an age-standardized incidence rate of approximately 4.0 per 100,000 population [5]. The disease disproportionately affects men and older individuals and exhibits marked socioeconomic disparities in incidence, stage at diagnosis, and mortality [6]. Despite advances in prevention and early detection, the burden of advanced-stage disease remains substantial in many regions.

Current management of oral cancer relies primarily on surgery, radiotherapy, chemotherapy, and, more recently, immunotherapy [7,8]. Although therapeutic innovations have improved locoregional control and survival in selected subgroups, overall outcomes for advanced-stage disease remain unsatisfactory [9]. Moreover, treatment-related morbidity is considerable and includes oral mucositis, xerostomia, dysphagia, opportunistic infections, and long-term impairment of speech and swallowing, all of which significantly compromise quality of life [10,11]. In addition, therapeutic resistance and locoregional recurrence continue to limit durable disease control [12]. These challenges underscore the need for complementary strategies that enhance antitumor efficacy while mitigating treatment-related toxicity.

In parallel, increasing attention has been directed toward the role of the oral microbiome in carcinogenesis. The concept of a tumor-associated microbiota has reshaped understanding of host–microbe interactions in cancer biology [13]. Microbial dysbiosis within the oral cavity may promote chronic inflammation, thereby facilitating malignant transformation [14]. Proposed mechanisms include enhanced oxidative stress, activation of pro-inflammatory signaling pathways such as NF-κB, dysregulation of immune surveillance, and increased production of cytokines including interleukin-6 and tumor necrosis factor-α [15]. These alterations contribute to a permissive tumor microenvironment characterized by sustained proliferation, angiogenesis, and immune evasion [16]. Consequently, modulation of the oral microbiota has emerged as a potential therapeutic avenue in oral oncology.

Within this context, probiotics, defined by the Food and Agriculture Organization/World Health Organization (FAO/WHO) as live microorganisms that confer a health benefit when administered in adequate amounts, have gained interest as microbiota-modulating agents [17]. Their proposed mechanisms include competitive exclusion of pathogenic species, reinforcement of epithelial barrier function, production of antimicrobial compounds and bioactive metabolites, and immunomodulatory effects at both local and systemic levels [18]. Beyond ecological rebalancing, preclinical studies suggest that specific probiotic strains may exert direct or indirect antitumor effects, including inhibition of cellular proliferation, induction of apoptosis, modulation of inflammatory mediators, and interference with oncogenic signaling pathways [19,20].

Emerging clinical evidence further indicates a potential adjuvant role for probiotics in the management of treatment-related complications, particularly radiation- or chemotherapy-induced oral mucositis, as well as in restoring microbial equilibrium following oncologic therapy [21]. However, the available data remain fragmented and heterogeneous, with variability in strains, doses, formulations, routes of administration, and outcome measures. No comprehensive mapping of the therapeutic and adjuvant effects of probiotics in oral cancer has yet clarified the scope, consistency, and limitations of the existing literature. Given this evolving but methodologically diverse body of evidence, a scoping review is warranted to systematically map current research, identify knowledge gaps, and delineate future investigative priorities. The present review, therefore,

aims to comprehensively examine the therapeutic and adjuvant effects of probiotics in the management of oral cancer, encompassing in vitro, in vivo, and clinical studies.

Research questions

This scoping review addressed the following research questions:

- What is the scope, nature, and strength of the available preclinical and clinical evidence regarding the therapeutic effects of probiotics in oral cancer?
- To what extent do probiotics exert clinically relevant adjuvant effects and biological activity, and what key gaps and limitations persist in the current evidence base?

2. Results

2.1. Study Selection and General Characteristics of Included Studies

A total of 21 studies published between 2012 and 2026 were included in this scoping review, encompassing in vitro, in vivo, and clinical investigations (Figure 1). Preferred Reporting Items for Systematic reviews (PRISMA-ScR) Checklist can be found in the Supplementary Materials. Geographically, the majority of studies originated from Iran, India, China, Kuwait, Uganda, and Singapore. The distribution of study types comprised 13 in vitro studies, 3 in vivo preclinical studies, and 6 clinical trials. The total number of included studies was 21 rather than 22, as one study contributed to both in vitro and in vivo categories (Table 1). The evidence base is largely preclinical, with a substantial proportion of in vitro studies employing a range of OSCC cell lines to evaluate the antiproliferative and cytotoxic effects of probiotic strains. The most frequently utilized cell lines include HeLa-derived KB (ATCC CCL-17) [22–26], OSCC ATCC CRL-1628 [22,23,25], HNO97 [27,28], GMNL-346 [29], Cal27 [30], HN5 [31], HSC4 [32], Tca8113, SCC-9, and SAS [33]. These in vitro models have been used to assess a variety of probiotic interventions, including live bacterial cultures, cell-free supernatants (CFS), lysates, and heat-inactivated preparations, enabling evaluation of dose-dependent cytotoxicity and selectivity for cancer versus normal cells.

In vivo investigations utilized diverse animal models to replicate oral carcinogenesis and assess the therapeutic potential of probiotics. Experimental approaches included the 4-nitroquinoline 1-oxide (4NQO)-induced oral carcinogenesis model in rats [27,34], the 7,12-dimethylbenz[a]anthracene (DMBA) and liquid paraffin-induced buccal pouch model in golden Syrian hamsters [35], and xenograft models employing SAS cells in immunodeficient mice [29,36]. These models facilitated the evaluation of tumor incidence, tumor volume reduction, and the systemic safety profile of administered probiotic strains.

Clinical investigations, predominantly Phase Ib to III trials, focused on the adjuvant use of probiotics for the management of treatment-related oral complications in patients with head and neck cancers, including oral cancer. Primary endpoints included the prevention or mitigation of radiation-induced oral mucositis and secondary fungal infections [37–41]. Clinical studies included a total of 482 participants; notable heterogeneity was observed in study design, patient populations, and group allocation, with participants generally assigned to either a probiotic intervention or a control (placebo or standard care) group.

Across preclinical and clinical studies, a wide range of probiotic strains was investigated. *Lactobacillus acidophilus* [26,27] and *Lactiplantibacillus plantarum* strains (MCC 3016, Y33, Y8) [22–24,30] were among the most frequently studied. Other commonly examined strains included *Limosilactobacillus fermentum* KUMS-C9 and *Lactiplantibacillus plantarum* KUMS-C47 [25], *Lacticaseibacillus paracasei* GMNL-346 [29], *Lactobacillus salivarius* REN [34,42], *Lactobacillus casei* [28,42], *Lactobacillus brevis* CD2 [37,41], *Lactococcus lactis* [38], *Lactobacillus rhamnosus* GG [33], *Bacillus clausii* UBBC-07 [36], *Acetobacter syzygii* [26], *Lactobacillus fermentum* and *Lactobacillus crispatus* [31], marine-derived *Lactobacillus* species

(TLMP1–TLMP5) [35], and the yeast *Pichia fermentans* YSH [32]. Multi-strain probiotic formulations were also assessed, including combinations of *Lacticaseibacillus rhamnosus* GG, *L. casei*, *L. acidophilus*, *L. delbrueckii* subsp. *bulgaricus*, *Bifidobacterium infantis*, *B. brevis*, and *Streptococcus thermophilus* [40], as well as alternative cocktails containing *Bifidobacterium breve*, *B. longum*, *L. acidophilus*, *L. casei*, *L. bulgaricus*, *L. rhamnosus*, and *Streptococcus salivarius* subsp. *thermophilus* [39].

The majority of probiotics investigated were Gram-positive microorganisms of human origin (oral or intestinal) or derived from traditional dairy products such as cheese and yogurt. Administration routes included suspensions, powders, lozenges, and mouthwashes, with dosing regimens ranging from 10^5 to 10^{10} CFU/mL or per day [33,38].

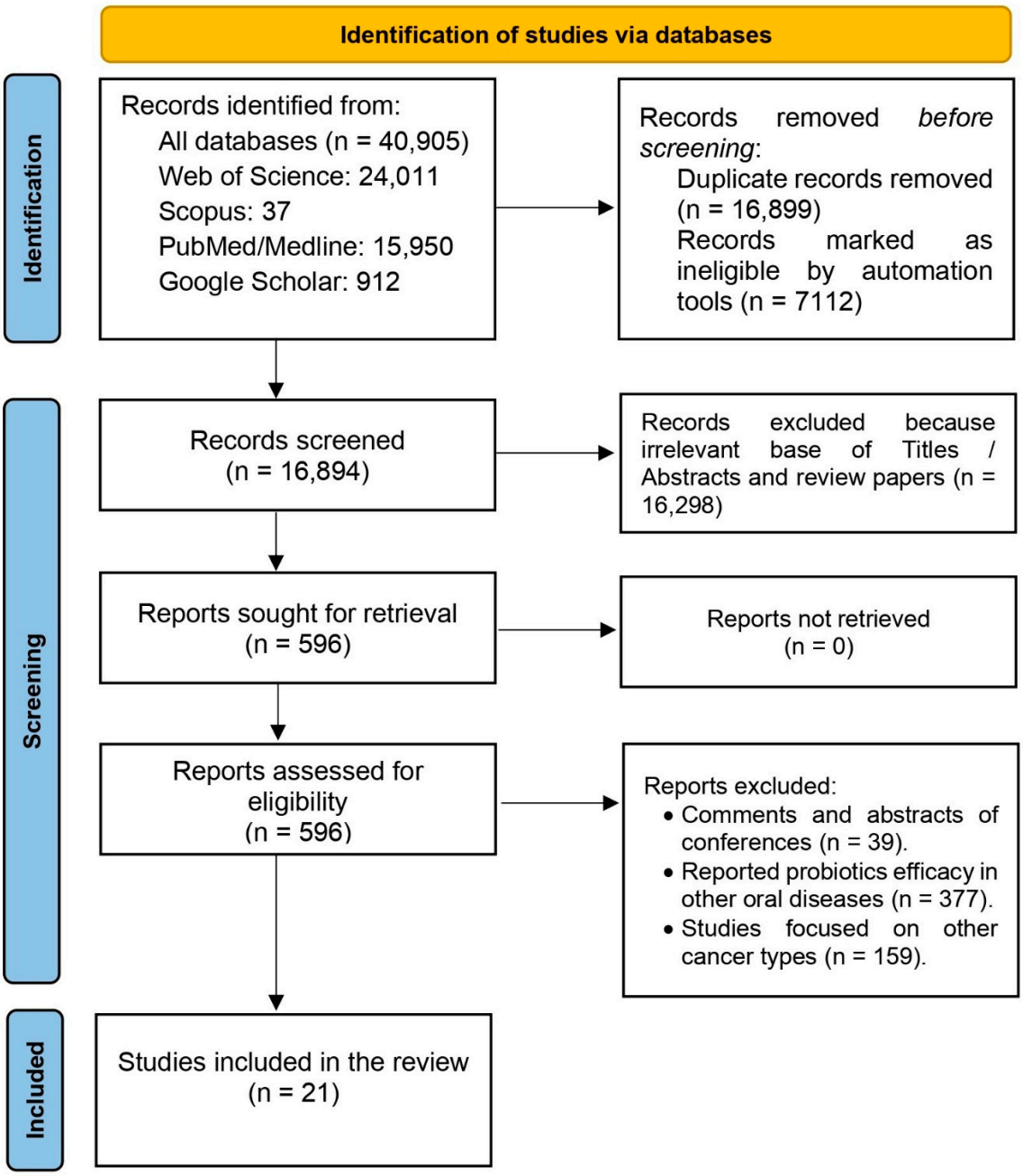


Figure 1. PRISMA 2020 flow diagram for the selection of studies. The numbers (n) indicate the number of records identified at each stage of the screening process.

Table 1. Summary of characteristics of included studies.

Author(s), Year, Country	Probiotic Strain(s) and Administered Dose/Concentration	Cancer Model or Study Population (Cell Density/Sample Size)	Experimental Design	Comparator or Reference Treatment/Normal Cell Line	Biological Origin of Strain(s)
Vidya et al., 2024, Uganda [35]	*Lactobacillus* spp. (TLMP1, TLMP2, TLMP3, TLMP4, and TLMP5)	DMBA+ liquid paraffin induced oral carcinogenesis	In vivo (male golden Syrian hamsters)	5-Fluorouracil (20 mg/kg bw)	Soil samples, Pichavaram mangroves, India
Zhang et al., 2013, China [34]	*Lactobacillus salivarius* REN (5×10^6–5×10^{10} cfu/kg body weight)	4-NQO-induced oral cancer	In vivo (male F344 rats)	-	Fecal samples from healthy centenarians (Bama, China)
Wang et al., 2016, China [42]	*L. salivarius* REN metabolites (1, 2, 3 × 10^9 CFU/mL), *L. casei* metabolites (2 × 10^9 CFU/mL)	TCA-8113 (5×10^4 cells/well)	In vitro (MTT assay)	NS-398 (10 mM)	Fecal samples from healthy centenarians (Bama, China)
Udompatanakorn and Ratthawongjirakul, 2024, Thailand [33]	*Lactobacillus rhamnosus* GG [ATCC 53103] (10^5–10^8 CFU/mL) + curcumin (5–80 µg/mL)	SCC-9 (ATCC 53103) (5×10^3 cells/well)	In vitro (MTT assay)	Human gingival fibroblasts (HGF; PCS-201-018)	American Type Culture Collection
Tavallaei et al., 2025, Iran [25]	*Limosilactobacillus fermentum* (KUMS-C9) and *Lactiplantibacillus plantarum* (KUMS-C47) (10^8 CFU/mL)	HeLa-derived KB and OSCC (2×10^4 cells/mL)	In vitro (MTT assay)	Doxorubicin (0.7 µg/mL); Paclitaxel (0.5 µg/mL) Normal fibroblast & HUVEC lines	Traditional Iranian cheese
Rehaman et al., 2026, Kuwait [28]	*Lactobacillus casei* (5×10^7 and 1×10^8 CFU/mL)	HNSCC (27×10^4 cells/well)	In vitro (MTT assay)	/	Culture collection University of Gothenburg
Shamloo et al., 2020, Iran [32]	*P. fermentans* PTCC 5296	HSC4 (1.2×10^4 cells/well)	In vitro (MTT assay)	Cisplatin Epithelial normal cell line (KDR)	Traditional yogurt (Eastern Azerbaijan, Iran)
Nami et al., 2024, Iran [23]	*Lactiplantibacillus plantarum* Y33	HeLa-derived KB and OSCC (2×10^4 cells/mL)	In vitro (MTT assay)	Doxorubicin; Paclitaxel	Iranian dairy products (Cheese; Milk; Yogurt)
Al-Asfour et al., 2024, Kuwait [27]	*L. acidophilus* ATCC 4356	HNO97 (27×10^4 cells/well)	In vitro (MTT assay)	/	Culture collection University of Gothenburg
Mokhtari et al., 2021, Iran [31]	*Lactobacillus fermentum*, *Lactobacillus crispatus* (10^9 CFU/mL)	HN5 (10,000 cells)	In vitro (MTT assay)	/	Healthy adult human mouth

Table 1. *Cont.*

Author(s), Year, Country	Probiotic Strain(s) and Administered Dose/Concentration	Cancer Model or Study Population (Cell Density/Sample Size)	Experimental Design	Comparator or Reference Treatment/Normal Cell Line	Biological Origin of Strain(s)
Haghshenas et al., 2023, Iran [22]	*Lactiplantibacillus plantarum* (KUMS-Y8, C14, M22, M42), *Lactobacillus acidophilus* PTCC 1643	HeLa-derived KB and OSCC (2×10^4 cells/mL)	In vitro (MTT assay)	Doxorubicin; Paclitaxel; Normal cell line (HUVEC)	Iranian dairy products (Cheese; Milk; Yogurt)
Fida et al., 2025, India [30]	*Lactiplantibacillus plantarum*	Cal27 (ATCC-CRL-2095) (5000 cells/well)	In vitro (MTT assay)	/	Healthy adult human gut
Chen et al., 2025, Taiwan [29]	*Lacticaseibacillus paracasei* GMNL-346 (1×10^9 cells/mL; 1×10^9 cells/mouse/day)	HSC3 (4×10^3 cells/well)	In vitro (WST-1) and in vivo (male mouse xenograft model)	/	Genmont Biotech Inc., Tainan, Taiwan
Asoudeh-Fard et al., 2017, Iran [24]	*Lactobacillus plantarum*	HeLa-derived KB cells (1.0×10^4 cells/cm^2)	In vitro (MTT assay)	/	Traditional Greek cheese dairy products
Aghazadeh et al., 2017, Iran [26]	*Acetobacter syzygii*	HeLa-derived KB (1.2×10^4 cells/well)	In vitro (MTT assay)	Cisplatin Normal cell line	Iranian traditional dairy products (cheese, yogurt, curd, shiraz)
Manifar et al., 2023, Iran [39]	Multi-strain formulation (*Bifidobacterium breve* (2×10^{10} CFU), *Bifidobacterium longum* (7×10^9 CFU), *L. acidophilus* (2×10^9 CFU), *L. casei* (7×10^9 CFU), *L. bulgaricus* (2×10^8 CFU), *L. rhamnosus* (1.5×10^9 CFU), *Streptococcus salivarius* subsp. Thermophiles (1.5×10^{10} CFU)	64 cancer patients	Double-blind randomized clinical trial	Normal saline mouthwash	Familact, Zist Takhmir Company, Tehran, Iran
De Sanctis et al., 2019, Italy [37]	*L. brevis* CD2 (2×10^9 CFU)	75 cancer Patients	A multicentric randomized study	Sodium bicarbonate mouthwash	CD Investments Ltd., Rome, Italy
Limaye et al., 2013, USA [38]	AG013 mouth rinse (*Lactococcus lactis*, 2.0×10^{11} CFU/15 mL)	25 cancer patients	Clinical trial	Placebo rinse matched for appearance and taste	/

Table 1. *Cont.*

Author(s), Year, Country	Probiotic Strain(s) and Administered Dose/Concentration	Cancer Model or Study Population (Cell Density/Sample Size)	Experimental Design	Comparator or Reference Treatment/Normal Cell Line	Biological Origin of Strain(s)
Mirza et al., 2022, India [36]	*Bacillus clausii* UBBC-07 spores	46 cancer patients	Clinical trial	Distilled Water	/
Pereira-Riveros et al., 2025, Spain [40]	Multi-strain cocktail (*Lacticaseibacillus rhamnosus* GG (1×10^{10} CFU); *L. casei*; *L. acidophilus*; *L. delbrueckii* subsp. *bulgaricus*; *Bifidobacterium infantis*; *B. brevis*; and *Streptococcus thermophilus* (1×10^{9} CFU)).	72 cancer patients	Randomised Clinical Trial	Placebo containing inactive excipients	ITF Reseach Pharma SLU (Madrid, Spain)
Sharma et al., 2012, India [41]	*L. brevis* CD2 lozenges (>2×10^{9} cells)	200 cancer patients	Randomized double-blind placebo-controlled study	Placebo rinse matched for appearance, color, and taste	CD Pharma India Pvt (Delhi, India)

Columns include: (i) study identification (author, year, country), (ii) intervention details specifying probiotic strain(s), formulation (live organisms, metabolites, or multi-strain preparations), dosage/concentration, and route of administration where applicable, (iii) cancer model or study population, including cell line, animal model, or patient cohort with corresponding sample size or cell density, (iv) study design (in vitro, in vivo, or clinical trial), (v) comparator or reference treatment, including untreated controls, chemotherapeutic agents, or normal cell lines, and (vi) biological origin of probiotic strains where reported. DMBA: 7,12-dimethylbenz[a]anthracene; 4-NQO: 4-Nitroquioline 1-Oxide; OSCC: oral squamous cell carcinoma; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; HUVEC: Human umbilical vein endothelial cells; WST-1: Water-soluble tetrazolium salt; CFU: Colony-forming units.

2.2. Preclinical Therapeutic Efficacy of Probiotics in the Management of Oral Cancer

Lactobacillus acidophilus

Preclinical evidence suggests that *L. acidophilus* from traditional fermented dairy products exerts biologically relevant antitumor effects in OSCC models (Table 2). In vitro, strain PTCC 1643 reduced HeLa-derived KB cell proliferation by 48.5%, compared with 57.6% for cisplatin under similar conditions [26]. Strain ATCC 4356 also demonstrated significant cytotoxicity, decreasing HNO97 cell viability by 53% after 24 h [27]. Notably, enzymatic treatment of ATCC 4356-secreted metabolites enhanced cytotoxicity to 72.72% (pronase) and 51.5% (lipase) in HeLa-derived KB cells, whereas similarly treated cisplatin achieved only 42.4% inhibition [26], suggesting that proteinaceous or lipid-associated bacterial fractions may mediate antitumor activity. Mechanistically, apoptosis induction, potentially involving TRAIL-related pathways, has been proposed, although protein-level confirmation remains inconsistent [27]. Importantly, cytotoxic effects were markedly lower in normal KDR cells, indicating a degree of tumor selectivity [26]. Although limited to preclinical systems, these findings support further translational investigation of *L. acidophilus* as a potential adjunctive strategy in the management of oral cancer.

Table 2. Summary of in vitro anti-oral cancer effects of probiotics.

Strain	Cell Line	Key Quantitative Results	Selectivity	Reference
Acetobacter syzygii	HeLa-derived KB	51.5% inhibition; 75.7% apoptosis (60 µg/mL)	9.36% apoptosis KDR	[26]
L. acidophilus PTCC1643	HeLa-derived KB	48.5% inhibition	Lower toxicity vs. cisplatin on KDR	[26]
L. acidophilus ATCC4356	HNO97	53% viability reduction (24 h)	—	[27]
L. plantarum MCC3016	Cal27	48% (MOI10); 60% (MOI100); IC50 5-FU reduced 7.2 → 3.8 µM	No toxicity fibroblast/HUVEC	[30]
L. plantarum C47	HeLa-derived KB	IC50: 13.22 µg/µL (48 h); 3.03 µg/µL (72 h)	PBMC IC50 2153.3 vs. 29.8 (paclitaxel)	[25]
L. fermentum C9	HeLa-derived KB	IC50: 7.53 µg/µL (48 h); 5.77 µg/µL (72 h)	PBMC IC50 2453.6	[25]
L. rhamnosus GG	SCC-9	49.0% (24 h); 41.6% (48 h) viability alone and 84.12% viability in combination with curcumin	Combination toxic to normal cells	[33]
L. salivarius REN	Tca8113	49% inhibition (3×10^9 CFU/mL)	—	[42]
P. fermentans YSH	HSC4	85% inhibition (24 h)	>91% normal KDR viability	[32]
L. paracasei GMNL-346	SAS/HSC3	IC50: 7.12 Log cells/mL	—	[29]

PBMCs: Peripheral Blood Mononuclear Cells; MOI: multiplicity of infection; 5-FU: 5-Fluorouracil; CFU: Colony-forming units; KDR: normal epithelial cells; HUVEC: Human umbilical vein endothelial cells; PTCC: Persian Type Culture Collection; ATCC: American Type Culture Collection; IC50: half-maximal inhibitory concentration. →: go to.

Lactiplantibacillus plantarum (formerly *Lactobacillus plantarum*)

Isolated from traditional fermented dairy products, particularly Greek cheeses and milk [22,43], *Lactiplantibacillus plantarum* is the most extensively investigated probiotic species in preclinical oral cancer research. In vitro, strain MCC 3016 reduced Cal27 cell

viability by 48% at a multiplicity of infection (MOI) of 10 and by 60% at MOI 100 after 6 h of exposure [30]. The term Multiplicity of Infection (MOI) is the ratio of bacterial cells to target cancer cells in bacterium–host interaction assays, distinguishing it from its conventional virological usage. Notably, co-administration with 5-fluorouracil (5-FU) significantly enhanced chemosensitivity, lowering the 5-FU IC50 from 7.2 μM alone to 3.8–4.1 μM in the presence of either live bacteria or their cell-free supernatant [30]. Secreted metabolites from strains C14, M22, M42, and Y8 demonstrated IC50 values ranging from 3.44 to 6.4 μg/μL against HeLa-derived KB cells after 72 h [22], while strains C5, C28, M45, and Y33 exhibited IC50 values between 3.213 and 19.625 μg/μL at concentrations below 25 μg/mL [23].

Strain KUMS-C47 displayed one of the most pronounced selective effects, with an IC50 of 3.03 μg/μL at 72 h on HeLa-derived KB cells, compared with 2153.3 μg/μL on normal peripheral blood mononuclear cells (PBMCs), indicating superior tumor selectivity relative to paclitaxel and doxorubicin in normal cells [25]. Mechanistically, *L. plantarum* strains have been shown to induce apoptosis by increasing SMAC, caspase-3, and p53 expression; decreasing survivin levels; enhancing reactive oxygen species (ROS) production; and reducing the secretion of IL-6, IL-8, TNF-α, and VEGF. Additional modulation of PTEN activation and inhibition of the MAPK pathway have been reported [23–25,30]. Importantly, no significant cytotoxicity was observed in fibroblasts or HUVEC endothelial cells, reinforcing a favorable safety profile in vitro.

Lacticaseibacillus paracasei (formerly *Lactobacillus paracasei*)

Originating from traditional Taiwanese and Iranian foods [44], *Lacticaseibacillus paracasei* GMNL-346 has demonstrated both in vitro and in vivo antitumor activity. Heat-inactivated GMNL-346 exhibited an IC50 of 7.12 log cells/mL in SAS and HSC3 cell lines after 72 h [29]. Treatment induced cell-cycle arrest in the G0/G1 phase in SAS cells and S phase in HSC3 cells, reduced DNA replication, upregulated RB and p16INK4a, downregulated CDK6, and suppressed tumor stemness markers including OCT4, SOX2, BMI1, EZH2, and c-Myc [29]. In an OSCC xenograft mouse model, oral administration of 1×10^9 cells/day, five days per week for five weeks, increased survival to 40% compared with 0% in controls, reduced tumor weight by 85% in HSC3 and 26% in SAS tumors, and restored gut microbiota diversity with increased propionic and isobutyric acid levels [29]. No systemic toxicity was reported, supporting translational relevance.

Limosilactobacillus fermentum (formerly *Lactobacillus fermentum*)

L. fermentum is a probiotic lactic acid bacterium naturally present in the human microbiota and commonly found in fermented foods such as dairy and plant products [45,46]. Data on *L. fermentum* strain 4–17 are heterogeneous. Strains GMNL-117 and GMNL-299 demonstrated IC50 values of 8.28 and 20.23 log cells/mL, respectively, for human OSCC cells [29]. Strain KUMS-C9 exhibited IC50 values of 7.53 μg/μL and 5.77 μg/μL at 48 and 72 h, respectively, in HeLa-derived KB cells, compared with 2453.6 μg/μL in normal PBMCs, indicating selective apoptosis associated with increased SMAC and decreased survivin expression [29]. Conversely, no significant anticancer activity was observed on HN5 cells, although acidic conditions reduced proliferation [31]. The residual viability values for Lactobacillus fermentum were 93%, 80%, 65%, 27%, 19%, and 11% at concentrations of 5, 10, 20, 30, 40, and 50 units, respectively, indicating a gradual, concentration-dependent reduction in tumor cell viability that remained broadly comparable to the control conditions (MRS and MP media) across lower and intermediate concentrations [31].

Lactobacillus crispatus

L. crispatus is a Gram-positive, lactic acid-producing bacterium that naturally inhabits the female urogenital tract and vertebrate gastrointestinal tract, where it helps protect

against bacterial vaginosis [47]. Unlike several other *Lactobacillus* species evaluated in oral squamous cell carcinoma models, *L. crispatus* strain SJ-3C-US has not demonstrated significant antiproliferative activity under the experimental conditions reported to date. In the HN5 cell line, exposure to this strain did not result in a measurable reduction in tumor cell viability [31]. The apparent decrease in cell viability observed with *L. crispatus* must be interpreted in the context of the experimental controls. Although residual viability declined from 89% to 8% across increasing concentrations, a comparable reduction was also observed in the control groups containing only the culture media (MRS and MP), which produced similar viability profiles [31]. This indicates that the observed cytotoxicity was largely attributable to the culture media conditions rather than to a strain-specific antiproliferative effect. Accordingly, compared with these controls, neither strain demonstrated a statistically significant antiproliferative activity in this experimental model, which supports the interpretation reported in the original study. The absence of detectable anticancer activity with *L. crispatus* underscores the need for systematic, strain-level functional evaluation rather than extrapolation based on taxonomic proximity.

Lacticaseibacillus casei subsp. *casei* (formerly *Lactobacillus casei* subsp. *casei*)

L. casei is a lactic acid bacterium naturally present in the human and animal gastrointestinal tract, oral cavity, and vaginal mucosa, and is also commonly isolated from dairy products such as milk and cheese, fermented vegetables, and decomposing organic substrates [48]. In preclinical oral cancer models, strain-specific antiproliferative activity has been reported. At a density of 1×10^8 CFU/mL, *L. casei* reduced proliferation of the HNO97 oral squamous cell carcinoma cell line by approximately 50% after 24 h of exposure, an effect associated with upregulation of TRAIL expression, suggesting activation of apoptosis-related signaling pathways [28]. However, this activity appears to be cell-line-dependent. No significant anticancer effect was observed in the TCA-8113 cell line, even at a higher concentration of 2×10^9 CFU/mL [42]. This differential responsiveness underscores the importance of the tumor-specific biological context and highlights the variability of probiotic effects across distinct oral cancer cellular models.

Lacticaseibacillus rhamnosus (formerly *Lactobacillus rhamnosus*)

L. rhamnosus is a lactic acid bacterium naturally present in the human intestinal and vaginal microbiota, first isolated in 1983, and also found in fermented dairy products such as yogurt and kefir, with notable acid tolerance [49]. The culture supernatant of *L. rhamnosus* GG at 10^8 CFU/mL (25% *v*/*v*) reduced SCC-9 cell viability to 49.0% and 41.6% after 24 and 48 h, respectively, compared with >94% in controls [33]. Combination with curcumin enhanced cytotoxicity but reduced selectivity, lowering normal cell viability to 84.12%. Mechanistically, apoptosis induction was linked to an increased Bax/Bcl-2 ratio, consistent with mitochondrial pathway activation [33].

Ligilactobacillus salivarius (formerly *Lactobacillus salivarius*)

L. salivarius is a Gram-positive probiotic lactic acid bacterium naturally present in the human and animal microbiota (oral cavity, small intestine, and vagina), and has also been isolated from fermented foods and is valued for its antimicrobial properties [50]. At 3×10^9 CFU/mL, *L. salivarius* REN inhibited TCA-8113 proliferation by 49% within 24 h, comparable to the COX-2 inhibitor NS-398 (50.94%), and was associated with downregulation of COX-2 expression [42]. In a 4-nitroquinoline-1-oxide (4NQO)-induced murine oral carcinogenesis model, oral administration of 5×10^{10} CFU/kg/day reduced tumor incidence from 65% to 0%, decreased oxidative DNA damage (8-OHdG), and lowered PCNA and COX-2 expression without detectable toxicity [34], providing one of the most compelling in vivo demonstrations of probiotic-mediated chemoprevention in oral cancer (Table 3).

Table 3. Summary of in vivo anti-oral tumour effects of probiotics.

Strain	Model	Key Results	Safety	Reference
L. salivarius REN	4-NQO rat	Neoplasm incidence 65% → 0% (5×10^{10} CFU/kg/d)	No toxicity	[34]
Marine *Lactobacillus* TLMP2	DMBA hamster	Tumor volume 34.94 mm^3 in control group vs. 1.04–7.08 mm^3 in traited groups	Crude TLMP2 prevented tumor	[35]
L. paracasei GMNL-346	Xenograft	Survival +40%; tumor weight −85% (HSC3), −26% (SAS)	Safe	[29]

DMBA: 7,12-dimethylbenz[a]anthracene; 4-NQO: 4-Nitroquioline 1-Oxide; →: go to.

Lactobacillus spp. and Bacteriocins

Experimental studies in a DMBA-induced oral carcinogenesis model in Syrian golden hamsters demonstrated that administration of *Lactobacillus* spp. or purified bacteriocins (2.5 mg/kg) markedly reduced tumor volumes from 34.94 mm^3 to 1.04–7.08 mm^3 and effectively inhibited progression to invasive squamous cell carcinoma [35]. Notably, purified bacteriocins did not induce mucositis, unlike whole probiotic cells, whereas 5-fluorouracil treatment resulted in severe alopecia [35]. Mechanistic analyses suggest that lactobacillary proteins interact with the α catalytic subunit of AMP-dependent protein kinase, providing a plausible pathway for the observed antiproliferative activity. Collectively, the preclinical evidence summarized in this review demonstrates that lactic acid bacteria exert robust antiproliferative and pro-apoptotic effects across diverse OSCC cell lines. These effects involve modulation of key signaling pathways, including TRAIL, p16INK4a/CDK6, PTEN/MAPK, NF-κB, and inflammatory mediators, while exhibiting selective cytotoxicity towards tumor cells (Table 4) [35]. In vivo data corroborate both preventive and therapeutic potential in chemically induced or xenograft models, with an overall favorable safety profile, supporting the translational promise of *Lactobacillus* species and their bacteriocins as adjunctive agents in oral oncology [35].

Table 4. Summary of biological mechanisms of action identified with probiotics against tumour cells.

Strain/Species	Model	Key Molecular Effects	Pathways Involved	Reference
L. plantarum MCC 3016	Cal27	↓ IL-6, IL-8, TNF-α; ↓ VEGF; ↑ p53; ↑ caspase-3; ↑ ROS	NF-κB inhibition; apoptosis induction	[30]
L. plantarum (KB)	HeLa-derived KB	↑ PTEN; ↓ MAPK signaling	Cell cycle suppression	[24]
L. plantarum Y33	HeLa-derived KB, OSCC	↑ SMAC; ↓ SURVIVIN	Mitochondrial apoptosis	[23]
L. plantarum C47	HeLa-derived KB, OSCC	↑ SMAC; ↓ SURVIVIN	Selective apoptosis	[51]
L. paracasei GMNL-346	SAS, HSC3	↑ p16INK4a; ↑ RB; ↓ CDK6; ↓ OCT4, EZH2, BMI1, SOX2, c-Myc	Cell cycle arrest (G0/G1); stemness suppression	[29]
L. acidophilus ATCC 4356	HNO97	53% viability reduction; TRAIL upregulation	TRAIL-mediated apoptosis	[27]
L. casei	HNO97	50% inhibition at 1×10^8 CFU/mL; ↑ TRAIL	Extrinsic apoptosis	[28]
L. salivarius REN	Tca8113	↓ COX-2; ↑ apoptosis; ↓ PCNA	Anti-inflammatory + antiproliferative	[34,42]
L. reuteri DSM17938/PTA5289	5-FU OM model; TR146	↓ NF-κB, IL-1β, TNF-α, MPO; ↓ 8-OHdG, 4-HNE; ↑ Nrf-2, SOD-1, GPx-1, HO-1; ↑ Ki-67	Nrf-2-dependent cytoprotection	[52]

Table 4. *Cont.*

Strain/Species	Model	Key Molecular Effects	Pathways Involved	Reference
P. fermentans YSH	HSC4	85% inhibition; ↑ BAX; ↑ CASP-9; ↓ ERBB2, ERBB3, BCL-2, BCL-XL	Mitochondrial apoptosis	[32]
A. syzygii	HeLa-derived KB	75.7% apoptosis (60 µg/mL); 9.36% apoptosis KDR	Selective cytotoxicity	[26]

TNF-α: Tumor Necrosis Factor-alpha; IL: Interleukin; VEGF: Vascular Endothelial Growth Factor; p53: p53 protein; ROS: oxygen reactive species; PTEN: Phosphatase and Tensin homolog; MAPK: Mitogen-Activated Protein Kinase; SMAC: Second Mitochondria-derived Activator of Caspases; CDK6: Cyclin-dependent kinase-6; OCT4: Octamer-binding transcription factor 4; EZH2: Enhancer of zeste homolog 2; BMI1: B lymphoma Mo-MLV insertion region 1 homolog; SOX2: SRY-box transcription factor 2; TRAIL: TNF-related apoptosis-inducing ligand; COX-2: cyclooxygenase-2; PCNA: Proliferating cell nuclear antigen; NF-κB: Nuclear factor kappa B; SOD: Superoxide dismutase; GPx-1: Glutathione peroxidase-1; HO-1: Heme oxygenase-1; 4-HNE: 4-Hydroxy-2-nonenal; 8-OHdG: 8-hydroxy-2′-deoxyguanosine; CASP-9: Caspase-9; BAX: Bcl-2 Associated X-protein; Bcl-xL: B-cell lymphoma-extra large; BCL2: B-cell lymphoma 2; "↓": Decrease; "↑": Increase.

2.3. Clinical Effects of Probiotics as Adjuncts in Oral Cancer Management

2.3.1. Modulation of Antitumor Immune Response

Across the included studies, modulation of the antitumor immune response emerges as a central mechanistic pathway, predominantly documented in preclinical models. Administration of *L. reuteri* DSM 17938 and ATCC PTA 5289 in a murine model of 5-fluorouracil-induced mucositis significantly attenuated NF-κB p65 activation and reduced pro-inflammatory cytokine expression, including IL-1β and TNF-α. This was accompanied by decreased tissue infiltration of inflammatory cells and myeloperoxidase (MPO) activity [52]. Concomitantly, the cytoprotective Nrf2 axis was upregulated, evidenced by increased SOD-1, GPx-1, and HO-1 expression, with corroborative in vitro findings in TR146 oral epithelial cells demonstrating enhanced nuclear Nrf2 translocation and improved GSH/GSSG ratio [52]. Although classical adaptive antitumor immune markers, such as CD8+ T cells, NK cells, CD8+/Treg ratios, or tumor-infiltrating lymphocytes, were not systematically quantified in clinical trials, these preclinical results suggest a microenvironment less skewed toward chronic inflammation, potentially favoring effective antitumor immune activity [52].

2.3.2. Enhancement of Immunotherapy Response

No included study directly evaluated the impact of probiotics on objective response rate (ORR), progression-free survival (PFS), or overall survival (OS) in patients receiving immune checkpoint inhibitors, such as pembrolizumab or nivolumab. Nonetheless, observed modulation of the gut and oral microbiota, along with reduced systemic inflammation, provides a biologically plausible rationale for potential synergistic effects. This may involve attenuating immunosuppressive mediators and stabilizing the tumor microenvironment, thereby potentially enhancing responsiveness to immunotherapy [40,52].

2.3.3. Reduction in Treatment-Related Adverse Effects

The most robust clinical evidence pertains to mitigating anticancer treatment-related toxicities. Administration of *B. clausii* UBBC-07 significantly delayed mucositis onset (median 10 versus 8 days; $p < 0.01$), shortened its duration (12 versus 14 days; $p < 0.05$), and reduced severe cases (34.8% versus 69.6%; $p < 0.05$), with an overall clinical response rate of 65% compared to 30.4% in the placebo group [36]. Similarly, synbiotic mouth rinses reduced the grade 3 mucositis incidence to 11.59% versus 36.45% in controls ($p < 0.001$), with significant improvement in mean severity scores by the 30th radiotherapy session (1.75 versus 2.4; $p < 0.001$) and progressive benefit from the seventh session [39]. *L. lactis* AG013 decreased mean days with ulcerative mucositis by 35% and reduced unplanned

consultations (36% versus 60%) without evidence of bacteremia or serious probiotic-related adverse events [38]. Conversely, a randomized trial of *L. brevis* CD2 showed no significant reduction in severe mucositis (40.6% versus 41.6%; $p = 0.974$), with tumor stage as the sole independent predictive factor (OR = 0.164; 95% CI, 0.040–0.673; $p < 0.05$) [37].

2.3.4. Modulation of Oral and Gut Microbiota

Probiotic administration has been shown to effectively modulate the oral and intestinal microbiota. *Streptococcus salivarius* demonstrated high viability (>1 × 10^9 CFU), successful colonization with 17 ± 3% relative salivary abundance, and maintenance of alpha diversity (~182 ± 12 observed species; $p > 0.05$), without inducing dysbiosis. Network analysis revealed 8591 interactions, including 2141 negative interactions with periodontopathogens such as *Campylobacter rectus* and *Treponema* spp., indicating competitive ecological effects [53]. A multi-strain formulation including *L. rhamnosus* GG, *L. casei*, *L. acidophilus*, *L. delbrueckii* subsp. *bulgaricus*, *B. infantis*, *B. brevis*, and *S. thermophilus* significantly enhanced stimulated salivary flow ($p = 0.0016$), reduced total bacterial load ($p = 0.0209$), and decreased *F. nucleatum* prevalence ($p = 0.0080$ by qPCR; $p = 0.0026$ by culture) with strong methodological correlation (r = 0.923; $p < 0.001$) [40].

2.3.5. Impact on Tumor Growth in Preclinical Models

Preclinical models suggest that probiotics may indirectly inhibit tumor growth by reducing inflammation, activating antioxidant pathways, and maintaining epithelial integrity. Increased Ki-67 expression observed with *L. reuteri* in damaged oral epithelium reflects enhanced cell regeneration, while decreased oxidative stress markers, such as 8-OHdG and 4-HNE, confirm cytoprotective effects that limit chemotherapy-induced lesion progression [52].

2.3.6. Metabolic and Inflammatory Parameters

Although less frequently measured, systemic metabolic and inflammatory markers consistently indicate reduced inflammation and stabilized mucosal barriers. No systemic bacterial translocation or probiotic-related sepsis was reported, even in immunocompromised patients, supporting a favorable safety profile [38,40,52].

2.3.7. Patient-Reported Outcomes and Quality of Life

Improvements in quality of life, indirectly assessed through reductions in severe mucositis, fewer unplanned consultations, and enhanced salivary flow, suggest clinically meaningful functional benefits. However, standardized instruments such as the EORTC QLQ-C30 did not consistently reveal significant intergroup differences [37,39]. Overall, evidence converges to support a clinically relevant adjuvant effect of probiotics in oral cancer management, primarily through modulation of inflammation, stabilization of the microbiota, and mitigation of treatment-related toxicities, while maintaining a robust safety profile.

3. Discussion

This scoping review indicates that the field remains at an exploratory stage, predominantly supported by in vitro evidence, with comparatively limited in vivo validation and a small number of clinical trials. The strong concentration of studies in Asian countries likely reflects strong regional expertise in microbiome research and functional food sciences, alongside a strategic interest in cost-effective, biologically based adjuncts to conventional oncologic therapies [54]. However, this geographical clustering may introduce microbiological, dietary, and population-specific biases that restrict external validity, thereby underscoring the need for rigorously designed, multicenter trials across diverse populations

to enhance global generalizability and support regulatory standardization of probiotics in oral cancer management.

A significant translational gap persists between experimental evidence and clinical applicability. Most studies rely on simplified in vitro OSCC cell line models assessed by metabolic assays, which, although suitable for preliminary strain screening, fail to reproduce the complexity of the tumor microenvironment, including immune, stromal, and microbiome interactions [55,56]. Most findings derive from controlled experimental systems that do not fully capture the biological complexity of human oral cancer, thereby limiting the extrapolation of observed effects to clinical settings. In vivo models based on chemical carcinogenesis (4-NQO, DMBA) or xenografts provide greater biological relevance but remain heterogeneous and only partially reflective of human disease [29,34,35]. While these models allow evaluation of tumor growth dynamics, inflammatory modulation, and systemic safety, they only partially reproduce the multifactorial etiology and immunological landscape of human oral cancer [57,58]. Moreover, the reported antitumor efficacy in animal models may reflect optimized experimental conditions that are not directly translatable to real-world clinical scenarios, and the observed effects are frequently strain-specific and context-dependent, further constraining generalizability. Importantly, the lack of large-scale randomized trials evaluating hard oncological endpoints, such as overall or progression-free survival, limits clinical interpretability, confining current evidence primarily to mechanistic and supportive effects rather than definitive antitumor efficacy [59]. Taken together, these findings should be interpreted as mechanistic and proof-of-concept evidence supporting a predominantly adjunctive role of probiotics, rather than as evidence of curative or standalone antitumor efficacy, underscoring the urgent need for robust, adequately powered clinical trials to validate these preliminary observations.

A central finding of this review is the pronounced inter-strain variability in antiproliferative activity, underscoring that probiotic effects in oral cancer cannot be generalized across species. It can also be explained by genetic and molecular heterogeneity within species [60]. Differences in accessory genomes, including strain-specific gene clusters encoding bacteriocins, exopolysaccharides, adhesion factors, and secondary metabolites, lead to distinct bioactive profiles [61]. Variability in secreted metabolites, cell wall structures, and surface proteins influences host receptor engagement and downstream signaling pathways, thereby modulating apoptosis, inflammation, and chemosensitivity [62]. Additionally, strain-specific transcriptional regulation and metabolic plasticity yield divergent functional outputs under similar conditions, supporting a strictly strain-dependent paradigm for probiotic-based strategies in oral cancer management [63]. These findings argue against a uniform "class effect" and strongly support a strain-specific paradigm.

When extrapolated to molar equivalents, the IC_{50} values reported for *L. plantarum* MCC3016, *L. plantarum* C47, *L. fermentum* C9, and *L. paracasei* GMNL-346 seldom fall within the $\leq$10 μg/μL range, a threshold considered indicative of very strong cytotoxic activity [64]. Accordingly, their intrinsic cytotoxic potency appears modest relative to conventional chemotherapeutic agents such as cisplatin, 5-fluorouracil, doxorubicin, or paclitaxel. Notably, exceptions have been reported: secreted metabolites of *P. fermentans* YSH demonstrated antiproliferative activity comparable to that of cisplatin in HSC4 cells [32], and *L. salivarius* showed effects on TCA-8113 cells comparable to those of NS-398 [42]. Beyond absolute potency, several probiotic strains display a comparatively favorable selectivity profile, characterized by higher inhibitory thresholds in normal fibroblasts or gingival epithelial cells than in malignant cell lines [25,26]. Although moderate in magnitude, this differential cytotoxicity suggests a pharmacologically relevant therapeutic window, particularly when combined with or used as an adjuvant in therapeutic strategies.

Preclinical investigations consistently demonstrate that live probiotic strains exert the most pronounced and selective antiproliferative effects against oral squamous cell carcinoma (OSCC) models. For instance, a live *L. plantarum* strain exhibited an IC50 of 3.03 µg/µL on KB cells, reflecting high tumor specificity [25]. Non-viable preparations, including heat-inactivated *L. paracasei* GMNL-346, produced an IC50 of 7.12 log cells/mL in SAS and HSC3 cells [29], whereas cell-free supernatants from *L. acidophilus* ATCC 4356, when enzymatically treated, increased cytotoxicity to 72.7% in KB cells, indicating that secreted metabolites contribute substantially to antiproliferative activity [27]. Collectively, these data underscore that while live organisms often achieve maximal tumor-selective effects, non-viable preparations retain mechanistic relevance and may serve as functionally active postbiotic interventions [65]. Nevertheless, direct quantitative comparisons are constrained by heterogeneous reporting units, underscoring a critical need for standardized expression of biological activity in future studies to enable rigorous cross-strain and preparation-type comparisons.

An additional methodological consideration concerns the historical use of the KB cell line (ATCC CCL-17) as a model of oral squamous cell carcinoma. It is now well established that KB cells are cross-contaminated with HeLa and are therefore classified as a HeLa derivative rather than a genuine oral cancer cell line, a limitation explicitly acknowledged by [66,67]. Consequently, studies reporting antiproliferative effects of probiotics using KB cells should be interpreted with caution, as the observed responses may reflect biological properties of cervical carcinoma rather than oral squamous cell carcinoma. While these experiments remain informative regarding general anticancer or cytotoxic potential, their disease specificity for oral cancer is limited, highlighting the importance of validating findings in well-authenticated OSCC cell lines.

However, such comparisons must be interpreted cautiously. Methodological heterogeneity, including non-standardized reporting units (CFU/mL versus µg/mL), divergent preparation types (live bacteria, cell-free supernatants, lysates), absence of formal synergy analyses, and variability in seeding densities, substantially limits cross-study comparability. These inconsistencies likely contribute to the wide dispersion of reported activities and complicate robust benchmarking against conventional chemotherapeutics. A further limitation arises from the heterogeneous reporting of probiotic activity across studies, including percentage inhibition, IC_{50} values expressed in µg/µL, and bacterial densities reported as log cells/mL, which are not directly convertible due to the biological nature of living microorganisms. Future research should adopt standardized reporting based on viable counts (CFU/mL or log CFU/mL) combined with clearly defined dose–response curves and IC_{50} calculations derived from these biological units, thereby enabling more consistent and biologically meaningful cross-study comparisons.

Regarding in vivo models, chemically induced carcinogenesis via 4-NQO or DMBA offers advantages in terms of reproducibility and stepwise dysplasia-to-carcinoma progression, partially mimicking carcinogen-driven human oral tumorigenesis [34,35]. Nevertheless, these models rely on acute, controlled exposures and do not capture the genetic heterogeneity, lifestyle-associated cofactors, or endogenous microbiome dynamics characteristic of human oral cancer. Xenograft models [29], while useful for tumor growth assessment, are conducted in immunodeficient animals and therefore preclude meaningful evaluation of immune-mediated mechanisms, which are central to the proposed probiotic mode of action [68–70]. The limited number of in vivo studies remains a critical barrier to translational extrapolation.

Despite experimental heterogeneity, a coherent mechanistic pattern emerges. Probiotics and their metabolites appear to activate mitochondrial apoptotic pathways (increased Bax/Bcl-2 ratio, caspase activation), modulate TRAIL signaling, restore p16INK4a expres-

sion, inhibit CDK6, activate PTEN, and suppress MAPK and NF-κB signaling [25,29,42]. While these pathways overlap with those targeted by conventional cytotoxic agents, the distinctive feature of probiotics lies in their multimodal and microenvironment-oriented activity [71]. Evidence of reduced oxidative stress [49], modulation of inflammation via NF-κB and COX-2 suppression, and alterations in oral microbial composition [40,53] suggest that probiotics may act upstream of direct DNA damage, reshaping the inflammatory and ecological context that sustains tumor progression [71]. This systems-level modulation supports the emerging concept of oncobiotics or microbiome-based interventions [72], wherein microbiome-directed strategies complement tumor-targeted therapies.

Clinically, the most consistent benefits of probiotic administration in oral cancer have been observed in the prevention and mitigation of radiotherapy- and chemotherapy-induced mucositis. Trials assessing single strains such as *L. brevis* CD2 [41] and *B. clausii* [36], as well as multistrain synbiotic formulations [39,40], have demonstrated reductions in mucositis severity and/or delayed onset, although these outcomes have not been uniformly confirmed in multicenter randomized settings [37]. Overall safety profiles appear favorable, with no significant signals of probiotic-related bacteremia; however, cautious risk–benefit evaluation remains necessary in severely immunocompromised patients. Collectively, the available clinical evidence more strongly supports positioning probiotics as adjuvants rather than primary anticancer therapies, a conclusion consistent with data reported in other oncologic contexts [73,74]. Their most plausible therapeutic contribution resides in modulating the tumor microenvironment, attenuating treatment-induced inflammation, and enhancing tolerability and supportive care outcomes within comprehensive multimodal cancer management strategies [75,76].

4. Limitations

Several limitations must be acknowledged when interpreting the current body of evidence. First, the translational maturity of the field remains limited, as rigorous evaluation of clinically meaningful oncologic endpoints has not yet been systematically undertaken, thereby constraining conclusions regarding direct antitumor efficacy in patients. Furthermore, the limited number of in vivo studies (3) represents a critical gap, restricting the ability to validate preclinical findings in complex biological systems and to accurately predict therapeutic efficacy and safety in clinical contexts. Second, substantial methodological heterogeneity across experimental designs, including variability in strain selection, preparation methods, dosing strategies, treatment duration, and outcome measures, impairs comparability and precludes quantitative synthesis or standardized dose–response assessment. The absence of harmonized IC50 reporting standards and formal pharmacodynamic or synergy analyses further complicates cross-study interpretation. Reproducibility and external validity also represent critical concerns. Most clinical investigations are single-center studies with relatively small sample sizes, which limit statistical power and increase susceptibility to contextual bias. Geographic clustering of research activity may additionally restrict generalizability across diverse populations, microbiome backgrounds, and dietary patterns. Mechanistic insights, although suggestive of coherent signaling modulation, are frequently derived from reductionist models and rarely supported by integrated multi-omics validation. Finally, the inclusion of heterogeneous head and neck cancer cohorts in several trials complicates extrapolation specifically to oral squamous cell carcinoma, thereby limiting disease-specific precision in clinical inference. Additionally, the substantial heterogeneity across clinical studies, including differences in design, overall sample size (482 participants), and interventions, limits direct comparability and generalization of the results.

5. Future Perspectives

Future research should prioritize rigorous multicenter randomized trials incorporating survival endpoints and validated mechanistic biomarkers to establish clinical relevance. Standardized GMP-grade, genomically characterized formulations are essential to ensure reproducibility and regulatory credibility. Strategic integration with immunotherapies, microbiome-based patient stratification, and the development of defined postbiotics should be pursued, supported by integrated multi-omics and tumor microenvironment analyses to clarify mechanisms and optimize the positioning of probiotics within multimodal oral cancer management.

6. Methodology

6.1. Study Design

This scoping review was conducted in accordance with the methodological framework proposed by Arksey and O'Malley and further refined by Westphaln et al. [77], and reported in compliance with the PRISMA-ScR guidelines [78]. The review protocol was registered in the Open Science Framework (OSF) as part of the associated project: https://osf.io/pb625 (accessed on 6 March 2026). The objective was to comprehensively map the available evidence regarding the therapeutic and adjuvant effects of probiotics in the management of oral cancer, including preclinical and clinical investigations. Given the heterogeneity of study designs and outcomes, a scoping methodology was selected to identify knowledge gaps, characterize mechanistic pathways, and synthesize translational evidence across experimental and clinical settings.

6.2. Eligibility Criteria

Studies were deemed eligible for inclusion if they investigated probiotic strains administered as single- or multi-strain formulations, encompassing live microorganisms, heat-inactivated preparations, bacterial lysates, metabolites, or cell-free supernatants. To ensure conceptual consistency with the objectives of this scoping review, only studies evaluating therapeutic, preventive, or adjuvant effects in the context of oral cancer, particularly OSCC, were considered. Eligible studies included experimental investigations conducted in vitro using established OSCC cell lines, in vivo studies employing animal models of oral carcinogenesis or xenograft systems, and interventional or observational clinical trials involving patients diagnosed with oral or head and neck cancers. Furthermore, studies were required to report measurable outcomes of biological, mechanistic, tumor-related, microbiological, or clinical relevance, thereby allowing comprehensive mapping of both preclinical and translational evidence.

No restrictions were applied regarding probiotic strain taxonomy, dosage, formulation, route of administration, or comparator groups to ensure comprehensive coverage and reflect the translational heterogeneity of probiotic interventions. No temporal limits were imposed during the initial search to capture the full historical scope of the field. However, eligibility was restricted to studies published in English and available up to 10 February 2026. The final selection was restricted to original, peer-reviewed research articles published in English. Reviews, editorials, conference abstracts without complete datasets, case reports, and non-peer-reviewed publications were excluded to preserve methodological rigor and analytical consistency consistent with standards for high-impact pharmacological research.

6.3. Information Sources and Search Strategy

A comprehensive literature search was conducted in major biomedical databases, including PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. The search strategy combined controlled vocabulary (MeSH terms for PubMed, Emtree for Scopus)

and free-text keywords related to: "oral cancer" OR "oral squamous cell carcinoma" AND "probiotics" OR "*Lactobacillus*" OR "Synbiotics" AND "Anti-oral cancer" OR "adjuvant therapy" OR "antiproliferative effect". The final search strategy was adapted to each database. An exhaustive search strategy was implemented in Google Scholar, ClinicalTrials.gov, and the reference lists of included studies, including original clinical studies involving heterogeneous oncological populations, to provide a broad contextual framework. Studies addressing head and neck cancers were systematically screened, and data specifically related to oral cancer were extracted and analyzed separately whenever possible to enable a focused and clinically relevant synthesis. In cases where trials involved mixed populations of head and neck cancers but explicitly stated that patients with oral cancer were included, without reporting oral cancer–specific outcomes, these studies were retained only when the effects of the intervention were reported consistently across the overall cohort, and no evidence suggested differential or contradictory responses in patients with oral cancer. This approach was adopted to preserve clinically relevant data on radiotherapy- and chemotherapy-associated mucositis, an adverse event common to head and neck malignancies, while acknowledging the current limitations in disease-specific reporting.

6.4. Study Selection

All identified records were imported into a reference management software, and duplicate entries were systematically removed prior to screening. Study selection was conducted independently by two reviewers (GTK and EJN) using a structured two-stage approach. In the first phase, titles and abstracts were screened to exclude studies that were clearly irrelevant to the scope and objectives of the review. In the second phase, the full texts of potentially eligible articles were retrieved and assessed in detail according to the predefined inclusion and exclusion criteria. Any discrepancies between reviewers were resolved through discussion and consensus; when agreement could not be reached, a third reviewer was consulted to ensure methodological rigor and selection transparency.

6.5. Data Charting Process

A standardized data extraction form was developed and pilot-tested to ensure consistency, clarity, and reproducibility in data charting. For each included study, detailed information was systematically collected, including the authors, year of publication, country of origin, and study design (in vitro, in vivo, or clinical trial). Specific characteristics of the probiotic intervention were documented, including the strain(s) investigated, formulation, and administered concentration or dose (expressed as CFU/mL, CFU/day, or equivalent units).

Information regarding the experimental or clinical cancer model was recorded, encompassing OSCC cell lines, animal models of oral carcinogenesis or xenograft systems, and defined patient populations. Comparator conditions or standard anticancer treatments were also extracted when applicable. Outcome measures were comprehensively documented and included primary and secondary endpoints, including cell viability, IC50 values, apoptosis-related markers, tumor volume, inflammatory mediators, mucositis grading, microbiological parameters, and survival outcomes. Safety data, including adverse events and tolerability profiles, were systematically recorded. Additionally, the biological origin of the probiotic strains (e.g., human-, dairy-, or environmental-derived) was documented to facilitate translational interpretation. Data extraction was independently performed by two reviewers, and cross-verification was conducted to ensure accuracy, completeness, and methodological reliability.

6.6. Data Synthesis and Mapping of Evidence

Given the substantial heterogeneity in study designs, experimental models, and reported endpoints, a descriptive analytical framework was adopted to systematically map and synthesize the available evidence. The included studies were stratified into three principal domains reflecting the translational continuum from bench to bedside.

The first domain comprised in vitro investigations, which predominantly explored antiproliferative activity, induction of apoptosis, modulation of intracellular signaling pathways, such as TRAIL-mediated cascades, PTEN/MAPK signaling, and NF-κB inhibition, and the selective cytotoxicity of probiotic-derived interventions toward malignant versus non-malignant cells. These studies were conducted using established OSCC cell lines, thereby providing mechanistic insights into direct tumor-cell interactions.

The second domain encompassed in vivo preclinical models, including 4-nitroquinoline-1-oxide (4NQO)-induced rat models of oral carcinogenesis, 7,12-dimethylbenz[a]anthracene (DMBA)-induced hamster buccal pouch models, and xenograft mouse systems. These studies evaluated outcomes such as tumor incidence, tumor volume reduction, modulation of oxidative stress biomarkers, histopathological alterations, and systemic safety parameters, thereby facilitating translational interpretation of probiotic-mediated effects in complex biological environments.

The third domain included clinical trials assessing the adjuvant role of probiotics in patients with oral and head and neck cancers, particularly in the management of treatment-related oral complications. Clinical endpoints primarily focused on radiation- or chemotherapy-induced mucositis severity and incidence of fungal or bacterial infections, salivary flow dynamics, patient-reported quality-of-life measures, and safety outcomes. Across all domains, probiotic interventions were further characterized and mapped according to taxonomic classification, formulation (single-strain versus multi-strain combinations), administered dose range (10^5–10^{10} CFU/mL or per day), route of administration (oral capsules, suspensions, lozenges, or mouthwash), and biological origin (human-derived, dairy-derived, or environmental), enabling a structured and pharmacologically relevant synthesis of the evidence landscape.

6.7. Risk of Bias Assessment

In line with scoping review methodology, a formal quantitative risk-of-bias assessment was not performed. However, methodological characteristics, including study design, sample size, comparator use, and reporting transparency, were descriptively examined to contextualize the strength and limitations of the available evidence.

7. Conclusions

In conclusion, current evidence does not support probiotics as primary cytotoxic agents in oral cancer, yet selected strains, particularly *L. plantarum* and *L. paracasei* GMNL-346, demonstrate reproducible in vitro efficacy, chemosensitizing potential, and preliminary in vivo antitumor effects. While their absolute cytotoxic potency is modest compared with conventional chemotherapeutics, several strains exhibit favorable selectivity for malignant cells over normal tissues. Clinically, probiotics consistently reduce treatment-related mucosal toxicity, highlighting their adjuvant value. Rather than direct cytotoxic agents, probiotics modulate the tumor microenvironment, immunity, and inflammatory signaling, aligning with the "oncobiotics" paradigm. Collectively, mechanistic plausibility, strain-specific activity, chemosensitization potential, and safety profiles support further investigation, with rigorous multicenter trials and standardized formulations required to establish their role as evidence-based adjuncts in integrative oral cancer therapy.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ddc5020030/s1, Supplementary Material S1: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist.

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