Journal of Dentistry 155 (2025) 105623

Contents lists available at ScienceDirect

Journal of Dentistry

journal homepage: www.elsevier.com/locate/jdent

Review article

Methods used to deliver adjunctive probiotic treatment during the non-surgical management of periodontitis: A scoping review

Ryan O'Donnell *, Richard Holliday, Nick Jakubovics, Ellie Benfield

Newcastle University School of Dental Sciences, Framlington Place, Newcastle Upon Tyne, NE2 4BW, UK

ARTICLE INFO

Key words:
Periodontitis
Non-surgical
Probiotic

ABSTRACT

Objective: To identify which methods have been used to deliver adjunctive probiotics during the non-surgical management of periodontitis in clinical trials. This review also investigates which probiotics have been used and at what dose, along with the periodontal treatment outcomes achieved.
Data: Conducted in accordance with the Joanna Briggs Institute methodology for scoping reviews.
Sources: MEDLINE, Embase, Web of Science, and Scopus were searched on 02/02/2024 from inception with no date limits applied.
Study Selection: Clinical trials investigating the use of probiotics as an adjunctive treatment to non-surgical periodontal therapy in humans.
Conclusions: Out of 4769 studies 66 met the inclusion criteria. Over 30 different probiotics were identified along with 18 different delivery methods with varying dosages and duration. 48 of the included studies reported a beneficial effect when a probiotic was used, 14 reported no difference, 3 found the outcomes comparable to the use of antibiotics, and 1 study reported a better outcome from the control group. The probiotic used, its dosage, delivery method, duration of application, and outcome measures differ across studies making it difficult to draw conclusions on their efficacy. This scoping review highlights the need for further research to establish a uniform treatment protocol and to identify the most effective probiotic bacteria.
Clinical Significance: Despite the majority of included studies indicating a potential benefit from the use of probiotics during the non-surgical management of periodontitis, the high level of heterogeneity between interventions they currently cannot be recommended for use in clinical practice.

1. Introduction

Periodontitis is an inflammatory disease which results in the irreversible loss of the tooth supporting structures [1]. The disease is multifactorial in origin with the initial aetiological agent being dental plaque biofilms. The primary characteristics of periodontitis include alveolar bone loss, the formation of periodontal pockets due to the loss of periodontal attachment, and in more severe cases tooth loss [1]. According to the World Health Organisation (WHO) there are over 1 billion cases of severe periodontitis, those with periodontal probing depths of >6mm, worldwide [2]. The consequences of periodontitis can include difficulty with chewing or speaking, impaired social interaction, and negative links to general wellbeing [2]. For these reasons the WHO classified severe cases of periodontitis as a public health concern [2].

Surgical and non-surgical techniques are available for the treatment of periodontitis, the overriding aim of both treatment modalities is to reduce periodontal pocket depths through professional mechanical plaque removal (PMPR), also known as scaling and root planing or root surface debridement, which reduces the bacterial load and restores the oral microbiota to one more associated with health [3,4]. These treatments have been proven to be effective in improving the periodontal health of patients with gains in clinical attachment, and reductions in probing depths and bleeding on probing being detectable following treatment [4]. Nevertheless, periodontal therapies have several limitations including but not limited to: deep / complex sites being difficult to access for thorough instrumentation, specific periodontal pathogens being able to invade cells escaping mechanical removal and the immune system, and patient engagement in effective personal plaque can be hard to maintain over time [5–7].

In addition to PMPR treatments, adjunctive therapies are available which can be used to attempt to overcome PMPR treatment limitations and improve treatment outcomes [8]. Common adjunctive treatments

* Corresponding author at: 11 Bolihope Grove, Bishop Auckland, DL14 0SA, UK.
E-mail address: Ryan.O'Donnell@newcastle.ac.uk (R. O'Donnell).

https://doi.org/10.1016/j.jdent.2025.105623
Received 25 November 2024; Received in revised form 5 February 2025; Accepted 11 February 2025
Available online 12 February 2025

include systemic antibiotics and antiseptics. The use of systemic antibiotics has demonstrated efficacy at both a clinical level in improving treatment outcomes and at a microbiological level in reducing periodontal pathogen levels [9]. However, due to concerns about patients' general health and the public health risk of antibiotic resistance, the routine use of systemic antibiotics as an adjunct to PMPR is not recommended [10]. Daily use of an antiseptic chlorhexidine mouthwash has been found to improve pocket depth outcomes by 0.24 mm at 180 days following PMPR treatment [11]. However, chlorhexidine has several undesirable side effects including staining, parotid gland swelling, taste disturbances, and the risk of hypersensitivity [9–11].

An additional adjunctive therapy available for the treatment of periodontitis is the administration of probiotics. Probiotics have been defined as living micro-organisms which, when administered in a sufficient amount, can have a beneficial effect on the host [12]. Several modes of action have been identified through which probiotics may have a beneficial health effect [13]. Probiotics may compete with pathogenic bacteria for resources and adhesion sites, inhibit the growth of pathogens through the production of bacteriocins, modulate cell proliferation and apoptosis, and stimulate the mucosal immune system [14,15]. These mechanisms are thought to mediate health through creating an environment more hostile towards pathogenic microbes, down regulating inflammation, and an improving the immune response to antigenic challenges [13]. These benefits have been explored in the field of periodontal research in an attempt to achieve greater clinical outcomes from PMPR, with a number of studies reporting positive outcomes from the adjunctive use of a variety of probiotic strains. *Limosilactobacillus reuteri* (formerly *Lactobacillus reuteri*) has been demonstrated to reduce gingival bleeding scores, plaque scores, periodontal pocket depths, and the level of periodontal pathogens including *Aggregatibacter actinomycetemcomitans, Prevotella intermedia* and *Porphyromonas gingivalis* [16,17]. Other probiotic species have also been observed to provide improvements in periodontal treatment outcomes including *Lacticaseibacillus casei, Lacticaseibacillus rhamnosus*, and *Ligilactobacillus salivarius* [13]. Despite the evidence of improved periodontal treatment outcomes there are still challenges when it comes to the selection of a probiotic that is to be used in the treatment of periodontitis. The selected probiotic must be able to colonise the hard and soft oral tissues and become part of the dental biofilm [14], with the recommendation of a sustained released device to be investigated to try and overcome these issues [18].

The primary aim of this scoping review is to systematically map the evidence surrounding the use of probiotics as an adjunctive treatment during the non-surgical management of periodontitis through the identification of existing probiotic delivery methods used in clinical trials, the probiotic bacteria used in this treatment, the frequency and dose at what they were delivered, and to record the main findings of the included studies. The findings of this review will be used in the development of future research into contemporary delivery methods for probiotics to be used in the treatment of periodontitis. A preliminary search of MEDLINE Ovid, Web of Science, and the Cochrane Library was carried out which identified three existing narrative reviews which discuss oral health probiotic products, but no systematic or scoping reviews were identified which answered the below questions [19–21].

The "Patient, Concept, Context" (PCC) approach was used to develop the research questions below to meet the aim of this review:

1. To adults ≥18 years of age (P), what methods have been used to deliver adjunctive probiotic treatment (C) during the management of periodontitis in clinical trials (C)?
2. What probiotics have been delivered during periodontal treatment and at what frequency and dose?
3. What differences, if any, were observed in the outcomes of periodontal treatment following the adjunctive use of probiotics during the non-surgical management of periodontitis?

2. Materials and methods

This scoping review has been conducted in accordance with the Joanna Briggs Institute (JBI) methodology for scoping reviews [22] and the protocol is registered on Open Science Framework (https://osf.io/3q6hk/).

2.1. Eligibility criteria

The participants of interest are adult periodontitis patients, aged ≥18 years old, undergoing subgingival PMPR treatment (or similar treatment with different terminology: scaling and root planing or root surface debridement) with the administration of adjunctive probiotics. This review was open to any setting in which a clinical trial was carried out. Experimental and quasi-experimental study designs were considered, including randomised controlled trials (RCT) and non-randomised controlled trials. Unpublished and gray literature were also considered for inclusion, but qualitative studies and existing reviews were excluded.

2.2. Search strategy

An initial limited search of MEDLINE and Web of Science was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles were used to develop a full search strategy with the input of an expert librarian. MEDLINE, Embase, Web of Science, and Scopus were searched on 02/02/2024 from inception with no date limits applied. The search strategy, including all identified keywords and index terms, was adapted for each included database. The reference lists of included studies were screened for additional studies. Studies published in any language were considered for inclusion if translation to English was possible. The full MEDLINE search strategy can be found in supplementary file 1 and the Web of Science search strategy in supplementary file 3.

2.3. Source of evidence selection

Following the search, all identified citation were uploaded into the reference management software Covidence and duplicates removed. Titles and abstracts were screened by four independent reviewers with two members of the team acting as primary reviewers for all citations. Sources that were potentially relevant from their title and abstract were retrieved in full and the full text was assessed in detail against the inclusion by the two primary reviewers. The justification for any exclusions at the full text screening stage are reported in the scoping review. Any disagreements on the inclusion or exclusion of a source of evidence was resolved through discussion until a consensus is reached. The results of the search and inclusion process are reported and presented in the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping review (PRISMA-ScR) flow diagram [23].

2.4. Data extraction

Data were extracted from the included studies by one primary reviewer using a Microsoft Excel spreadsheet, a second reviewer then cross-checked 10 % of the extracted data for accuracy. Originally it was planned that two independent reviewers would extract the data but due to the simplicity of the data being extracted it was deemed that a 10 % sample was sufficient for a double review.

The collected data included the author names, year of publication, journal of publication, study design, country where the study was conducted, participant details, severity of periodontitis, control / comparator treatment, intervention treatment, probiotic strain used, dose of the probiotic, probiotic delivery method, probiotic duration, outcome measurers used, and the study's main findings.

A critical appraisal was not performed within this scoping review, as

our aim was to map interventions, not to assess their efficacy.

2.5. Presentation of results

The extracted data are presented in a table, a narrative summary of findings will accompany the tabulated data. This review aims to provide

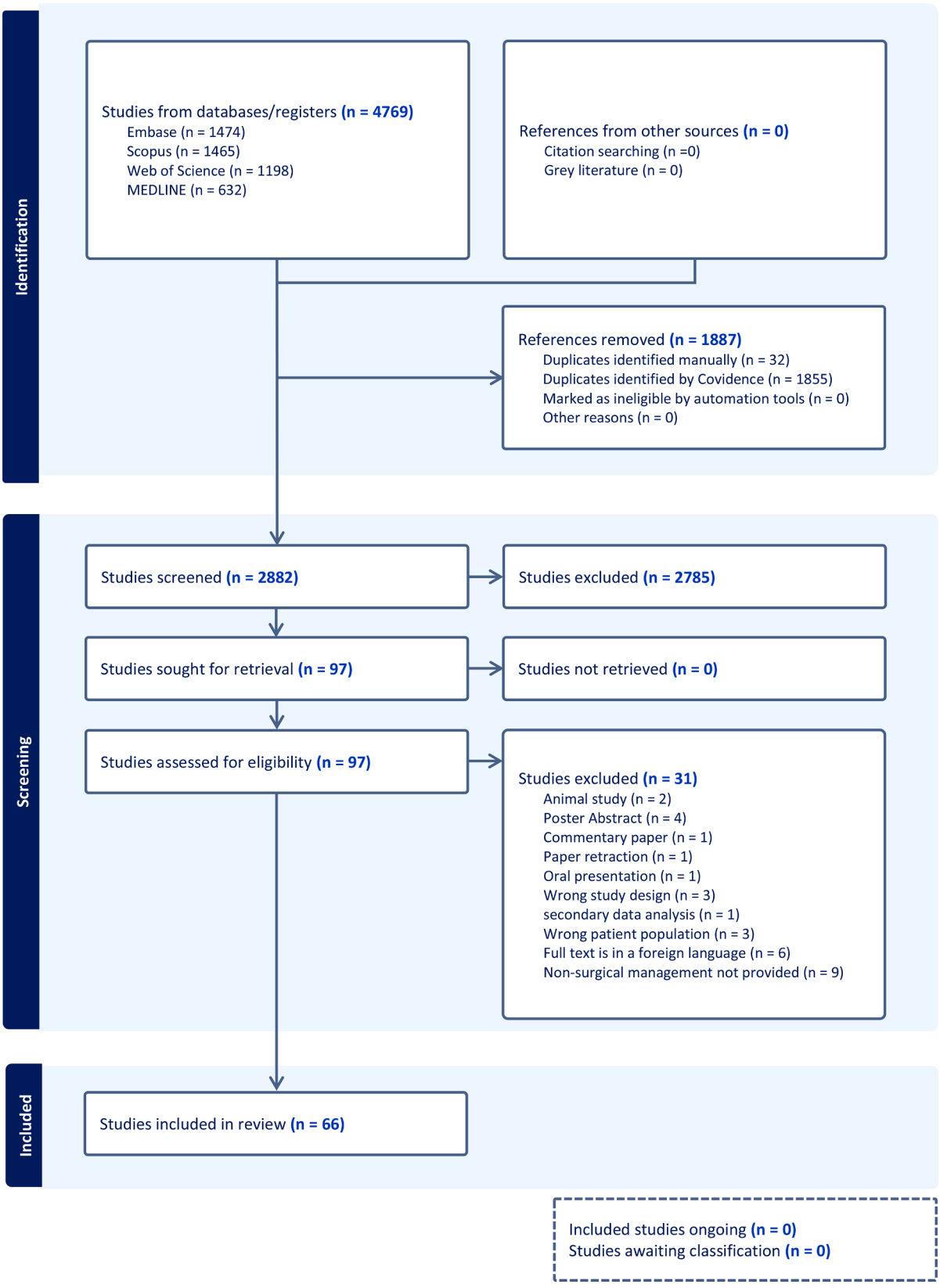

Fig. 1. PRISMA flow chart of the search.

a broad overview of how probiotics have been delivered in investigative studies as adjuncts to the non-surgical management of periodontitis.

3. Results

3.1. Search results

The database search yielded 4769 potentially relevant studies. 1887 studies were identified as duplicates and removed from the screening process. The title and abstract of 2882 studies were screened to determine their eligibility for full text screening. Subsequently 97 studies were screened at the full text stage. Following comprehensive review of the full texts, 31 studies were excluded and as a result 66 studies were included in this scoping review (Fig. 1). The extracted data can be viewed in Table 1 and details of the excluded studies and reasons for their exclusion can be found in supplementary file 2.

3.2. Study characteristics

The 66 included studies were published between 2009 and 2024. 15 from India [17,30,37,38,51,54,63,70–73,74,78,79,81,86], 8 from Brazil [29,36,48–50,69,76,84], 6 from Italy [31–35,43], 6 from Turkey [47,53,57,64,82,83], 5 from Pakistan [42,44,45,46,87], 4 were from Saudi-Arabia [18,24,26,39], 3 from Iran [28,41,71], 3 from Chile [60–62], 2 from Russia [52,67], 2 from Belgium [55,56], 1 was from each of Iraq [25], Malaysia [27], Spain [40], Serbia [58], Republic of Macedonia [59], Germany [65], China [66], Slovenia [68], Indonesia [75], Romania [77], Poland [80], and Japan [85]. 60 of the included studies were RCTs, 4 implemented a split mouth design, and 5 did not disclose if randomisation was conducted.

3.3. Probiotic delivery methods

From the included studies multiple different carriers have been used to administer probiotics, see table 1 for details. 24 investigated a lozenge, 8 investigated a mouthwash, 7 used tablets, 6 studies tested a powder dissolved in water which was then consumed by the patient, 4 used a gel, 3 studies used powder mixed with water that the patient then brushed their teeth with, 3 investigated a toothpaste, 2 used a probiotic paste, 2 a capsule, 2 a milk drink, 2 used drops, 2 chewing gum, 2 a suspension, 1 applied powder directly into the periodontal pocket, 1 used a probiotic yogurt, 1 used pocket irrigation, 1 mixed a powder with gum and saline, and another mixed the probiotic with saline.

In addition to the carrier used, the individual responsible for administering the probiotic can be categorised into dental professional application, patient home application, or a combined application of professional and patient (see table 1 for study details). 8 of the studies carried out professional dental application only. Patient home application only was investigated in 51 of the included studies. A combination of professional and home use was investigated in 7 studies.

3.4. Probiotic species, frequency, and dose

The included studies investigated the following probiotic bacteria: L. *rhamnosus, Lactobacillus acidophilus*, L. *casei, Bifidobacterium bifidum*, L. *salivarius, Levilactobacillus brevis, Lactiplantibacillus plantarum, Lactobacillus delbrueckii* subsp. *bulgaricus* (formerly L. *bulgaricus*), *Bifidobacterium breve, Bifidobacterium longum, Streptococcus thermophilus*, unspecified *Bifidobacterium* species, unspecified *Lactobacillus* species, L. *reuteri, Limosilactobacillus fermentum, Bifidobacterium lactis, Bifidobacterium animalis, S. salivarius, Streptococcus oralis, Streptococcus uberis, Streptococcus rattus, Bifidobacterium infantis, Enterococcus faecium, Bifidobacterium coagulans, Heyndrickxia coagulans* (commonly known as *Lactobacillus sporogenes*), *Enterococcus faecalis, Clostridium butyricum, Bacillus mesentericus, Saccharomyces boulardii*, and *Bacillus subtilis*. The duration of probiotic administration ranged from a single application post treatment to 6 months of daily consumption with a range of different doses investigated (table 1).

3.5. Summary of study findings

48 of the included studies reported a beneficial effect on outcome measures when probiotics were used, 14 studies reported no difference when probiotics were used, 3 studies found the use of probiotics comparable to the use of antibiotics, and 1 study reported a better outcome from the control group. 16 of the included studies reported a greater reduction in probing depths in favour of probiotic treatments when compared to no probiotic [25,26,34,35,43,47,55,58,59,72,77,79,82,83,86,87]. A greater reduction in bleeding on probing was observed in 7 of the included studies when probiotics were used [34,35,43,71,77,82,87]. A reduction in periodontal pathogens was reported in the main findings of 2 included studies [52,81]. A statistically significant reduction in gingival inflammation was reported in favour of probiotic treatment groups across 8 studies [34,71–73,79,81,82,86].

4. Discussion

The primary aim of this scoping review was to systematically map the available evidence surrounding the use of probiotics as an adjunctive treatment during the non-surgical management of periodontitis through the identification of existing probiotic delivery methods used in clinical trials, the probiotic bacteria used in this treatment, the frequency and dose at what they were delivered, and to record the main findings of the included studies.

Periodontitis is a multifactorial disease involving interactions between bacteria and the host's immune response. Non-surgical PMPR treatment consists of manual or powered instrumentation of the periodontal pocket to disrupt the biofilm to create a shift to a less pathogenic environment. This shift towards health is short lived even if adjunctive antiseptics or antibiotics have been used [88–90]. From the studies included in this review, there is a positive trend to suggest probiotics may have a beneficial effect on the outcome of non-surgical PMPR.

It is thought that the mechanisms through which probiotics benefit the host include direct interactions with pathogens, modulation of the immune response, and the production of antimicrobial products. These beneficial mechanisms align with the existing specific plaque hypothesis [91]. This hypothesis states that periodontitis is a result of an overgrowth of specific periodontal pathogens such as *Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola* which interact with the host's immune system, manipulate inflammatory responses, and produce virulence factors leading to tissue destruction [92]. A reduction in periodontal pathogens was reported in 2 included studies. Koroleva et al. [52] reported that the use of *S. salivarius* resulted in a significant decrease in the incidence and, in some cases, the complete elimination of periodontal pathogens in periodontal pockets compared to the control group. Tapashetti et al. [81] found a probiotic mouthwash significantly reduced the levels of red complex bacteria including *T. denticola* and *T. Forsythia.*

The use of over 30 different probiotic bacteria were identified in this review with the majority being either a member of the lactobacilli or the *Bifidobacterium* genus. L. *reuteri* was investigated in 45 % of the included studies and has been found to have a number of beneficial properties. This probiotic can produce antimicrobial molecules such as reuterin which can inhibit a wide range of gram-negative bacteria [93], can remodel the commensal microbiota composition [94], and can modulate the host immune response through down regulating the production of pro-inflammatory cytokines [95]. Reuterin is a secondary metabolite that exerts antimicrobial activity by modifying thiol groups and imposing oxidative stress [96]. It is not a protein, and is therefore not sensitive to proteases, which are commonly present in oral biofilms and can limit the activity of antimicrobial peptides. In addition, L. *reuteri* will continuously produce reuterin within the oral environment, providing

Table 1
Included studies and data extraction.

Author and Year	Journal	Study Design	Participants	Severity of Periodontitis	Comparator / Control	Intervention	Probiotic Strain Used as Named in Study	Probiotic Dosage / CFU	Probiotic Delivery Method	Probiotic Duration	Outcome measures	Main Findings
Alhamoudi et al., 2023[24]	European Review for Medical and Pharmacological Sciences	RCT	72	PD ≥3 mm in at least 30 % sites; and BOP in at least 30 % sites	Non-surgical mechanical debridement alone.	1) Non-surgical mechanical debridement + probiotic therapy. 2) Probiotic therapy + oral hygiene instructions. 3) probiotic therapy alone.	L. rhamnosus	2 × 107	powder dissolved in water which was then consumed by the patient: x1 powder sachet taken daily at home dissolved in water after morning toothbrushing	6 weeks of taking the probiotic daily	PI, GI, PD, CAL, number of missing teeth, salivary flow rate and cortisol levels.	There was no statistically significant correlation between all groups at baseline and follow-up.
Ali et al., 2021 [25]	Journal of Research in Medical and Dental Science	Split mouth clinical trial	25	Chronic periodontitis with pocket depths of 5–7.5 mm	SRP + chlorhexidine paste application	SRP + probiotic paste application	N/A	N/A	Probiotic paste: applied after SRP	1 treatment visit with a 4 week review	PI, GI, PD, and bleeding on probing.	The probiotic had a significant effect on the treatment of pocketing in periodontal disease.
Alshareef et al., 2020[26]	European Journal of Dentistry	RCT	25	moderate to severe chronic periodontitis	SRP only	SRP + Probiotic	L. acidophilus, L. casei, B. bifidum, L. rhamnosus, and L. salivarius	N/A	Lozenge: x2 probiotic lozenges daily	30 days	PI, BI, PD, CAL, and immunological testing.	probiotics might have a beneficial effect on clinical and immunological outcomes.
Ann et al., 2017 [27]	Journal of Pharmaceutical Negative Results	Randomised split mouth clinical trial	22	Chronic periodontitis with pocket depths of 46-mm	Scaling root debridement	Scaling root debridement + photodynamic therapy + probiotics	L. brevis and L. plantarum	N/A	Gel: Following photodynamic therapy probiotic gel was applied into the pocket	Single application following scaling root debridement	PD, CAL	A single application of PDT + probiotics with SRD did not show any additional clinical benefits.
Bazyar et al., 2020[28]	Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy	RCT	47	Chronic periodontitis PPD 4.50 mm ± 0.97	Non-surgical periodontal therapy + placebo capsule	Non-surgical periodontal therapy + probiotic capsule	L. acidophilus, L. casei, L. rhamnosus, L. bulgaricus, B. breve, B. longum, S. thermophilus	2 × 109 7 × 109 1.5 × 109 2 × 108 2 × 109 7 × 109 1.5 × 109	Capsule: x1 500 mg capsule taken daily	8 weeks	PD, CAL, BOP, Plaque	Synbiotic supplementation with NSPT may be beneficial in improving periodontal status in T2DM patients with CP.
Bilouro et al., 2022[29]	Food Science and Technology	RCT	24	CAL detected in 2 or more non-adjacent interproximal sites; or PPD of 3 mm or more in the buccal or lingual / palatine in at least 2 teeth.	NSPT + conventional milk drink	NSPT + probitic milk drink	L. casei	8–9 log CFU/ mL	Milk drink: x1 100 ml drink per day	15 days	PPD, CAL, Visible Plaque Index, BOP, Oral health quality of life	Probiotic milk drinks may be used as an adjuvant therapy for the treatment of periodontitis

(*continued on next page*)

Table 1 (*continued*)

Author and Year	Journal	Study Design	Participants	Severity of Periodontitis	Comparator / Control	Intervention	Probiotic Strain Used as Named in Study	Probiotic Dosage / CFU	Probiotic Delivery Method	Probiotic Duration	Outcome measures	Main Findings
Boyeena et al., 2019[30]	Indian Society of Periodontology	RCT	30	PPD ≥5 mm and BOP	SRP + sub gingivally delivered probiotics only	1) SRP + sub gingivally delivered tetracycline fibres. 2) SRP + sub gingivally delivered probiotic + tetracycline fibres	L. acidophilus, L. rhamnosus, B. bifidus, and B. longum	0.60 billion CFU each	powder with gum and saline: probiotic powder mixed with tragacanth gum and saline	Single application following treatment	PI, Sulcular Bleeding Index, PD, CFU.	There may be benefits of administering both tetracycline fibres and probiotic synergistically to treat periodontitis.
Butera et al., 2021[31]	MDPI Microorganisms	RCT	60	periodontal disease (stage II–III)	SRP +chlorhexidine-based toothpaste	2) SRP + probiotics-based toothpaste. 3) SRP + probiotics-based toothpaste + probiotics-based chewing-gum	Toothpaste: Bifidobacterium *, Lactobacillus *. Chewing gum: L. reuteri, L. salivarius, L. plantarum.	N/A	Toothpaste and chewing gum: x2 daily use of toothpaste. x1 daily 20 mins of chewing on the probiotic gum.	Toothpaste: 6 months. Chewing gum: The last 10 days of each month.	PPD, CAL, BOP, BS, Sulcus Bleeding Index, PI, Adherent Gingiva, Gingival Recession, and Pathological Sites.	The new probiotics-based toothpaste and chewing gum tested in this study seem to be a valid support to SRP
Butera et al., 2022[32]	MDPI microorganisms	RCT	40	presence of periodontal disease (severity: grade II–III; complexity: grade I–II)	Group 1 SRP + Curasept Intensive Treatment 0.2 % chlorhexidine)	Group 2 SRP + BiorepairPeribioma toothpaste + Biorepair Peribioma Mousse mouthwash	Lactobacillus and Bifidobacterium	N/A	Mouthwash and toothpaste: x2 daily use of toothpaste and mousse mouthwash.	6 months	PPD, CAL, BOP, BS, Sulcus Bleeding Index, Approximal Plaque Index, PI, Adherent Gingiva, Gingival Recession, and Pathological Sites.	the experimental toothpaste and mouthwash tested represent an effective protocol for the domiciliary maintenance of oral health.
Butera et al., 2022[33]	MDPI antibiotics	RCT	30	Periodontitis PPD 2–10mm	SRP + Chlorhexidine gel	SRP + postbiotic gel	L. Ferment	N/A	Gel: Professional and patient home application	Delivered over a 6 month period	BOP, PPD, gingival recession, PCR, and dental mobility	no significant differences compared with a conventional chlorhexidine gel
Butera at al., 2022[34]	MDPI applied sciences	RCT	40	grades II–III and complexity between grades I–II	SRP + Natural extract toothpaste	SRP + Biorepair Peribioma toothpaste + Biorepair Peribioma Mousse mouthwash	Bifidobacterium *, Lactobacillus *	N/A	Toothpaste: x2 daily use at home	6 months	PPD, BOP, BS, PI	significant decrease in PPD, CAL, BS and BOP parameters.
Costacurta et al., 2018[35]	Oral & Implantology	RCT	40	At least two ≥4 mm PPDs in each quadrant	SRP alone	SRP + Probiotic	L. reuteri DSM 17,938 and L. reuteri ATCC PTA 5289	For both strains 10^8	Tablet: dissolved in the mouth x1 daily	4 weeks	BOP, PPD, CAL	SRP and probiotics showed significant reduction of BOP and PPD.
deOliveira et al., 2022[36]	Journal of Periodontology	RCT	48	periodontitis stage III/IV, grades B/C.	Subgingival instrumentation + placebo	Subgingival instrumentation + probiotic capsule	five strains of Lactobacillus spp. and three of Bifidobacterium spp.	N/A	Capsule: x1 per day	30 days	Number of missing teeth, PD, BOP, Suppuration, Supragingival plaque, Gingival bleeding	Systemic probiotic provided additional clinical benefits in the treatment of periodontitis

(*continued on next page*)

Table 1 (*continued*)

Author and Year	Journal	Study Design	Participants	Severity of Periodontitis	Comparator / Control	Intervention	Probiotic Strain Used as Named in Study	Probiotic Dosage / CFU	Probiotic Delivery Method	Probiotic Duration	Outcome measures	Main Findings
Durga, Ravindra, and Halami 2023[37]	Cumhuriyet Dental Journal	RCT	48	periodontal pocket depth ≥ 5mm	SRP + Placebo	SRP + Probiotic chewing gum	L. fermentum and B. longum	1×10^8	Chewing gum: 10 mins twice a day,	30 Days	PI, GI, PPD, Gingival Bleeding Index, bacterial count	Probiotics can be administered as an adjunct to SRP to manage periodontitis in systemically compromised subjects.
El-Bagoory et al., 2021[38]	Indian Society of Periodontology	RCT	12	moderate chronic periodontitis according to Armitage criteria	SRP alone	SRP + sub gingivally delivered probiotic	L. reuteri DSM 17,938	1×10^8	Suspension: subgingival delivery of 1 ml	Applied at baseline and then weeks 1, 2, and 4	PPD, BOP, CAL, PI.	The results proved L. reuteri probiotic as a promising adjunctive therapy in improving periodontal parameters.
Elsadek et al., 2020[39]	Photodiagnosis and Photodynamic Therapy	Clinical Trial	60	stage III and grade C generalized periodontitis	RSD alone	Group-A: underwent RSD with adjunct Photo Dynamic Therapy. Group-B: underwent RSD with adjunct Probiotic Therapy	L. reuteri DSM-17,938 and ATCC PTA5289	10^8	Lozenge: x2 lozenges per 24 hour period	3 weeks	PS, BOP, PD, CAL, serum levels of HbA1c	Photo Dynamic Therapy showed additional benefit in deep periodontal pockets.
Galofré 2018[40]	Journal of periodontal research	RCT	44	Peri-implantitis	Non-surgical mechanical therapy + placebo	Non-surgical mechanical therapy + probiotic lozenge	L. reuteri DSM 17,938 and ATCC PTA 5289	10^8	Lozenge: x1 loznege per day	30 days	PI, BI, BOP, and microbiological examination	The probiotic L. reuteri, together with therapy, produced an additional improvement
Ghasemi et al., 2020[41]	Journal of advanced periodontology and implant dentistry	RCT	36	Stage III grade A periodontitis	SRP + placebo	SRP + probiotic mouth wash	B. lactis, L. acidophilus, B. bifidum, L. rhamnosus	15×10^9	Mouthwash: Gargling for 60 ss daily	20 days	PD, BOP, CAL, PI	Probiotic supplementation as a mouthwash along with SRP had a positive effect on periodontal indices
Ghazal et al., 2023[42]	Clinical Advanced Periodontics	RCT	60	Stage III, Grade C generalized periodontitis	NSPT + OHI + amoxicillin and metronidazole for 7 days + placebo probiotics for 30 days.	NSPT + OHI + probiotic+ placebo antibiotics for 7 days.	L. reuteri	2×10^8	Tablet: x2 daily	30 days	PD, AL, and BOP	between the treatment groups differences were not statistically significant
Grusovin et al., 2020[43]	Clinical Oral Investigations	RCT	20	patients with treated Generalised Periodontitis stage III-IVC	Guided biofilm therapy + placebo	Guided biofilm therapy + probiotic	L reuteri DSM 17,938 and ATCC PTA 5289	N/A	Lozenge: x2 lozenges per day.	12 weeks	PPD, PAL, BOP and tooth survival rate	Mean PPD and mean PAL and percentages of sites with BOP were improved with the probiotic group showing

(*continued on next page*)

Table 1 (*continued*)

Author and Year	Journal	Study Design	Participants	Severity of Periodontitis	Comparator / Control	Intervention	Probiotic Strain Used as Named in Study	Probiotic Dosage / CFU	Probiotic Delivery Method	Probiotic Duration	Outcome measures	Main Findings
												the greatest improvements.
Ikram et al., 2019 [44]	Annals Abbasi Shaheed Hospital & Karachi Medical & Dental College	RCT	28	Chronic periodontitis	SRP + Placebo	SRP + Probiotic	L. reuteri	N/A	Powder mixed with water used when brushing teeth: applied with a toothbrush x2 daily following regular toothbrushing.	12 weeks	PI, BOP, PPD, CAL	L. reuteri containing probiotic along with SRP is superior
Ikram et al., 2019 [45]	Journal of Investigative and Clinical Dentistry	RCT	30	Chronic periodontitis	SRP + 7-day course of amoxicillin + metronidazole	SRP + Probiotic	L. reuteri	1.2 billion cfu/g	Powder mixed with water used when brushing teeth: mix the content of sachets in water and apply it with the help of a toothbrush around the gingival margins for 5 mins twice daily.	12 weeks	PI, BOP, PPD, CAL	The adjunctive use of L. reuteri and systemic antibiotics along with SRP showed similar improvement in all clinical periodontal parameters.
Ikram et al., 2023 [46]	Pakistan Journal of Medical and Health Sciences	RCT	60	Chronic periodontitis	SRP alone	Group A) SRP + antibiotic. Group B) SRP + local probiotics	L. reuteri	1.2 billion cfu/g	Powder mixed with water used when brushing teeth: apply using toothbrush for 2 mins after routine brushing & then rinse.	12 weeks	PI, BOP, PPD, CAL	systemic antibiotics and L. reuteri are comparable in efficacy.
Ince et al., 2015 [47]	Journal of periodontology	RCT	30	≥2 teeth each with approximal sites with a PD of 5 to 7 mm and gingival index (GI) of ≥2.	SRP + Placebo	SRP + Probiotic	L. reuteri	N/A	Lozenge: x2 daily after brushing	3 weeks	PI, GI, BOP, PPD	Mean values of attachment gain were significantly higher in the test group compared with the control
Invernici et al., 2020[48]	PLOS ONE	RCT	30	Generalised Chronic Periodontits	SRP + Placebo	SRP + Probiotic	B. animalis	10^9	Lozenge: taken x2 daily	30 days	Plaque index (PI) and bleeding on marginal probing (BOMP)	potential probiotic to be used in non-surgical periodontal therapy
Invernici et al., 2018[49]	Journal of Clinical Periodontology	RCT	41	chronic periodontitis	SRP + Placebo	SRP + Probiotic	B. animalis	10^9	Lozenge: taken x2 daily	30 days	BOP, PPD, CAL, and GR	probiotics provided additional

(*continued on next page*)

Table 1 (*continued*)

Author and Year	Journal	Study Design	Participants	Severity of Periodontitis	Comparator / Control	Intervention	Probiotic Strain Used as Named in Study	Probiotic Dosage / CFU	Probiotic Delivery Method	Probiotic Duration	Outcome measures	Main Findings
												benefits in the treatment of periodontal pockets
Jardini at al., 2024[50]	Clinical Oral Investigations	RCT	40	stage III and IV, grade B	Subgingival instrumentation + placebo	Subgingival instrumentation + probiotic	L. reuteri	10^8	Lozenge: taken x2 daily	21 days	PI, BOP, PPD, CAL, and GR	The use of L. reuteri probiotics had no additional effects compared with the placebo
Jebin, Shyam, and Padmanabhan 2021[51]	Contemporary Clinical Dentistry	RCT	30	Stage II/III and Grade A/ Grade B periodontitis	SRP alone	SRP + Probiotic	L. reuteri UBLRu-87	0.5 billion	Tablet: x1 daily after evening toothbrushing	1 month	PI, GI, PPD and CAL	L. reuteri may be a useful adjunct to improve clinical outcomes
Koroleva et al., 2021[52]	REVISTA LATINOAMERICANA DE HIPERTENSION	RCT	37	mild chronic generalized periodontitis	professional oral hygiene and correction of individual hygiene.	Subgroup 1 - periodontal pockets irrigated with an autoprobiotic, subgroup 2 - oral baths with autoprobiotic	S. salivarius	4×10^8 to 6 $\times 10^8$ CFU/m	Mouthwash and pocket irrigation: Pocket irrigation and oral baths.	2 applications spread over 9 days following initial examination	OHI-S, PI, CPITN, PMA %, BOP %	The local use of a probiotic causes a significant decrease in the incidence of periodontal pathogens.
Kuka et al., 2019 [53]	Biotechnology & Biotechnological Equipment	RCT	36	moderate horizontal bone loss; PD of 5 mm to 7 mm at proximal sites	Initial periodontal therapy + probiotic food supplement	Initial periodontal therapy + placebo	L. reuteri	2×10^8	Tablet: sucked on after toothbrushing x2 daily	3 weeks	PD, BOP, GCF nitrous oxide	significant differences in favour of the test group
Kumar et al., 2021[54]	Journal of periodontal & implant science	RCT	48	PPD $\geq$5 mm, CAL $\geq$4 mm, and presence of BoP	SRP + placebo	Group 2: SRR +x1 local probiotic application. Group 3: SRP + x3 local probiotic application.	L. reuteri	5.9 billion CFU/gram	powder directly into the periodontal pocket: incrementally placed	Up to 3 applications over a 4 week period	PI, GI, BOP, PPD, CAL, GCF biochemical test	incremental 3-time application of L. reuteri as a probiotic led to improvements in clinical and biochemical parameters.
Laleman et al., 2020[55]	Journal of Clinical Periodontology	RCT	39	moderate to severe chronic periodontitis	Subgingival debridement + placebo	Subgingival debridement + probiotic drops + probiotic lozenge	L. reuteri	2×10^8	Lozenge and Drops: Drops were applied sub gingivally immediately after treatment. Lozenges were taken at home x2 daily after brushing.	lozenges taken for 12 weeks	PPD, REC, CAL, PS, BS	The adjunctive consumption of L. reuteri lozenges after re-instrumentation improved the PPD reduction
Laleman et al., 2020[56]	Clinical oral implants research	RCT	19	peri-implantitis with a maximum mean PPD of 6 mm and maximum 3 mm bone loss	Debridement + placebo	Debridement + probiotic drops + probiotic lozenge	L. reuteri	10^8 per 5 drops. 10^8 per lozenge.	Lozenge and Drops: Drops were applied sub gingivally immediately after treatment. Lozenges were	lozenges taken for 12 weeks	full-mouth bleeding score, full-mouth plaque score, BOP, modified sulcus bleeding index, PPD, PI	No effects of the use of L. reuteri probiotics in the treatment of peri-implantitis were found.

(*continued on next page*)

Table 1 (*continued*)

Author and Year	Journal	Study Design	Participants	Severity of Periodontitis	Comparator / Control	Intervention	Probiotic Strain Used as Named in Study	Probiotic Dosage / CFU	Probiotic Delivery Method	Probiotic Duration	Outcome measures	Main Findings
				compared with loading					taken at home x2 daily after brushing.			
Laleman et al., 2015[57]	Journal of Clinical Periodontology	RCT	48	Advanced adult periodontitis	SRP + placebo	SRP + probiotic	S. oralis, S uberis, and S. rattus	10^8 per strain	Tablet: taken x2 daily	12 weeks	PPD, REC, CAL, BOP, GI, PI	No differences were detected when probiotic was used.
Minić, Pejčić, and Bradić-Vasić 2022[58]	International journal of dental hygiene	RCT	80	PPD ≥5 mm (at least two sites per tooth)	SRP only	SRP + local probiotic	L. acidophilus, B. infantis and E. aecium	10^7	Mixed with saline: applied into the periodontal pocket using a curette	daily application for 5 days	BOP and PPD	Topical probiotics led to improvements in PPD reduction
Mitic et al., 2017 [59]	Research Journal of Pharmaceutical, Biological and Chemical Sciences	RCT	30	Chronic periodontitis 5–7 mm PPD	SRP only	SRP + probiotic	B. coagulans, L. sporogenes, L. acidophilus, S. thermophilus, L. bulgaricus, B. bifidum	$>2.1 \times 10^9$	Lozenge: taken x2 daily	14 days	PI, GI, PD, CAL, microbiological analysis.	Adjunctive use of probiotics offers clinical benefit in PPD reduction and reduced gingival parameters
Morales et al., 2016[60]	Journal of Periodontology	RCT	28	at least five teeth with periodontal sites with PD 5 mm and CA 3 mm, 20 % BOP, and extensive radiographic bone loss.	SRP + placebo	SRP + probiotics	L. rhamnosus SP1	2×10^7	powder dissolved in water which was then consumed by the patient: powder sachet x1 daily	3 months	PD, BOP, CAL, supra-gingival plaque levels	oral administration of L. rhamnosus SP1 resulted in similar clinical improvemens compared with SRP alone.
Morales et al., 2021[61]	BMC Oral health	RCT	47	Stage 3 periodontitis	Group 1) SRP + Placebo	Group 2) SRP + Probiotic. Group 3) SRP + antibiotics-azithromycin	L. rhamnosus	2×10^7	powder dissolved in water which was then consumed by the patient: Dissolved in 150 ml of water and ingest it once a day after brushing their teeth	3 months	PPD, BOP, CAL, PI.	The use of probiotics or azithromycin as an adjunct to SRP failed to provide additional benefits
Morales et al., 2018[62]	Journal of applied oral science	RCT	47	at least five teeth with PPD ≥ 4 mm and CAL ≥1 mm, 20 % BOP and extensive radiographic bone loss	SRP + Placebo	SRP + Probiotic or SRP + antibiotics-azithromycin	L. rhamnosus	2×10^7	powder dissolved in water which was then consumed by the patient: Dissolved in 150 ml of water and ingest it once a day after	3 months	PD, BOP, CAL, microbial analysis	The adjunctive use of L. rhamnosus SP1 sachets and azithromycin resulted in similar improvements compared with the placebo group.

(*continued on next page*)

Table 1 (*continued*)

Author and Year	Journal	Study Design	Participants	Severity of Periodontitis	Comparator / Control	Intervention	Probiotic Strain Used as Named in Study	Probiotic Dosage / CFU	Probiotic Delivery Method	Probiotic Duration	Outcome measures	Main Findings
									brushing their teeth			
Murugesan et al., 2018[63]	Journal of India Society of Periodontology	RCT	60	Aggressive periodontitis	SRP + doxycycline + Placebo	SRP + doxycycline + Probiotic	prebiotics: S. Faecalis, C. butyricum, B. mesentericus and probiotics: L. Sporogenes.	30 million 2 million 1 million 50 million	Lozenge	x1 daily for 8 weeks	PD, CAL, oral hygiene index, and BOP	co-administration of synbiotic along with standard therapy is more efficacious than SRP and doxycycline in the treatment of AP.
Ozener et al., 2023[64]	Clinical Oral Investigations	RCT	30	stage III grade B	Supra / sub gingival instrumentation + placebo	Supra / sub gingival instrumentation + probiotic	B. lactis DN-173,010	$\geq 10^8$	Yogurt: 110g of yogurt	x1 yogurt daily for 28 days	PI, GI, BOP, PD, CAL, microbiological sampling	The administration of probiotics has shown beneficial effects in the management of periodontitis
Patyna et al., 2021[65]	Clinical Oral Investigations	RCT	48	untreated periodontitis (stages II and III, grade B)	Group 1) Subgingival debridement alone	Group 2) Subgingival debridement + light activated disinfection + placebo. Group 3) subgingival debridement + light activated disinfection + probiotic	L. brevis and L. plantarum	Gel: 6×10^9. Lozenge: 1.2×10^9	Lozenge & gel: Professionally applied gel and a lozenge consumed at home	x1 application of gel and 3 months of x1 daily lozenge	GI simplified, Plaque control record, PPD, CAL, BOP, microbial analysis	The combination of SD + LAD + probiotic treatment in group 3 led to further improvements of the inflammatory parameters.
Pelekos et al., 2019[66]	Journal of Clinical Periodontology	RCT	59	2 non-adjacent teeth with PPD $\geq$5 mm and evidence of radiographic bone loss	NSPT + Placebo	NSPT + Probiotic	L. reuteri	10^8 for each strain	Lozenge	x2 daily for 28 days	CAL, PPD, BOP, visible plaque	The adjunctive use of probiotics with NSPT did not show any additional clinical effectiveness
Penala et al., 2016[18]	Journal of Research in Pharmacy Practice	RCT	32	at least 4 teeth showing PD $\geq$5 mm, CAL $\geq$4 mm, and with clinically perceptible halitosis	SRP + Placebo	SRP + Probiotic	Lactobacillus salivarius and Lactobacillus reuteri	2×10^9 per species	Mouthwash: Subgingival delivery following SRP and home use mouth wash	14 days	PD, CAL, BI, PI, MGI	the adjunctive use of probiotics offers clinical benefit in terms of pocket depth reduction in moderate pockets
Petrushanko et al., 2020[67]	World of medicine and biology	RCT	28	chronic periodontitis of I and II degrees of severity	professional hygiene + NBF gingival gel	professional hygiene + probiotic	L. acidophilus and L. rhamnosus	N/A	powder dissolved in water which was then consumed by the patient: contents of one capsule were dissolved in 20 ml of warm	10 days	modified GI, Fedorov-Volodkina and Green-Vermillion indices, Radiographic bone assessment	Application of the probiotic "Lacidofil forte" can be used for topical treatment in the treatment of generalized, chronic periodontitis and at the stage of

(*continued on next page*)

Table 1 (*continued*)

Author and Year	Journal	Study Design	Participants	Severity of Periodontitis	Comparator / Control	Intervention	Probiotic Strain Used as Named in Study	Probiotic Dosage / CFU	Probiotic Delivery Method	Probiotic Duration	Outcome measures	Main Findings
									boiled water, resulting solution was carried out in the mouth for 2 mins, after which the patient swallowed the solution.			supportive treatment
Pudgar et al., 2021[68]	Clinical Oral Investigations	RCT	40	stage III or IV according to the AAP/EFP classification of 2018	SRP + Placebo	SRP + probiotic	L. brevis and L. plantarum.	Gel: 6×10^9. Lozenge: 1.2×10^9	Lozenge & gel: Professionally applied gel and a lozenge consumed at home	x1 gel application and 3 months of x1 lozenge daily	GBI, PI, PD, BOP, REC, CAL	The adjunctive use of probiotics resulted in a higher number of residual diseased sites when compared with SRP + placebo
Ramos et al., 2022[69]	Journal of oral applied science	RCT	45	Stage II and III Grade B periodontitis.	ultrasonic periodontal debridement + 500 mg amoxicillin + 400 mg metronidazole	ultrasonic periodontal debridement + probiotic	Lactobacillus reuteri(DSM 17,938 and ATCC PTA 5289	2×10^8 CFU/ tablet	Lozenge: x2 per day after brushing their teeth in the morning and at night	21 days	PI, BoP, PD, gingival recession, immunological analysis	none of the adjuvant therapies promoted additional benefits regarding probing depth reduction
Ranjith, Nazimudeen, and Baiju 2022 [70]	International journal of dental hygiene	RCT	60	stage II periodontitis	Full-mouth scaling and root debridement + placebo	Full-mouth scaling and root debridement + probiotic	L. acidophilus, L. rhamnosus, B. longum and S. boulard	1 g powder of 1.25 billion freeze-dried combination	powder dissolved in water which was then consumed by the patient: Dissolve: twice daily 30 mins after brushing. After rinsing the mouth for 60 s they were asked to swallow the rinse	1 month	PPD CAL, GI, PI and salivary IgA and pH	Probiotic administration significantly improved periodontal parameters and salivary IgA, as well as pH.
Sajedinejad et al., 2018[71]	Probiotics and Antimicrobial Proteins	RCT	90	moderate to severe periodontitis	SRP + Placebo	SRP + Probiotic	L. salivarius NK02	10^8	Mouthwash	28 days	PI, full mouth plaque score, BOP, PPD.	SRP+ probiotic treatment led to a significant decrease of GI and BOP compared with that of SRP + placebo
Scariya et al., 2015[72]	International Journal of Pharma and Bio Sciences	RCT	28	Moderate and severe gingivitis, and	SRP only	SRP + probiotic	Streptococcus salivarius M18	N/A	Lozenge	x2 lozenges per day f0r 30 days	PI, GI, mSBI, PPD	the reduction in all indices was seen to be

(*continued on next page*)

Table 1 (*continued*)

Author and Year	Journal	Study Design	Participants	Severity of Periodontitis	Comparator / Control	Intervention	Probiotic Strain Used as Named in Study	Probiotic Dosage / CFU	Probiotic Delivery Method	Probiotic Duration	Outcome measures	Main Findings
				moderate periodontitis								significantly better in all subjects that were supplemented with probiotic M18 tablets
Shah, Gujjari, and Chandrasekhar 2013[73]	Journal of Clinical and Diagnostic Research	RCT	30	probing depth and a loss of the clinical attachment level which were $\geq$ 5 mm, and with a radiographic evidence of bone loss.	SRP + doxycycline	1) SRP + probioitc. 2) SRP + Probiotic + doxycycline	L. brevis	10^8	lozenge	x2 daily for 14 days	PI, GI, PPD, CAL, microbial testing	decreases in the PI, GI, PPD and CAL was statistically significant in all groups
Shetty, Srigiri, and Sheikh 2020[74]	International Journal of Medical Research & Health Sciences	RCT	18	chronic periodontitis with presence of true periodontal pockets; 4 mm-6 mm in depth involving minimum 3 or more quadrants	SRP alone	1) SRP + x1 probiotic application. 2) SRP + x4 probiotic applications	streptococcus faecalis, Clostridium butyricum, Bacillus mesentericus, and Lactobacillus sporogenes	N/A	Professional intrapocket application	up to 4 applications over 4 weeks	PI, GI, PPD, Microbiological assessment	synbiotic therapy may have additional benefit and may contribute to the improvement of clinical, microbiological and biochemical parameters in patients with chronic periodontitis.
Sinulingga et al., 2020[75]	International Journal of Applied Pharmaceutics	RCT	16	periodontitis stages II, III, and IV	SRP alone	SRP + probiotics	lactobacillus reuteri	N/A	Lozenge	x1 daily for 14 days	CAL and IL-4 leve	SRP with L. reuteri in periodontitis patients resulted in decreased CAL and increased IL-4 levels compared with SRP only.
Soares, de Carvalho, and Tinoco 2019 [76]	American Journal Of Dentistry	RCT	60	Generalised periodontitis stages III / IV and grades B / C	Ultrasonic debridement + placebo	Ultrasonic debridement + probiotic	L. reuteri, L. salivarius, L. acidophilus	10^9, 10^9, 5×10^8	Mouthwash: 1 min per day	90 days	PPD, CAL. BOP, PI, GBI	Oral administration of Lactobacillus reduced periodontal parameters
Sufaru et al., 2022[77]	Applied Sciences	Split mouth clinical trial	40	periodontitis stages 3–4, with at least 20 teeth present onthe arches	SRP only	SRP + Probiotic	L. reuteri strain DSM 17,938	10^8	Suspension: local subgingival application	The procedure was performed inthe same session with SRP and repeated at 7, 14, 21, and 28 day	PD, CAL, BOP	Improvements in PD, CAL, and BOP were significantly better for SRP + *L.* reuteri treated sites

(*continued on next page*)

Table 1 (*continued*)

Author and Year	Journal	Study Design	Participants	Severity of Periodontitis	Comparator / Control	Intervention	Probiotic Strain Used as Named in Study	Probiotic Dosage / CFU	Probiotic Delivery Method	Probiotic Duration	Outcome measures	Main Findings
Sufia et al., 2018 [78]	International Journal of Pharma and Bio Sciences	RCT	30	Generalized chronic periodontitis with probing pocket depth of 5–6 mm	non-surgical therapy only	non-surgical therapy and pre & probiotic	L. sporogens, S. faecalis, C. butyrium and B. mesentericus	50 million, 30 million, 2 million, and 1 million.	Lozenge	x2 daily for 3 weeks	Full mouth PI, full mouth GI, full mouth bleeding score, PPD, CAL	prebiotic and probiotic lozenges as an adjunct to SRP demonstrated significant improvement
Meenakshi and Varghese 2018 [79]	ResearchGate	RCT	20	moderate periodontitis with a pocket depth <6 mm	SRP alone	SRP + probiotic	Lactobacillus casei strain Shirota	N/A	Milk drink: swish the probiotic drink in mouth for at least 10 s and then swallow.	x2 daily for 1 month	GI, PI, PPD, CAL	PI, GI. CAL, and PPD were significantly reduced in the test group
Szkaradkiewicz, Stopa, and Karpinski 2014 [80]	Archivum Immunologiae et Therapiae Experimentalis	Clinical Trial	38	moderate chronic periodontitis	SRP alone	SRP + probiotic	L. reuteri ATCC PTA5289	10^8	Tablet	x2 daily after brushing for 2 weeks	sulcus bleeding index, PPD, CAL, cytokine response	significant reduction of pro-inflammatory cytokine response and improvement of clinical parameters following the use of L. reuteri.
Tapashetti et al., 2022[81]	The journal of contemporary dental practice	RCT	20	Previously untreated chronic stage II moderate periodontitis with probing pocket depth <5 mm	SRP + Placebo	SRP + probiotic	L. acidophilus, Lactobacillus rhamnosus, Bifidobacterium longum, and Saccharomyces boulardii	1.25 billion freeze-dried combinations	Mouthwash: powder was dissolved in 20 mL of distilled water and used twice daily	14 days	GI, PI, Microbiological Analysis	the use of probiotic mouth-wash significantly reduces the levels of red complex bacteria along with significant improvement in clinical parameters.
Tekce et al., 2015 [82]	Journal of Clinical Periodontology	RCT	40	PD of 5–7 mm and gingival index (GI) of ≥2 in each quadrant.	SRP + Placebo	SRP + probiotic	Lactobacillus reuteri	10^8	Lozenge	x2 lozenges per day for 3 weeks	PI, GI, BOP, PD, microbiological analysis	PI, GI, BoP and PD were significantly lower in the probiotic group
Teughels et al., 2013[83]	Journal of Clinical Periodontology	RCT	30	untreated moderate to severe generalized adult periodontitis	SRP + Placebo	SRP + probiotic	L. reuteri strains DSM17938 and ATCCPTA5289	10^8 each strain	Lozenge	x2 lozenges per day for 12 weeks	PI, GI, PPD, REC, BOP, GI, PI, microbial analysis	significantly more PPD reduction and attachment gain in moderate to deep pockets; in the probiotic group.
Theodoro, Cláudio, and Nuernberg 2019[84]	Beneficial microbes	RCT	34	severe generalised chronic periodontitis	SRP + Placebo	SRP + probiotic	L. reuteri	10^8 each strain	Tablet	x2 per day for 21 days	PD, BOP, REC, CAL	The adjuvant use of L. reuteri was effective in controlling gingival inflammation and reducing deep pockets.

(*continued on next page*)

Table 1 (*continued*)

Author and Year	Journal	Study Design	Participants	Severity of Periodontitis	Comparator / Control	Intervention	Probiotic Strain Used as Named in Study	Probiotic Dosage / CFU	Probiotic Delivery Method	Probiotic Duration	Outcome measures	Main Findings
Tsubura et al., 2009[85]	European Journal of Clinical Microbiology and Infectious Diseases	Clinical Trial	54	at least eight sites with PD >4 mm on molar teeth.	Periodontal treatment + Neosteline Green rinse	Periodontal treatment + *E*-300 rinse	Bacillus subtilis	0.9 g/100 ml	Mouthwash	x2 rinses per day for 20 ss over 1 month	PPD, BOP, GI, Microbial assessment	Mouth rinsing with E-300 significantly reduced periodontal pathogens compared with NG.
Vishnusripriya et al., 2022[86]	Journal of Indian Society of Periodontology	Split mouth RCT	10	chronic periodontitis at three distinct quadrants with 5–6-mm pocket depth.	Group A) SRP alone. Group B) SRP + chlorhexidine local drug delivery	Group C) SRP + local probiotic	Lactobacillus sporogenes	N/A	Probiotic paste: locally delivered glycerol paste	x1 application following SRP	GI, BI, PPD, RPI, CAL	significant reduction in GI, BI, PPD, and gain of CAL in probiotic group
Vivekananda, Vandana, and Bhat 2010[17]	Journal of Oral Microbiology	RCT	30	chronic periodontitis (5–7 mm pockets)	SRP + Placebo	SRP + Probiotic	L. reuteri strains DSM17938 and ATCCPTA5289	10^8 each strain	Lozenge	x2 lozenges per day for 21 days	PI, GI, GBI, PPD, CAL, microbial assessment	L. reuteri Prodentis probiotic can be recommended during SRP and the maintenance phase of periodontal treatment.
Vohra 2020[87]	Journal of Periodontology	RCT	127 (63 shamma users and 64 controls)	Chronic Periodontitis	SRP alone	SRP + Probiotic	L. reuteri strains DSM17938 and ATCCPTA5289	10^8 each strain	Lozenge	x1 lozenge every 12 h, twice daily for 21 days, after toothbrushing.	PI, BOP, PD, and CAL	SRP with adjunct probiotics was more effective in reducing PI, BOP, and PD

enhanced efficiency and avoiding the costs of producing and purifying active compounds. This is important, since production costs are a major barrier to the development of antimicrobial peptides, particularly where biological production systems are not possible and solid-phase-peptide synthesis is required instead [97].

L. *reuteri* has been observed to improve treatment outcomes in both human and animal studies. Pelekos et al. [98] reported higher improvements in attachment levels and greater probability of shallow residual probing depths when L. *reuteri* was used. Similar positive outcomes from the use of L. *reuteri* have been observed across multiple other studies [35,40,47]. Conversely, Laleman et al. [56] found no significant different between treatment outcomes when L. *reuteri* was used. In the included studies L. *rhamnosus* was also frequently investigated as an adjunctive probiotic. Differing from L. *reuteri,* L. *rhamnosus* produces exopolysaccharides which have been investigated for their anti-viral, anti-bacterial, anti-tumor, and immunomodulatory effects [99]. 4 of the included studies observed no difference in outcomes when L. *rhamnosus* was administered as a single strain [24,60,61,62] and only 1 study could recommend its use as an adjunct to PMPR and supportive periodontal care [70].

The improvements in treatment outcomes following the administration of L. *reuteri* is encouraging but this is only 1 of the 30 probiotics identified in this review, each probiotic potentially has a different mechanism through which it may confer health benefits to the host meaning a single probiotic cannot be viewed as conclusive evidence that all probiotics have a potential benefit in the treatment of periodontitis.

The European Federation of Periodontology (EFP) S3-level clinical practice guidelines suggest not to use probiotics as an adjunctive treatment in the management of the disease [3]. This conclusion was drawn from the systematic review carried out by Donos et al. [100] which included 5 placebo-controlled trials that when combined investigated 5 different probiotics, whereas this review has identified 66 RCTs which in combination investigated over 30 probiotic species. The findings of this scoping review have highlighted that there is a high level of heterogeneity in the available literature on adjunctive probiotic use during the non-surgical management of periodontitis with no answer on which probiotic or delivery method works best. These findings support the conclusions of previous systematic reviews into the effectiveness of adjunctive probiotics in that further research is required with larger sample sizes and long-term follow ups to identify an effective probiotic protocol [101,102].

The limitations of this review are characteristic of the scoping review methodology. No formal assessment of the methodological quality or formal synthesis of the included studies was conducted. Therefore, the evidence from this review cannot be used to develop practice or policy. This review is at risk of publication bias which may be one explanation for the positive results in favour of probiotic use. Only studies which performed non-surgical PMPR were included, this may have restricted the breadth of data collected in relation to probiotics used for periodontal health. The evidence collected has a high level of heterogeneity with different probiotics and treatment protocols used making any comparisons across studies difficult. If future reviews aim to assess efficacy opposed to map evidence, then a narrower search may allow for data synthesis. Due to these limitations the evidence from this scoping review should be interpretated with caution, however the aims of this review to identify what probiotics delivery methods, species, dosage, duration, and their observed outcomes has been achieved.

5. Conclusion

This review has identified a large body of evidence investigating the use of probiotics as an adjunctive treatment in the non-surgical management of periodontitis. 18 different methods were used to administer the probiotic treatment with over 30 different probiotic bacteria investigated across the 66 included studies. The use of probiotics showed favourable results with superior treatment outcomes observed for reductions in periodontal probing depths, bleeding on probing, gingival inflammation, and the presence of periodontal pathogens. However, the probiotic used, its dosage, the delivery method, duration of application, and outcome measures differ across studies making them highly heterogeneous and difficult to draw conclusions from. The data extracted in this scoping review highlights the need for further research in the field of adjunctive probiotics to establish a uniform treatment protocol and to identify the most effective probiotic bacteria.

CRediT authorship contribution statement

Ryan O'Donnell: Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Richard Holliday:** Writing – review & editing, Supervision, Data curation, Conceptualization. **Nick Jakubovics:** Writing – review & editing, Supervision, Data curation, Conceptualization. **Ellie Benfield:** Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

"This review was conducted as part of a National Institute for Health and Care Research Fellowship, grant number: NIHR303395. The Views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health and Care Research or the Department of Health and Social Care."

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jdent.2025.105623.

References

[1] P.N. Papapanou, M. Sanz, N. Buduneli, T. Dietrich, M. Feres, D.H. Fine, T. F. Flemmig, R. Garcia, W.V. Giannobile, F. Graziani, H. Greenwell, D. Herrera, R. T. Kao, M. Kebschull, D.F. Kinane, K.L. Kirkwood, T. Kocher, K.S. Kornman, P. S. Kumar, B.G. Loos, E. Machtei, H. Meng, A. Mombelli, I. Needleman, S. Offenbacher, G.J. Seymour, R. Teles, M.S. Tonetti, Periodontitis: consensus report of workgroup 2 of the 2017 world workshop on the classification of periodontal and peri-implant diseases and conditions, J. Clin. Periodontol 45 (2018), https://doi.org/10.1111/jcpe.12946.

[2] World Health Organisation, Global Oral Health Status report: Towards Universal Health Coverage For Oral Health By 2030, 2022.

[3] M. Sanz, D. Herrera, M. Kebschull, I. Chapple, S. Jepsen, T. Berglundh, A. Sculean, M.S. Tonetti, Treatment of stage I–III periodontitis—the EFP S3 level clinical practice guideline, J. Clin. Periodontol. 47 (S22) (2020) 4–60, https://doi.org/10.1111/jcpe.13290.

[4] F. Graziani, D. Karapetsa, B. Alonso, D. Herrera, Nonsurgical and surgical treatment of periodontitis: how many options for one disease? Periodontol. 2000 75 (1) (2017) 152–188.

[5] J. Suvan, Y. Leira, F.M. Moreno Sancho, F. Graziani, J. Derks, C. Tomasi, Subgingival instrumentation for treatment of periodontitis, a systematic review, J. Clin. Periodontol. 27;47 (S22) (2020) 155–175.

[6] L.J.A. Heitz-Mayfield, N.P. Lang, Surgical and nonsurgical periodontal therapy, learned and unlearned concepts, Periodontol. 2000 62 (1) (2013) 218–231.

[7] A. Mombelli, Maintenance therapy for teeth and implants, Periodontol. 2000 20; 79 (1) (2019) 190–199.

[8] A. Routie, A. Blaizot, K. Agossa, M. Dubar, What do we know about the mechanisms of action of probiotics on factors involved in the pathogenesis of periodontitis? A scoping review of in vitro studies, Arch. Oral Biol 129 (2021) 105196.

[9] W. Teughels, M. Feres, V. Oud, C. Martín, P. Matesanz, D. Herrera, Adjunctive effect of systemic antimicrobials in periodontitis therapy: a systematic review and meta-analysis, J. Clin. Periodontol 27;47 (S22) (2020) 257–281.

[10] M. Sanz, D. Herrera, M. Kebschull, I. Chapple, S. Jepsen, T. Berglundh, A. Sculean, M.S. Tonetti, Treatment of stage I–III periodontitis—the EFP S3 level clinical practice guideline, J. Clin. Periodontol 47 (2020) 4–60, https://doi.org/10.1111/jcpe.13290.

[11] L.F.N.P. da Costa, S.F. Amaral C da, S. Barbirato D da, A.T.T. Leão, M.F. Fogacci, Chlorhexidine mouthwash as an adjunct to mechanical therapy in chronic periodontitis, J. Am. Dent. Assoc 148 (5) (2017) 308–318.

[12] F. Guarner, M. Sanders, H. Szajewska, H. Cohen, R. Eliakim, C. Herrera, T. Karakan, D. Merenstein, A. Piscoya, B. Ramakrishna, S. Salminen, World gastroenterology organisation global guidelines probiotics and prebiotics, World Gastroenterol. Organi. (2023).

[13] Y. Zhang, X. Wang, H. Li, C. Ni, Z. Du, F. Yan, Human oral microbiota and its modulation for oral health, Biomed. Pharmacother. 99 (2018) 883–893.

[14] W. Teughels, G. Loozen, M. Quirynen, Do probiotics offer opportunities to manipulate the periodontal oral microbiota? J. Clin. Periodontol. 38 (s11) (2011) 159–177.

[15] J. Meurman, I. Stamatova, Probiotics: contributions to oral health, Oral Dis. 13 (5) (2007) 443–451.

[16] K. Per, C. Birgitta, D. Carina, P. Annette, N. Åsa, S. Gabriela, Decreased gum bleeding and reduced gingivitis by the probiotic Lactobacillus reuteri, Swed. Dent. J 30 (2) (2006) 55–60.

[17] M.R. Vivekananda, K.L. Vandana, K.G. Bhat, Effect of the probiotic Lactobacilli reuteri (Prodentis) in the management of periodontal disease: a preliminary randomized clinical trial, J. Oral Microbiol. 2;2 (1) (2010) 5344.

[18] S. Penala, B. Kalakonda, K. Pathakota, A. Jayakumar, P. Koppolu, B. Lakshmi, et al., Efficacy of local use of probiotics as an adjunct to scaling and root planing in chronic periodontitis and halitosis: a randomized controlled trial, J. Res. Pharm. Pract 5 (2) (2016) 86.

[19] J. Meurman, I. Stamatova, Probiotics: contributions to oral health, Oral Dis 9;13 (5) (2007) 443–451. Sep.

[20] N.J. Jamesburg, Probiotics for bacterial disease treatment in the oral environment, Compend. Contin. Educ. Dent 35 (9) (2014) 658–663.

[21] Y.H. How, S.K. Yeo, Oral probiotic and its delivery carriers to improve oral health: a review, Microbio. (NY) 5;167 (8) (2021).

[22] E. Aromataris, Z. Munn, JBI manual for evidence synthesis, JBI (2020).

[23] A.C. Tricco, E. Lillie, W. Zarin, K.K. O'Brien, H. Colquhoun, D. Levac, D. Moher, M.D.J. Peters, T. Horsley, L. Weeks, S. Hempel, E.A. Akl, C. Chang, J. McGowan, L. Stewart, L. Hartling, A. Aldcroft, M.G. Wilson, C. Garritty, S. Lewin, C. M. Godfrey, M.T. Macdonald, E.V. Langlois, K. Soares-Weiser, J. Moriarty, T. Clifford, Ö. Tunçalp, S.E. Straus, PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation, Ann. Intern. Med 169 (2018) 467–473, https://doi.org/10.7326/M18-0850.

[24] N. Alhamoudi, T. Abduljabbar, F. Vohra, F. Javed, Influence of mechanical debridement with adjunct probiotic therapy on clinical status and salivary cortisol levels in patients with periodontal inflammation, Eur. Rev. Med. Pharmacol. Sci. 27 (18) (2023) 8360–8370.

[25] A.O. Ali, A.A. Al-Shikhdaher, R. Alziadi, W.A. Al-Obaidi, The Relation of Probiotic Treatment to Periodontal Pocket in Comparison to Chlorohexidine, J. Res. Med. Dent. Sci. 9 (12) (2021) 134–137.

[26] A. Alshareef, A. Attia, M. Almalki, F. Alsharif, A. Melibari, B. Mirdad, et al., Effectiveness of probiotic lozenges in periodontal management of chronic periodontitis patients: clinical and immunological study, Eur. J. Dent 14 (2) (2020) 281–287.

[27] L. Ann, G. C, Y. Fatimah, N. En, D. Dicksit, C. Kalyan, K. Muttalib, S. Ramachandra, Effectiveness of photodynamic therapy and probiotics as an adjunct to scaling and root debridement in the treatment of chronic periodontitis, J. Pharm. Negat. Results 8 (2017) 25, https://doi.org/10.4103/0976-9234.204908.

[28] H. Bazyar, L. Maghsoumi-Norouzabad, M. Yarahmadi, H. Gholinezhad, L. Moradi, P. Salehi, M.H. Haghighi-zadeh, A.Zare Javid, The impacts of synbiotic supplementation on periodontal indices and biomarkers of oxidative stress in type 2 diabetes mellitus patients with chronic periodontitis under non-surgical periodontal therapy. A double-blind, placebo-controlled trial, Diabet. Metab. Syndr. Obes. Volume 13 (2020) 19–29, https://doi.org/10.2147/DMSO.S230060.

[29] F.C. Bilouro, R.S. Rocha, J.T. Guimarães, T.C. Pimentel, M. Magnani, E. A. Esmerino, M.Q. de Freitas, M.C. Silva, A.G. da Cruz, A. Canabarro, Probiotic milk drink as adjuvant therapy for the treatment of periodontitis: a randomized clinical trial with 180 days follow-up, Food Sci. Technol. 42 (2022), https://doi.org/10.1590/fst.17922.

[30] L. Boyeena, R. Koduganti, V. Panthula, S. Jammula, Comparison of efficacy of probiotics versus tetracycline fibres as adjuvants to scaling and root planing, J. Indian Soc. Periodontol. 23 (6) (2019) 539–544.

[31] A. Butera, S. Gallo, C. Maiorani, D. Molino, A. Chiesa, C. Preda, F. Esposito, A. Scribante, Probiotic alternative to chlorhexidine in periodontal therapy: evaluation of clinical and microbiological parameters, Microorg 9 (1) (2021) 1–19.

[32] A. Butera, S. Gallo, M. Pascadopoli, C. Maiorani, A. Milone, M. Alovisi, A. Scribante, Paraprobiotics in non-surgical periodontal therapy: clinical and microbiological aspects in a 6-month follow-up domiciliary protocol for oral hygiene, Microorg 10 (2) (2022).

[33] A. Butera, S. Gallo, M. Pascadopoli, D. Taccardi, A. Scribante, Home oral care of periodontal patients using antimicrobial gel with postbiotics, lactoferrin, and aloe barbadensis leaf juice powder vs, Conven. Chlorhexid. Gel. 11 (1) (2022).

[34] A. Butera, M. Pascadopoli, S. Gallo, M. Alovisi, E. Lovati, A. Scribante, Domiciliary management of periodontal indexes and glycosylated hemoglobin (HbA1c) in Type 1 diabetic patients with paraprobiotic-based toothpaste and mousse: randomized clinical trial, Appl. Sci 12 (17) (2022).

[35] M. Costacurta, L. Sicuro, S. Margiotta, I. Ingrasciotta, R. Docimo, Clinical effects of lactobacillus reuteri probiotic in treatment of chronic periodontitis. A randomized, controlled trial, Oral Implantol 11 (4) (2018).

[36] O.A M. de, T.G.B. Lourenco, V. Colombo AP, Impact of systemic probiotics as adjuncts to subgingival instrumentation on the oral-gut microbiota associated with periodontitis: a randomized controlled clinical trial, J. Periodontol 93 (1) (2022) 21–44.

[37] K.R. Durga, S. Ravindra, R.M. Halami, Probiotic chewing gums for adjunctive treatment of periodontitis in diabetics, Cumhuriyet. Dent. J 26 (3) (2023) 220–226.

[38] G. El-Bagoory, H. El-Guindy, M. Shoukheba, E. El-Zamarany, The adjunctive effect of probiotics to nonsurgical treatment of chronic periodontitis: a randomized controlled clinical trial, J. Indian. Soc. Periodontol 25 (6) (2021) 525–531.

[39] M.F. Elsadek, B.M. Ahmed, D.M. Alkhawtani, Z.S. A, A comparative clinical, microbiological and glycaemic analysis of photodynamic therapy and Lactobacillus reuteri in the treatment of chronic periodontitis in type-2 diabetes mellitus patients, Photodiag. Photodyn. Ther 29 (2020) 101629.

[40] M. Galofré, D. Palao, M. Vicario, J. Nart, D. Violant, Clinical and microbiological evaluation of the effect of Lactobacillus reuteri in the treatment of mucositis and peri-implantitis: a triple-blind randomized clinical trial, J. Periodontal. Res. 53 (3) (2018) 378–390.

[41] S. Ghasemi, A.R. Babaloo, B. Mohammadi, M. Esmaeilzadeh, Evaluating the effect of probiotic supplementation in the form of mouthwash along with scaling and root planing on periodontal indices in patients with stage III and grade A generalized periodontitis: a randomized clinical trial, J. Adv. Periodontol. Implant. Dent 12 (2) (2020) 73–78.

[42] M. Ghazal, S. Ahmed, W.A. Farooqui, F. Khalid, S. Riaz, A. Akber, S. Shabbir, F. R. Khan, A. Sadiq, A placebo-controlled randomized clinical trial of antibiotics versus probiotics as an adjuvant to nonsurgical periodontal treatment among smokers with Stage III, Grade C generalized periodontitis, Clin. Adv. Periodont. 13 (3) (2023) 197–204.

[43] M.G. Grusovin, S. Bossini, S. Calza, V. Cappa, G. Garzetti, E. Scotti, E.F. Gherlone, M. Mensi, Clinical efficacy of Lactobacillus reuteri-containing lozenges in the supportive therapy of generalized periodontitis stage III and IV, grade C: 1-year results of a double-blind randomized placebo-controlled pilot study, Clin. Oral Investig. 24 (6) (2020) 2015–2024.

[44] S. Ikram, N. Hassan, S. Baig, S.A. Ansari, K.J.J. Borges, M.A. Raffat, Clinical Efficacy of Probiotics as An Adjunct to Scaling and Root Planning in The Treatment of Chronic Periodontitis, Annal. Abbasi. Shaheed Hospital Karachi Med. Dent. College 24 (1) (2019) 31–37.

[45] S. Ikram, N. Hassan, S. Baig, K.J.J. Borges, M.A. Raffat, Z. Akram, Effect of local probiotic (Lactobacillus reuteri) vs systemic antibiotic therapy as an adjunct to non-surgical periodontal treatment in chronic periodontitis, J. Investig. Clin. Dent 10 (2) (2019) e12393.

[46] S. Ikram, N. Hassan, S. Baig, J. Kishore, Z. Ahmed, M.A. Raffat, Is Probiotic an Alternative to Systemic Antibiotics in treating Chronic Periodontitis? Pakistan. J. Med. Health Sci 17 (6) (2023) 186–189.

[47] G. Ince, H. Gursoy, S.D. Ipci, G. Cakar, E. Emekli-Alturfan, S. Yilmaz, Clinical and biochemical evaluation of lozenges containing lactobacillus reuteri as an adjunct to non-surgical periodontal therapy in chronic periodontitis, J. Periodontol 86 (6) (2015) 746–754.

[48] M.M. Invernici, F.A.C. Furlaneto, S.L. Salvador, A.C. Ouwehand, S. Salminen, A. Mantziari, G. Vinderola, E. Ervolino, S.I. Santana, P.H.F. Silva, M.R. Messora, Bifidobacterium animalis subsp lactis HN019 presents antimicrobial potential against periodontopathogens and modulates the immunological response of oral mucosa in periodontitis patients, PLoS ONE 15 (2020) e0238425.

[49] M.M. Invernici, S.L. Salvador, P.H.F. Silva, M.S.M. Soares, R. Casarin, D. B. Palioto, S.L.S. Souza, M. Taba Jr, A.B. Novaes Jr, F.A.C. Furlaneto, M. R. Messora, Effects of Bifidobacterium probiotic on the treatment of chronic periodontitis: a randomized clinical trial, J. Clin. Periodontol. 45 (10) (2018) 1198–1210.

[50] M.A.N. Jardini, J.F. Pedroso, C.L. Ferreira, C.M.M. Nunes, C.O. Reichert, M. N. Aldin, A. Neto, D. Levy, N. Damasceno, Effect of adjuvant probiotic therapy (Lactobacillus reuteri) in the treatment of periodontitis associated with diabetes mellitus: clinical, controlled, and randomized study, Clin. Oral Investig. 28 (1) (2024) 80.

[51] A. Jebin, K. Nisha, S. Padmanabhan, Oral microbial shift following 1-month supplementation of probiotic chewable tablets containing Lactobacillus reuteri UBLRu-87 as an adjunct to phase 1 periodontal therapy in chronic periodontitis patients: a randomized controlled clinical trial, Contemp. Clin. Dent 12 (2) (2021) 121–127.

[52] V.I. Koroleva, S.E. Mikhaylova, S.E. Zhukovskaia, A.L. Kraeva, N.A. Suvorov, Clinical and microbiological evaluation of the efficacy of autoprobiotics in the combination treatment of chronic generalized periodontitis, Revista. Latinoamericana. De. Hipertension 16 (1) (2021) 14.

[53] G.I. Kuka, H. Gursoy, E. Emekli-Alturfan, U.V. Ustundag, B. Kuru, Evaluation of nitric oxide levels in chronic periodontitis patients treated with initial periodontal therapy and probiotic food supplements: a double blind, randomized controlled clinical trial, Biotechnol. Equip. 33 (1) (2019) 974–979.

[54] V. Kumar, R. Singhal, P. Rastogi, N. Lal, S. Pandey, A.A. Mahdi, Localized probiotic-guided pocket recolonization in the treatment of chronic periodontitis: a randomized controlled clinical trial, J. Periodontal. Implant Sci 51 (2021) 1–14.

[55] I. Laleman, M. Pauwels, M. Quirynen, W. Teughels, A dual-strain Lactobacilli reuteri probiotic improves the treatment of residual pockets: a randomized controlled clinical trial, J. Clin. Periodontol 47 (1) (2020) 43–53.

[56] I. Laleman, M. Pauwels, M. Quirynen, W. Teughels, The usage of a lactobacilli probiotic in the non-surgical therapy of peri-implantitis: a randomized pilot study, Clin. Oral Implant. Res 31 (1) (2020) 84–92.

[57] I. Laleman, E. Yilmaz, O. Ozcelik, C. Haytac, M. Pauwels, E.R. Herrero, V. Slomka, M. Quirynen, B. Alkaya, W. Teughels, The effect of a streptococci containing probiotic in periodontal therapy: a randomized controlled trial, J. Clin. Periodontol. 42 (11) (2015) 1032–1041.

[58] I. Minic, A. Pejcic, M. Bradic-Vasic, Effect of the local probiotics in the therapy of periodontitis a randomized prospective study, Int. J. Dent. Hyg 20 (2) (2022) 401–407.

[59] k. Mitic, A. Kaftandzieva, M. Popovska, K. Ivanovski, M. Pandilova, S. Georgieva, S. Pesevska, A. Atanasovska-Stojanovska, B. Kapusevska, E. Janev, A. Mijovska, Probiotics and oral health, Res. J. Pharm. Biol. Chem. Sci. 8 (3) (2017) 1021–1029.

[60] A. Morales, P. Carvajal, N. Silva, M. Hernandez, C. Godoy, G. Rodriguez, R. Cabello, J. Garcia-Sesnich, A. Hoare, P.I. Diaz, J. Gamonal, Clinical effects of lactobacillus rhamnosus in non-surgical treatment of chronic periodontitis: a randomized placebo-controlled trial with 1-year follow-up, J. Periodontol 87 (8) (2016) 944–952.

[61] A. Morales, R. Contador, J. Bravo, P. Carvajal, N. Silva, F. Strauss, J. Gamonal, Clinical effects of probiotic or azithromycin as an adjunct to scaling and root planning in the treatment of stage III periodontitis: a pilot randomized controlled clinical trial, BMC Oral Health 21 (1) (2021) 12.

[62] A. Morales, A. Gandolfo, J. Bravo, P. Carvajal, N. Silva, C. Godoy, J. Garcia-Sesnich, A. Hoare, P. Diaz, J. Gamonal, Microbiological and clinical effects of probiotics and antibiotics on nonsurgical treatment of chronic periodontitis: a randomized placebo- controlled trial with 9-month follow-up, J. Appl. Oral Sci. 26 (2018) e20170075.

[63] G. Murugesan, K.M. Sudha, M.K. Subaramoniam, T. Dutta, K.R. Dhanasekar, A comparative study of synbiotic as an add-on therapy to standard treatment in patients with aggressive periodontitis, J. Ind. Soc. Periodontol 22 (5) (2018) 438–441.

[64] H.O. Ozener, L. Kuru, T. Kadir, B. Kuru, Bifidobacterium animalis subsp. lactis as adjunct to non-surgical periodontal treatment in periodontitis: a randomized controlled clinical trial, Clin. Oral Invest. 27 (5) (2023) 1965–1972.

[65] M. Patyna, V. Ehlers, B. Bahlmann, A. Kasaj, Effects of adjunctive light-activated disinfection and probiotics on clinical and microbiological parameters in periodontal treatment: a randomized, controlled, clinical pilot study, Clin. Oral Invest 25 (6) (2021) 3967–3975.

[66] G. Pelekos, S.N. Ho, A. Acharya, W.K. Leung, C. McGrath, A double-blind, paralleled-arm, placebo-controlled and randomized clinical trial of the effectiveness of probiotics as an adjunct in periodontal care, J. Clin. Periodontol 46 (12) (2019) 1217–1227.

[67] T.O. Petrushanko, G.A. Loban, T.N. Moshel, O. Hancho, Therapeutic potential of lactobacilli-based drug in the treatment of generalised periodontitis, World Med. Biol 74 (4) (2020) 121–125.

[68] P. Pudgar, K. Povsic, K. Cuk, K. Seme, M. Petelin, R. Gaspersic, Probiotic strains of Lactobacillus brevis and Lactobacillus plantarum as adjunct to non-surgical periodontal therapy: 3-month results of a randomized controlled clinical trial, Clin. Oral Invest 25 (3) (2021) 1411–1422.

[69] T.C.S. Ramos, M.L. Boas, C.M.M. Nunes, C.L. Ferreira, C.M. Pannuti, M. P. Santamaria, M. Jardini, Effect of systemic antibiotic and probiotic therapies as adjuvant treatments of subgingival instrumentation for periodontitis: a randomized controlled clinical study, J. Appl. Oral Sci. 30 (2022) e20210583.

[70] A. Ranjith, N.B. Nazimudeen, K. Baiju, Probiotic mouthwash as an adjunct to mechanical therapy in the treatment of stage II periodontitis: a randomized controlled clinical trial, Intern. J. Dent. Hyg. 20 (2) (2022) 415–421.

[71] N. Sajedinejad, M. Paknejad, B. Houshmand, H. Sharafi, R. Jelodar, H. Zahiri, K. Noghabi, Lactobacillus salivarius NK02: a potent probiotic for clinical application in mouthwash, Probiot. Antimicrob. Proteins 10 (3) (2018) 485–495.

[72] L. Scariya, D. Nagarathna, M. Varghese, Probiotics in periodontal therapy, Intern, J. Pharma. Biol. Sci 6(1) 242–250.

[73] M.P. Shah, S.K. Gujjari, V.S. Chandrasekhar, Evaluation of the effect of probiotic (Inersan) alone, combination of probiotic with doxycycline and doxycycline alone on aggressive periodontitis - a clinical and microbiological study, J. Clin. Diagn. Res 7 (3) (2013) 595–600.

[74] S. Shetty, S.K. Srigiri, K.H. Sheikh, A comparative clinical, microbiological and biochemical evaluation of guided periodontal pocket recolonisation (GPR) using synbiotics as an adjunct to scaling and root planing in patients with chronic periodontitis: a pilot project, Intern. J. Med. Res. Health Sci 9 (5) (2020) 20–32.

[75] R.T.N. Sinulingga, Y. Soeroso, R. Lessang, D.F.S. Sastradipura, Probiotic lactobacillus reuteri effect's on the levels of interleukin-4 in periodontitis patients after scaling and root planing, Intern. J. Appl. Pharma 12 (2020) 66–68.

[76] L.G. Soares, E.B. Carvalho, E.M.B. Tinoco, Clinical effect of Lactobacillus on the treatment of severe periodontitis and halitosis: a double-blinded, placebo-controlled, randomized clinical trial, Am. J. Dent 32 (1) (2019) 9–13.

[77] I.G. Sufaru, L. Lazar, D.C. Sincar, M.A. Martu, L. Pasarin, E.O. Luca, A. Stefanescu, E. Froicu, S. Solomon, Clinical effects of locally delivered lactobacillus reuteri as adjunctive therapy in patients with periodontitis: a split-mouth study, Appl. Sci 12 (5) (2022).

[78] S.S. Sufia, C. Pannam, P. Harinath, A. Tadepalli, D. Ponnaiyan, Clinical outcomes using prebiotic and probiotic lozenges in non-surgical management of chronic periodontitis patients, Intern. J. Pharma. and. Biol. Sci 9 (1) (2018) 24–29.

[79] S. Meenakshi, S. Varghese, Adjunctive effect of probiotic (Lactobacillus casei Shirota) to scaling and root planing in the management of chronic periodontitis, Drug Invent. Today 10 (8) (2018) 1381–1386.

[80] A.K. Szkaradkiewicz, J. Stopa, T.M. Karpinski, Effect of oral administration involving a probiotic strain of lactobacillus reuteri on pro-inflammatory cytokine response in patients with chronic periodontitis, Arch. Immunol. et. Therapiae. Experimentalis 62 (6) (2014) 495–500.

[81] R.P. Tapashetti, M.W. Ansari, G. Fatima, N. Bhutani, N. Sameen, P. Hm, Effects of probiotics mouthwash on levels of red complex bacteria in chronic periodontitis patients: a clinico-microbiological study, J. Contemp. Dent. Pract 23 (3) (2022) 320–326.

[82] M. Tekce, G. Ince, H. Gursoy, D.I. S, G. Cakar, T. Kadir, S. Yılmaz, Clinical and microbiological effects of probiotic lozenges in the treatment of chronic periodontitis: a 1-year follow-up study, J. Clin. Periodontol 42(4) 363–372.

[83] W. Teughels, A. Durukan, O. Ozcelik, M. Pauwels, M. Quirynen, M.C. Haytac, Clinical and microbiological effects of Lactobacillus reuteri probiotics in the treatment of chronic periodontitis: a randomized placebo-controlled study, J. Clin. Periodontol 40 (11) (2013) 1025–1035.

[84] L.H. Theodoro, M.M. Claudio, M.A.A. Nuernberg, D.M.J. Miessi, J.A. Batista, C. Duque, V.G. Garcia, Effects of lactobacillus reuteri as an adjunct to the treatment of periodontitis in smokers: randomised clinical trial, Benef. Microbes 10 (4) (2019) 375–384.

[85] S. Tsubura, H. Mizunuma, S. Ishikawa, I. Oyake, M. Okabayashi, K. Katoh, M. Shibata, T. Iizuka, T. Toda, T. Iizuka, The effect of Bacillus subtilis mouth rinsing in patients with periodontitis, Eur. J. Clin. Microbiol. Infect. Dis 28 (11) (2009) 1353–1356.

[86] J. Vishnusripriya, A. Melath, M. Feroz, L. Subair, N. Chandran, Comparative evaluation of locally delivered probiotic paste and chlorhexidine gel as an adjunct to scaling and root planing in treating chronic periodontitis: a split-mouth randomized clinical trial, J. Indian Soc. Periodontol 26 (3) (2022) 262–268.

[87] F. Vohra, I.A. Bukhari, S.A. Sheikh, R. Albaijan, M. Naseem, M. Hussain, Effectiveness of scaling and root planing with and without adjunct probiotic therapy in the treatment of chronic periodontitis among shamma users and non-users: a randomized controlled trial, J. Periodontol 91 (9) (2020) 1177–1185.

[88] D.S. Harper, P.J. Robinson, Correlation of histometric, microbial, and clinical indicators of periodontal disease status before and after root planing, J. Clin. Periodontol 14 (1987) 190–196.

[89] I. Magnusson, J. Lindhe, T. Yoneyama, B. Liljenberg, Recolonization of a subgingival microbiota following scaling in deep pockets, J. Clin. Periodontol 11 (1984) 193–207.

[90] M. Quirynen, W. Teughels, M. Soete, D. Steenberghe, Topical antiseptics and antibiotics in the initial therapy of chronic adult periodontitis: microbiological aspects, Periodontol 28 (2000) 72–90.

[91] W.J. Loesche, The specific plaque hypothesis and the antimicrobial treatment of periodontal disease, Dent. Update 19 (1992) 68.

[92] M.N. Sela, Role of *treponema denticola* in periodontal diseases, Crit. Rev. Oral Biol. Med 12 (2001) 399–413.

[93] V. Cleusix, C. Lacroix, S. Vollenweider, M. Duboux, G.Le Blay, Inhibitory activity spectrum of reuterin produced by Lactobacillus reuteri against intestinal bacteria, BMC Microbiol 7 (2007) 101.

[94] Q. Mu, V.J. Tavella, X.M. Luo, Role of Lactobacillus reuteri inhuman health and diseases, Front. Microbiol 9 (2018) 757.

[95] F.C. Hsieh, C.C. Lan, T.Y. Huang, K.W. Chen, C.Y. Chai, W.T. Chen, A. Fang, Y. C. Wu, Heat-killed and live Lactobacillus reuteri GMNL-263 exhibit similar effects on improving metabolic functions in high-fat diet-induced obese rats, Food Funct. 7 (2016) 2374–2388.

[96] L. Schaefer, T.A. Auchtung, K.E. Hermans, D. Whitehead, B. Borhan, R.A. Britton, The antimicrobial compound reuterin (3-hydroxypropionaldehyde) induces oxidative stress via interaction with thiol groups, Microbiol 156 (2010) 1589–1599.

[97] S. Deo, K.L. Turton, T. Kainth, A. Kumar, H. Wieden, Strategies for improving antimicrobial peptide production, Biotechnol. Adv. 59 (2022) 107968.

[98] G. Pelekos, A. Acharya, N. Eiji, G. Hong, W.K. Leung, C. McGrath, Effects of adjunctive probiotic L. reuteri lozenges on S/RSD outcomes at molar sites with deep pockets, J. Clin. Periodontol 47 (9) (2020) 1098–1107.

[99] P. Paul, R. Nair, S. Mahajan, U. Gupta, M. Aalhate, I. Maji, P.K. Singh, Traversing the diverse avenues of exopolysaccharides-based nanocarriers in the management of cancer, Carbohydr. Polym 312 (2023) 120821.

[100] N. Donos, E. Calciolari, N. Brusselaers, M. Goldoni, N. Bostanci, G.N. Belibasakis, The adjunctive use of host modulators in non-surgical periodontal therapy. A systematic review of randomized, placebo-controlled clinical studies, J. Clin. Periodontol 47 (2020) 199–238.

[101] A. Vives-Soler, E. Chimenos-Küstner, Effect of probiotics as a complement to non-surgical periodontal therapy in chronic periodontitis: a systematic review, Med. Oral Patol. Oral Cir. Bucal 25 (2) (2020) 161–167.

[102] P. Jayaram, A. Chatterjee, V. Raghunathan, Probiotics in the treatment of periodontal disease: a systematic review, J. Indian Soc. Periodontol. 20 (5) (2016) 488–495.