Evaluation Of The Clinical Efficacy Of Locally Administered Probiotics As An Adjunct To Scaling And Root Planing In Patients With Chronic Periodontitis – A Systematic Review

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ABSTRACT:
Background: Periodontal disease is a chronic, multifactorial microbial infection that affects the attachment apparatus. Conventional treatment modalities for chronic periodontitis include scaling and root planing. Antimicrobial supplements, such as probiotics, photodynamic therapy, one-stage full-mouth disinfection, and local drug delivery (LDD), are being used as adjuncts to SRP to enhance the treatment outcome of periodontal disease. Antibiotic resistance and recolonization by pathogenic bacteria have driven the evolution of probiotics within the LDD system. The local delivery system offers advantages over systemic drug administration, and maintains effective pocket levels of antibacterial agents for extended periods, which help alter subgingival flora and promote the healing of the attachment apparatus. Therefore, the present systematic review aimed to assess the clinical efficacy of locally administered probiotics as an adjunct to scaling and root planing in patients with chronic periodontitis.
Materials and Methods: A systematic literature search in three databases: PubMed, Google Scholar, Cochrane, and a hand search of relevant scientific journals was performed for randomized clinical trials. Studies published in English language between January 2003 and December 2023 were included. Studies were assessed for quality using the Cochrane risk-of-bias tool for randomized trials version 2 (RoB 2) and were classified as high-quality studies.
Results - Five RCTs that met the eligibility criteria were included in the qualitative analysis. All of them demonstrated a low risk of bias. The clinical parameters assessed in all studies were Pocket Probing Depth (PPD), Bleeding on Probing (BOP), Clinical Attachment Level (CAL), Plaque Index (PI) and Gingival Index (GI). All the studies showed improvements in all clinical parameters in both groups, but with a significant improvement in the probiotic group.
Conclusion: This review indicates that locally administered probiotics, when used alongside SRP, led to more significant clinical improvements compared to SRP alone, highlighting probiotics as a potentially promising therapeutic option for patients with chronic periodontitis.

Keywords – Chronic Periodontitis, Probiotic, Scaling and Root Planing.

INTRODUCTION:

Periodontal disease is a biofilm-associated polymicrobial condition that involves a complex interplay between pathogenic bacteria and the host, and it is one of the two most prevalent oral health burdens worldwide.[1] The biofilm nature of the disease limits long-term treatment success, as the biofilm tends to re-establish itself over time. Traditional approaches in the treatment of periodontal disease primarily focuses on the mechanical disruption of the biofilm and the removal of its retentive factors through nonsurgical periodontal therapy (NSPT). In conjunction with effective oral hygiene, NSPT is considered the "gold standard" of periodontal treatment. However, scaling and root planing (SRP) is not always fully effective, as the microbiota of treated sites tends to recolonize with similar organisms present before therapy. This has led to the development of adjunctive therapies in combination with SRP to enhance the outcomes of non-surgical periodontal therapy. These adjunctive therapies include antibiotics, essential oils, probiotics, laser therapy, and photodynamic therapy.[2]
Probiotics are live microorganisms that confer health benefits to the host when administered in adequate amounts. They have been used for years in general medicine to treat inflammatory bowel disease, prevent allergies, manage vaginal infections, and prevent respiratory tract infections.[3] Early attempts to manipulate the oral microflora using bacteria were conducted by Hillman and Shivers, who found that *Streptococcus sanguis*

could inhibit the growth of *Actinobacillus actinomycetemcomitans* in gnotobiotic rats.[4,5] Over the following years, several animal studies have been conducted using *Lactobacillus* spp. and *Bifidobacterium* spp.[6]
In the past decade, probiotics have shown to modulate the immunological environment and increase the number of beneficial bacteria, aiding in the prevention of periodontal disease progression. Numerous studies have suggested that probiotics may help reduce bleeding on probing (BOP) and probing pocket depth (PPD) in patients with chronic gingivitis and periodontitis. Ince et al. observed that *Lactobacillus reuteri* could effectively reduce inflammation-associated markers and improve moderately deep pockets in patients with periodontitis.[7]
Despite the large number of studies published, some doubts remain regarding the effectiveness of probiotics in treating periodontal disease. Limited clinical evidence and inconsistent findings have emerged from studies evaluating adjunctive use of locally administered probiotic to SRP, necessitating a comprehensive systematic review to appraise and consolidate the existing evidence.
Thus, this systematic review aimed to critically evaluate the clinical efficacy of locally administered probiotics as an adjunct to scaling and root planing in patients with chronic periodontitis.

MATERIALS AND METHODS:

Protocol and registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) checklist and the registration of the study protocol was carried out at International Prospective Register of Systematic Reviews PROSPERO (Registration Number CRD42023455574).
The study was conducted with a focused question in the form of a specific PICO format “What is the clinical effect of locally administered Probiotics as an adjunct to scaling and root planing in patients with chronic periodontitis?”
Participant/population (P): Patients with age 20 to 70 years having moderate to severe periodontitis with a probing depth ≥4 mm and good general health with no significant systemic abnormalities will be included in the study. Pregnant female patients, lactating mothers, patients having history of consuming tobacco in any form and/or smoking will be excluded from the study.
Intervention (I): Probiotics administered locally as an adjunct to scaling and root planing.
Comparison (C): Patients undergoing only scaling and root planing.
Outcome (O): Pocket Probing depth (PPD), Clinical attachment level (CAL), Bleeding on Probing Scores (BOP), Gingival Index (GI) and Plaque Index (PI).
Study design (S): Randomized controlled clinical trials

Inclusion criteria:

All human randomized controlled trials, that evaluated the efficacy of locally administered probiotics as an adjunct to scaling and root planing in comparison to only scaling and root planing in chronic periodontitis between the age of 20 – 70 years assessing Plaque index (PI), Gingival index (GI), Pocket probing depth (PPD), Clinical attachment level (CAL) and Bleeding on probing scores published in the English language between 1st January 2000 and 31st December 2023 were included in the review.

Exclusion criteria:

All in-vitro, animal studies, non-randomized studies, observational studies, retrospective studies, studies in which systemic administration of probiotics was given, studies conducted on patients with systemic diseases, pregnant or lactating women, involving patients with habits such as tobacco product usage, smoking, or alcohol consumption and patients who underwent antimicrobial therapy within the preceding 6-12 months were excluded from the review.

Information sources and strategy:

The comprehensive data search of the scientific literature was performed through the following databases: PubMed, Google Scholar, and Cochrane from 1st January 2000 till December 31st 2023 in English language. Cross references and grey literature were checked for relevant articles. Hand searching of articles was done when the full texts of the relevant studies were not available through electronic database. The literature search was performed by two independent researchers namely ND and NS.
The search strategy utilized a combination of keywords, MeSH terms and Entry terms, including "probiotics," "local probiotics," "chronic periodontitis," "scaling and root planning," and "non-surgical periodontal therapy".

Selection of studies and data synthesis:

The eligibility of the articles retrieved from the electronic search was evaluated by two independent examiners independently. The titles and abstracts were evaluated to eliminate the irrelevant articles. Later the full text

articles were assessed by the two examiners individually and were cross checked. Disagreements were resolved by discussion. The primary outcomes included, Pocket Probing depth (PPD), and the secondary outcomes included Clinical attachment level (CAL), Bleeding on Probing Scores (BOP), Gingival Index (GI) and Plaque Index (PI).

Risk of bias assessment

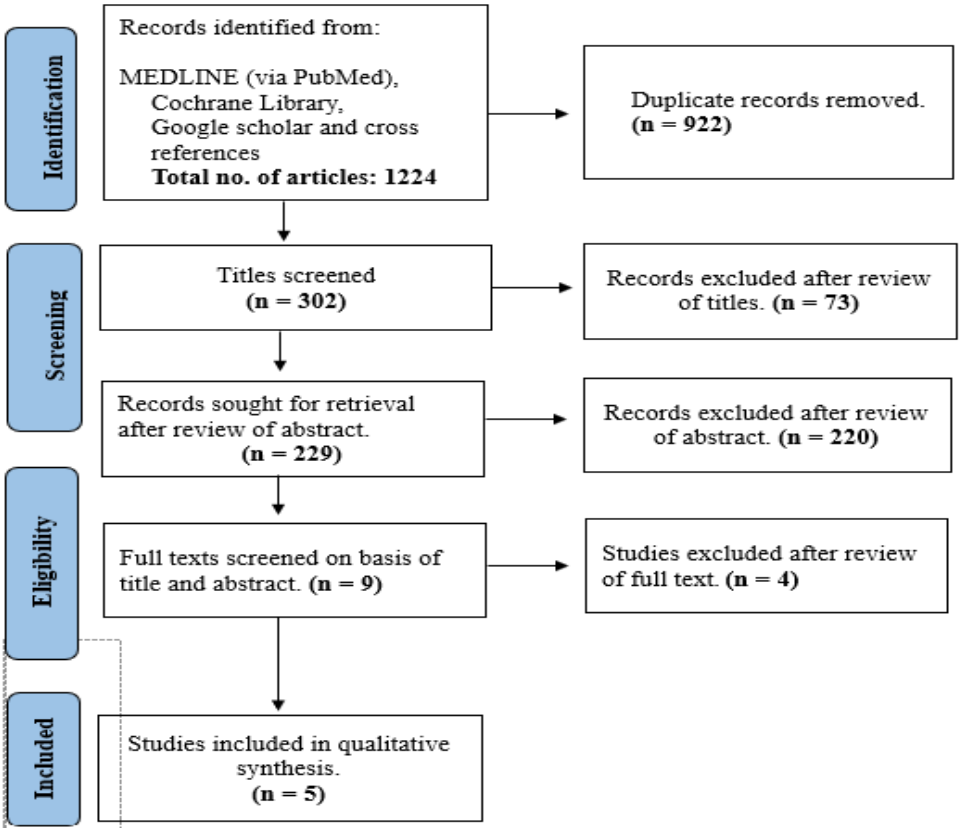
The quality of included studies for five domains ("Assessing Risk of Bias in Included Studies, through Cochrane ROB 2 tool") was methodologically and independently evaluated by two review authors. Based on domains and criteria, the overall risk for individual research was rated as low, moderate, or high risk.

RESULTS:

Selection of Studies

The electronic and manual searches identified 1223 articles and 01 from the cross-references. Of the 1224 articles obtained, 922 articles were duplicates and were excluded. Further, title screening was done for 302 articles and 73 articles were excluded after review of titles. Abstract screening was done according to the inclusion and exclusion criteria that had been set by the authors. 220 articles were excluded because they did not comply with the inclusion criteria. The remaining 09 studies had their full text read. Finally, a total of 05 articles were selected which met the inclusion criteria and answered the main focused question which was to evaluate the clinical efficacy of locally administered probiotics as an adjunct to scaling and root planing in patients with chronic periodontitis. The PRISMA flow diagram for the same has been depicted in Figure 1. The absence of a meta-analysis was attributed to the data's heterogeneity.

Figure No. 1: PRISMA FLOW CHART



Characteristics of included studies:

A total of 180 patients having chronic periodontitis were considered for the study. The age group of individuals incorporated in the studies that were included in this review was in the range of 20-55 years. (Table 1)

All the included studies in this review had a parallel group design with two arms for treating chronic periodontitis: A test group i.e., scaling and root planning along with locally delivered probiotics; and a control group i.e., scaling and root planning alone.

Table No. 1: Table showing data extraction sheet of all included studies

S.NO	AUTHOR AND YEAR OF PUBLICATION	LOCATION OF STUDY	STUDY DESIGN	SAMPLE SIZE (T/C)	AGE	MEAN AGE	GENDER (M/F)	CONTROL GROUP	TEST GROUP	FREQUENCY OF APPLICATION
1.	Rampalli Viswa Chandra et al., 2016[9]	Telangana, India	RCT Split mouth study	30 30/30	25 – 50 years	ND	ND	SRP	SRP + *Saccharomyces boulardii*	Probiotic Application - single application (immediately after SRP)
2.	Ivan Minić et al., 2021[10]	Serbia, Europe	RCT	80 40/40	35 – 55 years	ND	ND	SRP	SRP + *Lactobacillus acidophilus*, *Bifidobacterium infantis* and *Enterococcus faecium*	Probiotic Application - 5 times (1st, 2nd, 3rd, 4th, 5th day after SRP)
3.	Ghadeer Khalil Mohamed El-bagoory et al., 2021[10]	Egypt	RCT	12 6/6	35 – 55 years	39.33 years	M = 3 F = 9	SRP	SRP + *Lactobacillus reuteri*	Probiotic Application - 4 times (Baseline, 1st, 2nd, 4th, week after SRP)
4.	Irina-Georgeta Sufaru et al., 2022[11]	Romania, Europe	RCT Split mouth study	40 40/40	ND	48.65 years	M = 19 F = 21	SRP	SRP + *Lactobacillus reuteri*	Probiotic Application - 5 times (Baseline, 7th, 14th, 21st, 28th day after SRP)
5.	Heba Kamal Khalaf Nasr et al., 2023[12]	Egypt	RCT	18 9/9	24 – 47 years	ND	Male = 0 F = 18	SRP	SRP + *Lactobacillus brevis* and *Lactobacillus plantarum*	Probiotic Application - single application (immediately after SRP)

Primary outcome:

Pocket Probing Depth (PPD) was assessed in all the studies. 02 studies (Rampalli Viswa Chandra et al., 2016[9] and Ghadeer Khalil Mohamed El-bagoory et al., 2021[11]) assessed PPD at baseline, 3 and 6-month intervals, 01 study (Ivan Minić et al., 2021[10]) assessed PPD at the baseline, 7th day and 30th day, 01 study (Irina-Georgeta Sufaru et al., 2022[12]) assessed PPD at baseline and 3-month intervals and 01 study (Heba Kamal Khalaf Nasr et al., 2023[13]) assessed PPD at baseline, 1- and 3- month intervals. (Table 2)

Table No 2: Summary of primary outcomes:

S.NO	AUTHOR AND YEAR OF PUBLICATION	PRIMARY OUTCOME				
		POCKET PROBING DEPTH (PPD)				
			TEST		CONTROL	
			Mean	SD	Mean	SD
1.	Rampalli Viswa Chandra et al	Baseline 3 months	5.66 3.19	0.73 0.67	5.52 3.76	0.74 0.88

	(2016)[9]	6 months	2.19	0.97	3.61	0.97
2.	Ivan Minić et al (2021)[10]	Baseline 7th day 30th day	5.30 5.25 4.08	0.46 0.47 0.22	5.22 5.19 4.72	0.56 0.46 0.36
3.	Ghadeer Khalil Mohamed El-bagoory et al (2021)[11]	Baseline 3 months 6 months	5.10 2.90 3.30	0.32 0.32 0.48	5.30 3.50 4.30	0.48 0.71 0.67
4.	Irina-Georgeta Sufaru et al (2022)[12]	Baseline 4 months	6.04 5.13	0.42 0.54	6.09 5.58	0.51 0.49
5.	Heba Kamal Khalaf Nasr et al (2023)[13]	Baseline 1 month 3 months	4.09 2.64 2.13	0.9 0.5 0.6	3.90 2.66 2.53	0.9 0.5 0.4

Secondary outcomes:

04 out of 05 studies assessed Plaque Index (PI). 01 study (Rampalli Viswa Chandra et al., 2016[9]) assessed PI at baseline, 1 week, 3 and 6-month intervals, 01 study (Ivan Minić et al., 2021[10]) assessed PI at the baseline, 7th day and 30th day, 01 study (Ghadeer Khalil Mohamed El-bagoory et al., 2021[11]) assessed PI at baseline, 3 and 6-month intervals, and 01 study (Heba Kamal Khalaf Nasr et al., 2023[13]) assessed PI at baseline, 1- and 3- month intervals. (Table 3)

Table no 3: Summary of secondary outcomes:

S.NO	AUTHOR AND YEAR OF PUBLICATION	SECONDARY OUTCOME				
		PLAQUE INDEX (PI)				
			TEST		CONTROL	
			Mean	SD	Mean	SD
1.	Rampalli Viswa Chandra et al (2016)[9]	Baseline 1 week 3 months 6 months	1.58 0.52 0.54 0.64	0.34 0.10 0.15 0.28	1.79 0.65 0.85 0.92	0.36 0.39 0.23 0.27
.	Ivan Minić et al (2021)[10]	Baseline 7th day 30th day	2.00 0.00 0.10	0.56 0.00 0.04	1.92 0.25 0.61	0.53 0.01 0.03
3.	Heba Kamal Khalaf Nasr et al (2023)[13]	Baseline 1 month 3 months	2.64 0.53 0.93	0.5 0.1 0.2	2.58 0.70 1.11	0.6 0.1 0.6
4.	Ghadeer Khalil Mohamed El-bagoory et al (2021)[11]	Baseline 3 months 6 months	Percentage 100% 50% 50%		Percentage 100% 50% 30%	
		GINGIVAL INDEX (GI)				
			TEST		CONTROL	
			Mean	SD	Mean	SD
1.	Rampalli Viswa Chandra et al (2016)[9]	Baseline 1 week 3 months 6 months	2.09 1.19 0.85 0.90	0.30 0.40 0.35 0.30	2.19 1.52 1.09 1.80	0.50 0.51 0.30 0.92
2.	Heba Kamal Khalaf Nasr et al (2023)[13]	Baseline 1 month 3 months	2.49 0.89 0.98	0.3 0.4 0.9	2.41 1.02 1.03	0.4 0.5 0.6

			CLINICAL ATTACHMENT LEVEL			
			TEST		CONTROL	
			Mean	SD	Mean	SD
1.	Rampalli Viswa Chandra et al (2016)[9]	Baseline 3 months 6 months	3.57 1.42 0.61	0.74 0.59 0.58	3.52 1.90 1.80	0.74 0.88 0.92
2.	Ghadeer Khalil Mohamed El-bagoory et al (2021)[11]	Baseline 3 months 6 months	3.10 0.90 1.30	0.32 0.32 0.48	3.30 1.50 2.30	0.48 0.71 0.67
3.	Irina-Georgeta Sufaru et al (2022)[12]	Baseline 4 months	4.96 3.97	0.63 0.65	5.02 4.65	0.65 0.62
4.	Heba Kamal Khalaf Nasr et al (2023)[13]	Baseline 1 month 3 months	2.61 1.26 0.73	0.7 0.9 0.1	2.28 1.43 1.38	0.8 0.8 0.7
			BLEEDING ON PROBING (BOP)			
			TEST		CONTROL	
			Mean	SD	Mean	SD
1.	Ivan Minić et al (2021)[10]	Baseline 7th day 30th day	1.80 0.40 0.18	0.35 0.09 0.06	1.87 0.28 0.82	0.38 0.06 0.13
2.	Irina-Georgeta Sufaru et al (2022)[12]	Baseline 4 months	80.90 14.92	6.35 6.17	81.67 26.40	6.5 9.54
3.	Ghadeer Khalil Mohamed El-bagoory et al (2021)[11]	Baseline 3 months 6 months	Percentage 100% 70% 50%		Percentage 100% 50% 30%	

02 out of 05 studies assessed Gingival Index (GI). 01 study (Rampalli Viswa Chandra et al., 2016[9]) assessed GI at baseline, 1 week, 3 and 6-month intervals, 01 study (Heba Kamal Khalaf Nasr et al., 2023[13]) assessed GI at baseline, 1- and 3- month intervals.
04 out of 05 studies have studies assessed Clinical Attachment Level (CAL). 01 study (Rampalli Viswa Chandra et al., 2016[9]) assessed CAL at baseline, 3 and 6-month intervals, 01 study (Ghadeer Khalil Mohamed El-bagoory et al., 2021[11]) assessed CAL at baseline, 3 and 6-month intervals, 01 study (Irina-Georgeta Sufaru et al., 2022[12]) assessed CAL at baseline, 3-month and 01 study (Heba Kamal Khalaf Nasr et al., 2023[13]) assessed CAL at baseline, 1- and 3- month intervals.
03 out of 05 studies assessed Bleeding on Probing (BOP), 01 study (Ivan Minić et al., 2021[10]) assessed BOP at the baseline, 7th day and 30th day, 01 study (Ghadeer Khalil Mohamed El-bagoory et al., 2021[11]) assessed CAL at baseline, 3 and 6-month intervals, 01 study (Irina-Georgeta Sufaru et al., 2022[12]) assessed BOP at 3-month intervals.

Quality assessment
The risk-of-bias graph and summary generated by the RevMan software (v5.3) are shown in Figures 2 and 3, respectively. The research was categorized into six areas, and each study's methodology was evaluated and given a risk level. All 5 articles showed low risk of bias.

Figure No. 2: Graph showing the summary of risk of bias: Review authors' judgments about each risk of bias item for each included study.

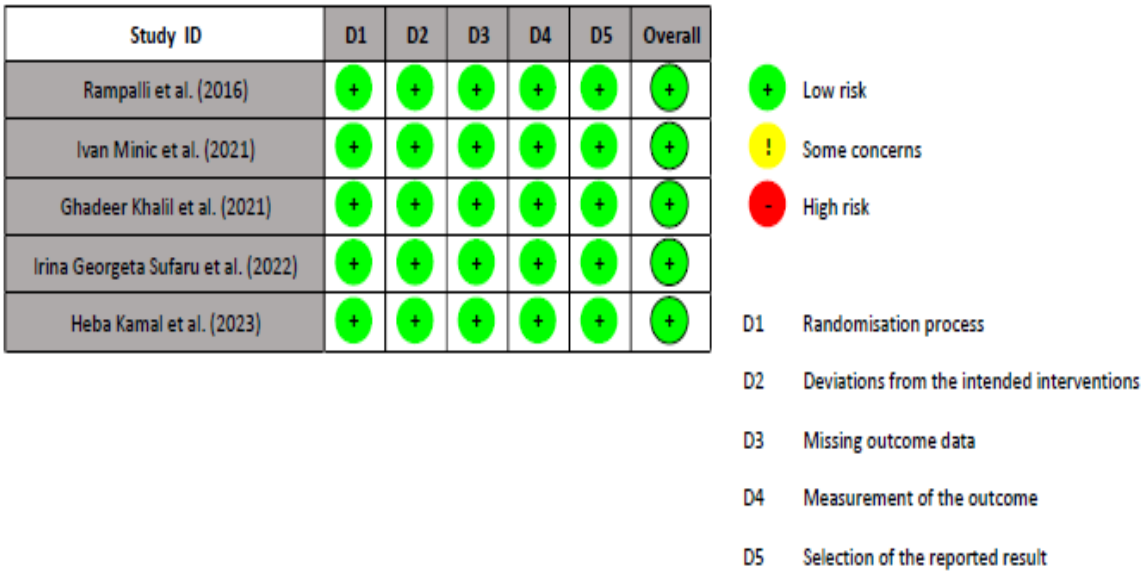


Figure No. 3: Graph showing Risk of bias: review authors' judgements about each other risk of bias item present as percentages across all included studies.

DISCUSSION:

Periodontitis is a chronic, multifactorial inflammatory condition caused by dysbiotic plaque biofilms, which leads to the gradual destruction of the tooth-supporting structures. Subgingival biofilm is regarded as the main contributor to the development of periodontitis, and its complete removal is crucial for effective treatment of the disease.[18] The combination of probiotics with SRP improves clinical outcomes and provides immunological benefits by regulating the balance between anti-inflammatory mediators and pro-inflammatory cytokines. The therapeutic effect of probiotics could be explained by three mechanisms. The first being that the probiotics competitively inhibit other pathogens by utilising essential nutrients; they also alter the environmental pH and restrict the adhesion of other pathogens.

Secondly, the probiotics produce antimicrobial substances, such as lactic acid, bacteriocins and hydrogen peroxide, which can kill or hamper the growth of periodontal pathogens. Finally, Probiotics can modulate the innate and adaptive host immune response by decreasing pro-inflammatory cytokines, interleukin (IL)-1β, IL-6 and tumour necrosis factor alpha (TNF-α), and upregulating anti-inflammatory cytokines, IL-10.[1,19]

Modulation of the host's microbiota may explain the beneficial effects of probiotics on periodontitis treatment. *L. reuteri* has been demonstrated that play an anti-inflammatory effect against periodontal pathogens such as *Aggregibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Fusobacterium nucleatum* and *Prevotella intermedia*. Haukioja et al. reported that the coaggregation of Bifidobacterium with *F. nucleatum* reduced the number of binding sites for periodontopathogens on the biofilm. Iniesta et al., stated that the level of *P. gingivalis* was significantly decreased when L. *reuteri* probiotic was used. Laleman et al. revealed that *Streptococcus sanguinis* and *Streptococcus uberis* decreased the number of *P. intermedia* and *A. actinomycetencomitans*. These indicated that the modulation of periodontal pathogens has a beneficial impact in the prevention and treatment of patients with periodontitis.[18,20]

Numerous strains of probiotic bacteria have been discovered and identified, with *Lactobacillus spp., Bifidobacterium spp.,* and *Saccharomyces spp*. being among the most important for the treatment of periodontitis.

S. boulardii is a non-pathogenic yeast that influences pro-inflammatory host responses by disrupting the host's signaling molecules, including the nuclear factor kappa B (NF-κB) and mitogen-activated protein (MAP) kinase pathways. It thrives in the subgingival environment and can be an effective oral probiotic for treating periodontitis.[9,19]

Studies revealed that the administration of *L. reuteri* reduced inflammation associated markers, including TNF-α, IL-1 βand IL-8, MMP-8 levels and increased the level of IL- 10, TIMP-1, which co-relates to the improvement in the clinical parameters following probiotic therapy.

Among the five studies included in the present systematic review, there was a significant improvement in all the clinical parameters from the baseline to the postoperative endpoints in the intra-group comparisons.

All the studies included demonstrated improved pocket probing depth (PPD) scores in both groups. Rampalli Viswa Chandra et al.[9] and Ghadeer Khalil Mohamed El-bagoory et al.[11] observed a statistically significant reduction of PPD from baseline to 3 and 6-months.

The rationale behind the use of probiotics in periodontal therapy is the conversion of a dysbiotic pocket microbiome into a symbiotic and beneficial microbiome to aid in healing. The improvement in periodontal pocket depth may have been due to the probiotic's protective role in the gingival epithelial barrier, where it helps maintain protein expression and prevents mucosal apoptosis. It could also be attributed to the inhibition of pathogen growth, the suppression of collagenases, and the reduction of inflammation-associated molecules.[3,20,21]

The studies that evaluated plaque and gingival indices demonstrated a reduction in scores from baseline to the postoperative intervals in both groups, with the test group showing better results. Ivan Minic et al.[10], reported a PI score of zero at 7 days from baseline which was highly statistically significant in both the groups which can be attributed to the strict oral hygiene measures followed by patients and was in agreement with the data in the reported by Buduneli et al. and Quirynen et al. This reduction may be due to the suppression of harmful bacteria in the oral cavity by the live microorganisms present in the probiotic, which subsequently led to decreased plaque accumulation and gingival inflammation. In contrary, Heba Kamal Khalaf Nasr et al.[13] reported no statistically significant difference was observed in the PI and GI score both the test and control groups after therapy.[22,23]

Bleeding on probing (BOP) is a key parameter for diagnosing gingivitis. When a probe is inserted to the bottom of the pocket, bleeding occurs if the gingiva is inflamed or if the pocket epithelium is atrophic or ulcerated, a condition thought to be mediated by subgingival pathogenic microorganisms. The studies that assessed BOP showed a reduction in both groups, with a statistically significant decrease in the test group. This substantial improvement is believed to result from the effect of probiotics on host responses, which is linked to shifts in biofilm composition rather than a reduction in periodontal pathogen counts.[3,10,11,12]

Clinical attachment level (CAL) is an important parameter for evaluating the loss of periodontal tissue support in periodontitis. It is crucial to recognize that the pro-inflammatory cytokine response plays a key role in the onset of periodontal disease. Several studies have indicated that treatment with the probiotic strain *Lactobacillus reuteri* leads to a reduction in the levels of TNF-α, IL-1β, and IL-17 in the periodontal pockets of patients with periodontitis, which is clinically significant. Rampalli Viswa Chandra et al.[9] and Ghadeer Khalil Mohamed El-bagoory et al.[11] reported a statistically significant improvement of CAL scores in the probiotic group from baseline to 3months and 6 months.

Similar results were stated by Heba Kamal Khalaf Nasr et al.[13], stating that the decrease in pro-inflammatory cytokine levels, induced by probiotics, explains the improvement in CAL scores in the test group compared to the control group.[3,24,25]

The authors of the included studies reported a few other findings in addition to the primary and secondary outcomes. Ghadeer Khalil Mohamed El-bagoory et al.[11] assessed the levels of *P. gingivalis* in GCF using Real time PCR at baseline and 3 and 6 months of treatment as *P. gingivalis* is known to be the key pathogen that can create dysbiosis between the host and dental plaque. Intergroup results showed a statistically significant difference in *P. gingivalis* load at 3 months and 6 months in the probiotic Group ($p < 0.05$), which can be

explained by the production of reuterin, which increases oxidative stress in pathogenic organisms, ultimately leading to their destruction.
Heba Kamal Khalaf Nasr et al.[13], assessed the levels of (OPG) Osteoprotegerin and IL- 10. The levels of OPG were not statistically significant. There was significant increase in the IL-10 levels over time from baseline to 3 months in the probiotic group. IL-10, a potent anti-inflammatory cytokine, plays a crucial role in regulating the secretion of pro-inflammatory cytokines like IL-1β, TNF-α, and IL-6. This helps reduce inflammatory destructive effects, such as bone resorption, while also promoting the periodontal healing process.

LIMITATIONS AND FUTURE PERSPECTIVES:
The primary limitation was the limited number of studies that met the inclusion criteria for being included in the qualitative analysis of periodontal outcomes. The time and frequency of application of probiotics varied among all the studies which could have an effect on the outcome of the study. Additionally, the included RCTs lacked pre- and post-treatment microbiological analysis to assess the microbiological flora, thus limiting the assessment of potential similarities in microbiological outcomes and reduction in periodontal pathogens. The substantial heterogeneity among the included RCTs concerning the probiotic parameters approaches precluded the possibility of conducting a meta-analysis.

CONCLUSION:
This review indicates that locally administered probiotics, when used alongside SRP, led to more significant clinical improvements compared to SRP alone, highlighting probiotics as a potentially promising therapeutic option for patients with chronic periodontitis. However, the selected studies in this systematic review showed variability in the frequency of applications and the probiotic strains used. Therefore, there is a need for well-designed, long-term randomized controlled clinical trials with standardized protocols for these parameters and extended follow-up periods to establish clear guidelines for using probiotics as an adjunct to SRP.

Source(s) of support: Nil

Presentation at a meeting: Nil

Conflicting Interest (If present, give more details): None

Contribution Details (to be ticked marked as applicable):

REFERENCES
1. Gatej S, Gully N, Gibson R, Bartold PM. Probiotics and periodontitis-a literature review. Journal of the International Academy of Periodontology. 2017 Apr 1;19(2):42-50.
2. Ho SN, Acharya A, Sidharthan S, Li KY, Leung WK, Mcgrath C, Pelekos G. A systematic review and meta-analysis of clinical, immunological, and microbiological shift in periodontitis after nonsurgical periodontal therapy with adjunctive use of probiotics. Journal of evidence Based dental Practice. 2020 Mar 1;20(1):101397.
3. Hardan L, Bourgi R, Cuevas-Suárez CE, Flores-Rodriguez M, Omana-Covarrubias A, Nicastro M, Lazarescu F, Zarow M, Monteiro P, Jakubowicz N, Proc P. The use of probiotics as adjuvant therapy of periodontal treatment: a systematic review and meta-analysis of clinical trials. Pharmaceutics. 2022 May 9;14(5):1017.
4. Hillman JD, Socransky SS, Shivers M. The relationships between streptococcal species and periodontopathic bacteria in human dental plaque. Arch Oral Biol. 1985; 30:791–5. doi: 10.1016/0003-9969(85)90133-5.
5. Hillman JD, Shivers M. Interaction between wild-type, mutant and revertant forms of the bacterium Streptococcus sanguis and the bacterium Actinobacillus actinomycetemcomitans in vitro and in the gnotobiotic rat. Arch Oral Biol. 1988; 33:395–401. doi: 10.1016/0003-9969(88)90196-3.
6. Jayaram P, Chatterjee A, Raghunathan V. Probiotics in the treatment of periodontal disease: a systematic review. Journal of Indian Society of Periodontology. 2016 Sep 1;20(5):488-95.
7. Ince G, Gürsoy H, Ipçi SD, Cakar G, Emekli-Alturfan E, Yilmaz S. Clinical and biochemical evaluation of lozenges containing Lactobacillus reuteri as an adjunct to non-surgical periodontal therapy in chronic periodontitis. J Periodontol. 2015; 86:746–54. doi: 10.1902/jop.2015.140612.
8. Amato M, Santonocito S, Polizzi A, Tartaglia GM, Ronsivalle V, Viglianisi G, Grippaudo C, Isola G. Local delivery and controlled release drugs systems: a new approach for the clinical treatment of periodontitis therapy. Pharmaceutics. 2023 Apr 21;15(4):1312.

9. Chandra RV, Swathi T, Reddy AA, Chakravarthy Y, Nagarajan S, Naveen A. Effect of a locally delivered probiotic-prebiotic mixture as an adjunct to scaling and root planing in the management of chronic periodontitis. J. Int. Acad. Periodontol. 2016 Jul 18; 18:67-75
10. Minić I, Pejčić A, Bradić-Vasić M. Effect of the local probiotics in the therapy of periodontitis A randomized prospective study. International Journal of Dental Hygiene. 2022 May;20(2):401-7.
11. El-Bagoory GK, El-Guindy HM, Shoukheba MY, El-Zamarany EA. The adjunctive effect of probiotics to nonsurgical treatment of chronic periodontitis: A randomized controlled clinical trial. Journal of Indian Society of Periodontology. 2021 Nov 1;25(6):525-31.
12. Sufaru IG, Lazar L, Sincar DC, Martu MA, Pasarin L, Luca EO, Stefanescu A, Froicu EM, Solomon SM. Clinical effects of locally delivered lactobacillus reuteri as adjunctive therapy in patients with periodontitis: A split-mouth study. Applied Sciences. 2022 Feb 26;12(5):2470.
13. Edrees MF, Nasr HK, Mowafy IM, Bakry AM. Evaluation of the Effect of Topically Applied Probiotics on Interleukin-10 and Osteoprotegerin as an Adjunctive Treatment of Stage I and П Grade A Periodontitis Cases. Al-Azhar Assiut Dental Journal. 2023 Apr 1;6(1):63-72.
14. Penala S, Kalakonda B, Pathakota KR, Jayakumar A, Koppolu P, Lakshmi BV, Pandey R, Mishra A. Efficacy of local use of probiotics as an adjunct to scaling and root planing in chronic periodontitis and halitosis: A randomized controlled trial. Journal of research in pharmacy practice. 2016 Apr 1;5(2):86-93.
15. Pudgar P, Povšič K, Čuk K, Seme K, Petelin M, Gašperšič R. Probiotic strains of Lactobacillus brevis and Lactobacillus plantarum as adjunct to non-surgical periodontal therapy: 3-month results of a randomized controlled clinical trial. Clinical oral investigations. 2021 Mar; 25:1411-22.
16. Kumar V, Singhal R, Rastogi P, Lal N, Pandey S, Mahdi AA. Localized probiotic-guided pocket recolonization in the treatment of chronic periodontitis: a randomized controlled clinical trial. Journal of Periodontal & Implant Science. 2021 Jun;51(3):199.
17. Abuazab DR, Una M, El-Daker MA. Efficacy of Locally Delivered Bifidobacterium Probiotic Gel as an Adjunctive Therapy in Periodontitis Patients (Clinical and Microbiological Study).
18. Hu D, Zhong T, Dai Q. Clinical efficacy of probiotics as an adjunctive therapy to scaling and root planning in the management of periodontitis: A systematic review and meta-analysis of randomized controlled trails. Journal of Evidence Based Dental Practice. 2021 Jun 1;21(2):101547.
19. Poulose M, Gujar D, Panicker S, Rokade S, Guruprasad M, Gopalakrishnan D. Efficacy and Viability of Subgingival Application of Probiotics as an Adjunct to Scaling and Root Planing in Periodontitis. Indian Journal of Dental Research. 2024 Jan 1;35(1):59-64.
20. Zhang Y, Ding Y, Guo Q. Probiotic species in the management of periodontal diseases: an overview. Frontiers in cellular and infection microbiology. 2022 Mar 25;12:806463.
21. Mennigen, R.; Nolte, K.; Rijcken, E.; Utech, M.; Loeffler, B.; Senninger, N.; Bruewer, M. Probiotic Mixture VSL# 3 Protects the Epithelial Barrier by Maintaining Tight Junction Protein Expression and Preventing Apoptosis in a Murine Model of Colitis. Am. J. Physiol.-Gastrointest. Liver Physiol. **2009**, 296, G1140–G1149.
22. Buduneli N, Buduneli E, Cetin EO, Kirilmaz L, Kütükcüler N. Clinical findings and gingival crevicular fluid prostaglandin E2 and 1β levels following initial periodontal treatment and shortterm meloxicam administration. *Expert Opin Pharmacother*. 2010;11(11):1805 1812.
23. Quirynen M, De Soete M, Boschmans G, et al. Benefit of "one-stage full-mouth disinfection" is explained by disinfection and root planning within 24 hours: a randomized controlled trial. *J Clin Periodontol*. 2006;33(9):639-647.
24. Servin, A.L. Antagonistic Activities of Lactobacilli and Bifidobacteria against Microbial Pathogens. FEMS Microbiol. Rev. 2004, 28, 405–440.
25. Vissers, Y.M.; Snel, J.; Zuurendonk, P.F.; Kleerebezem, M.; Wichers, H.J.; Savelkoul, H.F. Lactobacillus Strains Differentially Modulate Cytokine Production by HPBMC from Pollen-Allergic Patients. FEMS Immunol. Med. Microbiol. 2011, 61, 28–40.