AJMB
eISSN: 2600-8173

https://doi.org/10.37231/ajmb.2023.1.S.693
https://journal.unisza.edu.my/ajmb

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Asian Journal of Medicine and Biomedicine

A Meta-Analysis Investigation of the Impact of Probiotics on Mitigating Inflammatory Responses in Periodontal Disease

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Received: 8th August 2023 **Accepted: 23rd October 2023** **Published: 24th December 2023**

Abstract

Periodontal disease is primarily driven by pathogenic bacteria in dental plaque and the body's immune response to these bacteria. The immune response due to bacterial infection will leads to progressive pro-inflammatory activity in the affected tissue and systemic effect on the body. Probiotic bacteria were reported can immunomodulate and regulate the balance between pro-inflammatory and anti-inflammatory immune pathways, thus reducing the overall inflammatory response. This meta-analysis study aims to assess the potential of probiotic bacteria to reduce the magnitude of the inflammatory response, especially in the pro-inflammatory cytokines. Electronic databases such as Google Scholar, Science Direct, and PubMed were used to search keywords such as "effect of probiotic on the inflammatory response of periodontal disease," "probiotic role in periodontal disease," and "effect of probiotic in cytokine level of periodontal disease " were used during the literature search. The articles were searched from related articles from the year 2010 until 2021. Randomized Controlled Clinical Trials (RCTs) or controlled clinical trials were included in the study, whereby the concentration of IL-1β and TNF-α were chosen as the primary outcome variables. Research involving patients or subjects with systemic disease, cancer, or immunocompromised conditions was excluded. This is because the condition or disease can interfere with the study as the subjects are more susceptible to infections. Independent screening resulted in four eligible publications being included in the meta-analysis. However, the overall mean difference for the concentration of IL-1β (MD: -0.32; 95% CI: -1.88, 1.25; P = 0.69) and TNF-α (MD: 0; 95% CI: -0.20, 0.20; P= 0.98) did not show any statistical significance difference between probiotic and placebo groups. Therefore, the study results demonstrated weak evidence to support the usage of probiotics in reducing the magnitude of inflammatory response in patients with periodontal disease. Smaller sample sizes and limited available data may contribute to this conclusion. Hence, future randomized controlled clinical trials with larger sample sizes and a longer intervention period must be considered to evaluate the efficacy of probiotics in periodontal disease.

Keywords

Probiotics, periodontal disease, inflammatory response, cytokines, antimicrobial resistance.

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Introduction

Periodontal disease is a chronic inflammatory disorder that affects the periodontium of teeth, destroying the periodontal ligament and surrounding alveolar bone [1]. Changes in local microflora inhabiting the plaque biofilm from Gram-positive to Gram-negative facultatively anaerobic bacteria contribute to the disease emergence [2]. According to the Global Burden of Disease Report in 2015, periodontitis affected 538 million people all around the globe [3]. The inflammatory response during a periodontal infection, which includes conditions like gingivitis and periodontitis, is a complex biological reaction that occurs in the affected gum tissues in response to harmful bacteria. The body's immune system recognizes these bacteria as foreign invaders. The initial response is the activation of innate immunity, including cells like neutrophils and macrophages already present in the tissues. As the immune system detects the presence of bacteria, it releases chemical signalling molecules called cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α) [1]. These cytokines play a key role in initiating and amplifying the inflammatory response. The accumulation of immune cells, release of cytokines, and the presence of inflammatory mediators lead to localized inflammation in the gum tissues. This inflammation is characterized by redness, swelling, heat, and pain in the affected area. Standard treatment of periodontal disease includes non-surgical and surgical management followed by antibiotics, resulting in the development of antibiotic resistance and frequent recolonization of the periodontal pathogen in the treated site [4]. Uncertain efficacy of current periodontal therapy leads to insignificant improvement in a patient with periodontal disease. Therefore, probiotic as a new therapy model has been regaining popularity and interest among researchers in recent years, as they can alter the pathological plaque into a biofilm of commensalisms [5]. Probiotic, living microorganism consumed by humans for beneficial health effects, has a favourable impact on maintaining our periodontal health [6]. Hilman and Shivers introduce the first study that uses probiotic bacteria to alter microbiota in oral. They discovered that *Streptococcus sanguis* could prevent the growth of *Actinobacillus actinomycetemcomitans* in germ-free rats [7]. Another study has demonstrated that probiotics can prevent periodontal colonization, modulation of host defense, metabolite production against pathogenic microbes, and competitive exclusion mechanisms [8]. In periodontics, probiotic therapy can provide double benefits, such as preventing dysbiosis through competitive adhesion with the periodontal pathogen and altering the immune response to reduce the catastrophic inflammation in periodontitis. Moreover, using probiotics in gingivitis and mild periodontitis patients improves microbiological and clinical parameters such as probing pocket depth and clinical attachment level [5]. In terms of immune system modification, probiotics stimulate the dendritic cell to produce T-helper cell 1 (Th 1) or T-helper cell 2 (Th 2) response without causing any periodontal destruction [5]. The present study applies a meta-analysis to assess probiotic bacteria' potential to counteract periodontal disease. The finding of this study might serve as a reference for applying probiotics as an alternative treatment in the periodontics field.

Methods

Search strategy

A comprehensive search of the literature was carried out to identify the effects of probiotics on periodontal disease by assessing the influence of probiotic bacteria on the inflammatory response. The research question was formulated to assess the impact of probiotic interventions on the reduction of inflammatory markers in individuals with periodontal disease, compared to control groups receiving a placebo or probiotic. Academic databases such as PubMed, Google Scholar, and Scopus were used as a search strategy to identify all the related studies. Keywords such as "effect of probiotic on the inflammatory response of periodontal disease," "probiotic role in periodontal disease," and "effect of probiotic in cytokine level of periodontal disease" were used during the literature search. Additional studies were also included from

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references in the retrieved and relevant articles through hand searching to detect any eligible trials that might have been missed.

Inclusion and Exclusion Criteria

he inclusion criteria for this meta-analytical investigation comprise peer-reviewed studies, including randomized controlled trials and observational research involving human participants diagnosed with periodontal disease. Eligible studies must examine the effect of probiotic interventions, such as oral supplements or mouthwashes containing probiotics, and report quantitative data on periodontal inflammation indicators or relevant inflammatory markers. Studies without or with various types of comparison groups are considered. The publication should be only full-text articles issued between 2010 and 2020 in English and within a specified date range to ensure currency. Exclusion criteria encompass non-peer-reviewed sources, animal or in vitro studies, interventions lacking probiotics, studies without a relevant comparison group, non-quantitative outcome reporting, and non-English publications or those outside the designated publication date range. Furthermore, the study involving patients or subjects with systemic disease, cancer, or immunocompromised conditions was not included. The illness or disease can interfere with the investigation, making the issues more susceptible to contracting infections.

Study Selection Methods

Any duplicate studies were removed during the literature search, and article screening was done based on the title and abstract to choose related studies that matched the inclusion criteria. Selected full-text articles were retrieved, and only those eligible studies were incorporated into this research. Meanwhile, the irrelevant studies were removed due to exclusion criteria.

Data Extraction

Relevant data were extracted from each study, such as year of publication, first author's last name, sample size, number of participants in each group, type of probiotic strain, research design (randomized control trial/cross over/parallel), and study duration. In addition, quantitative data such as mean and standard deviation (SD) of the cytokines before and after intervention in probiotic and control groups; and mean changes in the cytokines after the intervention period in each group were extracted. If net changes in the probiotic and control groups were not directly reported, the mean difference was calculated by deducting the baseline from the follow-up value. As for the SD of the mean changes, they were calculated using the formula, [SD= square root [$(SD\ baseline)^2$ +$(SD\ post\text{-}treatment)^2$ – (2R × SD baseline × post-treatment); R=0.5] (Tavakoly et al., 2019).

Literature Quality Evaluation

The quality and risk of bias in the individual study were evaluated using the Cochrane Collaboration's Risk of Bias tool. The assessment tool consists of seven domains: sequence generation, allocation concealment, blinding of participants and investigators, blinding of outcome assessment, incomplete data outcome, selective outcome reporting, and potential sources of bias. Funnel plot analysis was performed to measure publication bias, while the heterogeneity test was calculated using Cochran's Q and I2 statistics.

Statistical Analysis

The meta-analysis used the Cochrane Program Review Manager (RevMan) version 5.4. Mean difference (MD) and standard deviation (SD) of changes in the cytokines level between probiotic and control groups were collected to estimate the effect sizes. The overall effect sizes were calculated using the fixed-effects model, as the included studies showed high homogeneity. The mean difference with a 95% confidence

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interval and P-values < 0.05 were considered statistically significant. Funnel plot analysis was performed to measure publication bias, while the heterogeneity test was measured using Cochran's Q and I^2 statistics. The average variance and a 95% confidence range (CI) were computed for each experiment and are displayed in a forest plot.

Result

Study Selection

The initial literature search through electronic databases such as Google Scholar, PubMed, and ScienceDirect yielded 500 studies. Out of these, 20 duplicated studies were excluded. After screening the remaining 480 studies based on title and abstract, only 40 articles were selected for full-text reading. The other 440 studies were eliminated as they needed to fulfil the eligibility criteria. After the final selection stage, four studies were chosen and processed for data extraction. The study identification flowchart according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the reasons for the article removal are shown in Figure 1.

Basic Characteristics of Included Studies

The primary features of four included studies investigating the impact of probiotics on the concentration of cytokines in periodontal disease patients are presented in Table 1. Two studies were done on moderate gingivitis patients [9,10]. One was on healthy individuals using the experimental gingivitis model [12], and another study was done on chronic periodontitis patients [11]. All of these articles were issued between 2010 and 2020. Moreover, all studies were conducted on both genders [9, 10, 11] except for one study on females [12]. The intervention (probiotic) and placebo/ control groups had a total sample size of 91 and 81, respectively, with 68% female and 32% male from the four studies. Three of these studies were randomized controlled trials with two parallel arms [9, 10, 11], and one study was a randomized controlled trial with a cross-over [12]. In these publications, all participants were healthy individuals without any systemic disease, not pregnant or breastfeeding, non-smokers, and had no history of medication or antibiotics intake in the previous several weeks before participating in the trial. Moreover, the participants in these studies took probiotic supplements or placebos as tablets, lozenges, or yogurt-based drinks. The administered probiotics consist of *Lactobacillus* and *Bifidobacterium* species. The clinical trial duration for these studies ranged from two to six weeks, while the outcomes measured were the concentration of cytokines using the immunoassay technique. All these studies reported mean ± SD of the cytokine concentration before and after the intervention.

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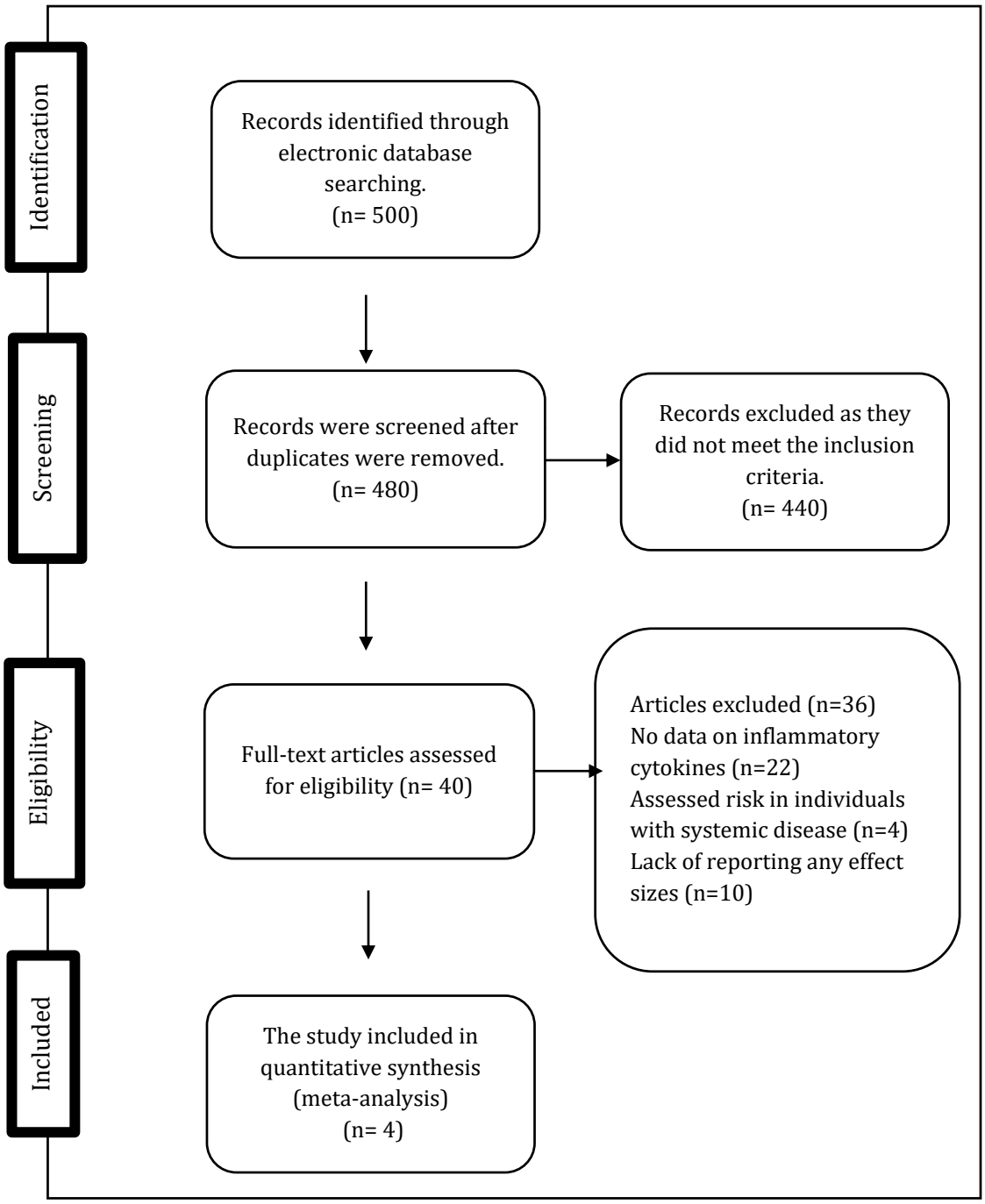

Figure 1: Study identification flowchart. This flowchart was made according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA guidelines.

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Table 1: Basic Characteristics of the Included Studies

Author, Year	Study-design	Number of subjects in each group	Sample size, mean age in years (range)	Probiotic strains	Intervention type		Outcomes
					Intervention (name & composition)	Control (name & composition)	
(Hallström et al., 2013)	Randomized controlled trial with cross-over	Probiotic=18 Placebo=18	18, 38 years	*Lactobacillus. reuteri* ATCC55730 and *Lactobacillus. reuteri* ATCC PTA5289	Probiotic lozenges (1×10^8 CFU of each strain) were given twice a day during the clinical trial period.	Placebo was also given as lozenges twice daily during the clinical trial period.	-IL-1β (↑), IL-6 (↔), IL-8 (↓), IL-10 (↔), IL-18 (↑), TNF-α (↔), MIP-1β (↓)
(Keller et al., 2018)	A randomized controlled trial with two parallel arms	Probiotic=23 Placebo=24	47, 26.9 & 25.7 years (18-50 years)	*Lactobacillus rhamnosus* PB01 DSM14869 and *Lactobacillus curvatus* EB10 DSM32307	Probiotic tablet ($\leq10^8$ CFU of both strains) was taken two times daily	Tablets with similar size and form containing placebo without the addition of probiotic strains were taken two times daily.	-IL-1β (↔), IL-10 (↔), IL-8 (↔), IL-6 (↔), TNF-α (↔)

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(Kuru et al., 2017)	A randomized controlled trial with two parallel arms	Probiotic=26 Placebo=25	51, 21.6 & 22.8 years (16-26 years)	*Bifidobacterium animalis* subsp. *lactis* DN-173010	110 g of probiotic plain yogurt/day containing ≥10^8 CFU/g *B. animalis* subsp. *lactis* DN-173010 were taken	110 g of plain yogurt without probiotic bacteria was taken	-IL-1β (↓)
(Szkaradkiewicz et al., 2014)	A randomized controlled trial with two parallel arms	Probiotic=24 Placebo=14	38, (31-46 years)	*Lactobacillus reuteri* PTA 5289	Probiotic suction tablets containing 10^8 CFU of *L. reuteri* were taken two times every day within the clinical trial period.	No probiotic tablets were applied.	-IL-1β (↓), IL-17 (↓), TNF-α (↓)

(↓); Significantly lower concentration compared to placebo.
(↑): Significantly higher concentration compared to placebo.
(↔): The difference is not significant compared to placebo.

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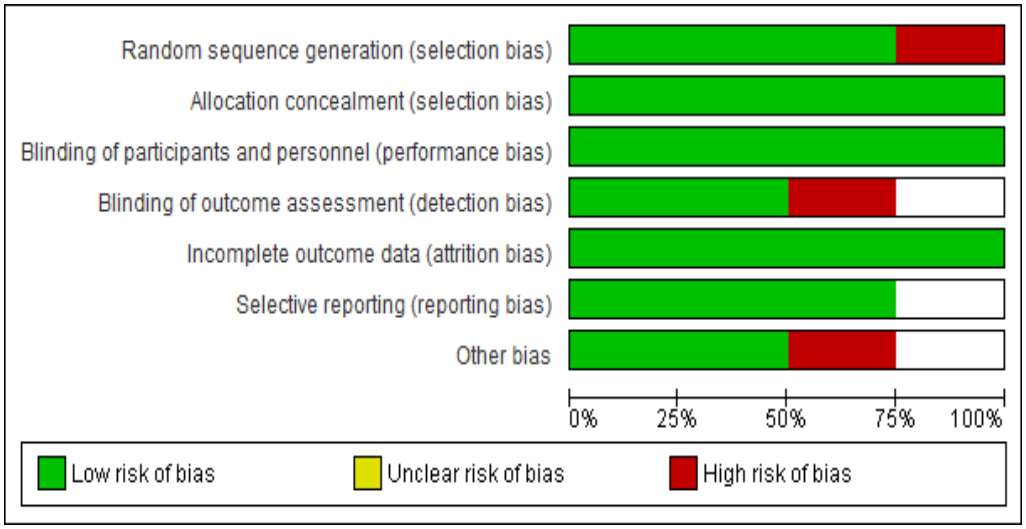

Figure 2: Risk of bias graph; review the author's judgment about each risk of bias item demonstrated as percentages across all the included studies.

The Dominant Inflammatory Cytokines

The included studies' clinical trials evaluated probiotics' influence on various inflammatory cytokines such as IL-1β, IL-6, IL-8, IL-10, IL-17, IL-18, TNF-α, and MIP-1β. However, only two inflammatory cytokines, IL-1β and TNF-α, were chosen for meta-analysis as they were the most common cytokines influenced by probiotics in all four studies. Meanwhile, other cytokines cannot proceed with meta-analysis as they are not significantly affected by probiotic administration and are absent in some of the included studies. Therefore, a comparison of effect sizes to evaluate probiotics' effectiveness in these inflammatory cytokines through forest plots cannot be performed.

Interleukin-1 beta (IL-1β)

Combining findings from four studies [9, 10, 11, 12] with four effect sizes, there was no statistically significant reduction in the concentration of IL-1β after probiotic consumption (MD: -0.32; 95% CI: -1.88, 1.25; P = 0.69) (Figure 3) as 0 is included in the 95% confidence intervals. Besides that, the qualitative visual analysis indicates variation among studies whereby the individual breakdown of the treatment effect estimates is on the opposite sides of the line of no effect. However, they do not align on a vertical axis, demonstrating a variance in the treatment effect sizes between studies. In addition, the confidence intervals for each study's treatment effect overlap. Still, CI's upper and lower limits do not constantly line up on a vertical axis, suggesting variability in assessing the population treatment effect between studies. On the other hand, the quantitative test of heterogeneity (I^2 = 10%, P = 0.34) suggests no significant between-study heterogeneity.

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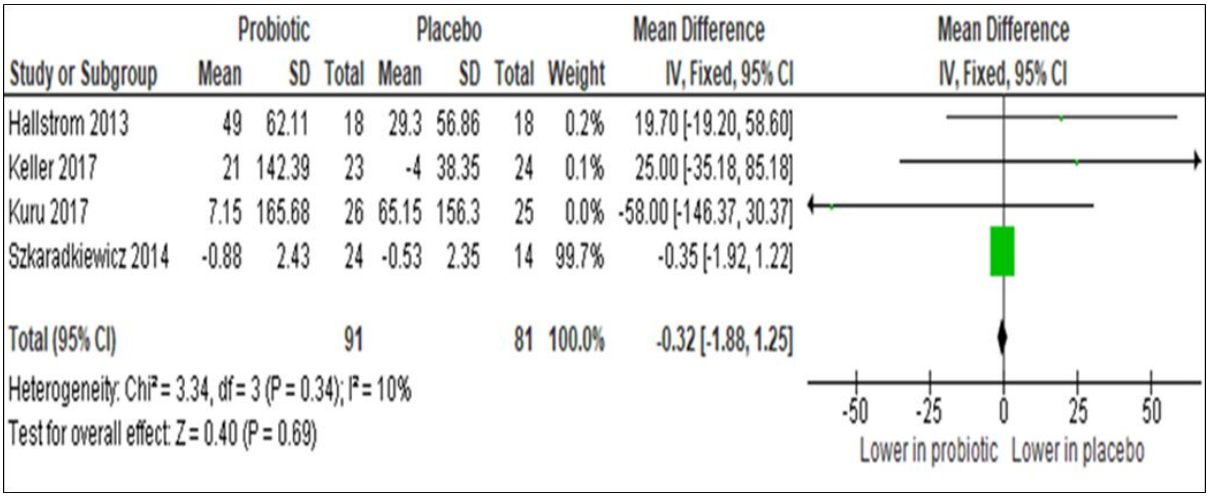

Figure 3: Forest plot presenting concentration of IL-1β. The comparison was made between the probiotic and placebo group. CI; confidence interval, SD; standard deviation.

Tumor Necrosis Factor-alpha (TNF-α)

In the case of TNF-α concentration, there was also no statistically significant reduction was observed after probiotic administration (MD: 0; 95% CI: -0.20, 0.20; P= 0.98) (Figure 4) when combining three effect sizes from three studies [9, 11, 12]. The qualitative visual analysis of the studies indicates slight variance among studies, in which the individual research of the treatment effect estimates is on the same side of the line of no effect and closely lines up on a vertical axis, demonstrating a comparable treatment effect magnitude. In addition, the confidence intervals for each study's treatment effect overlap. Still, CI's upper and lower limits do not constantly line up on a vertical axis, suggesting variability in assessing the population treatment effect between studies. On the other hand, the quantitative test of heterogeneity (I^2 = 0%, P = 0.89) suggests no significant between-study heterogeneity.

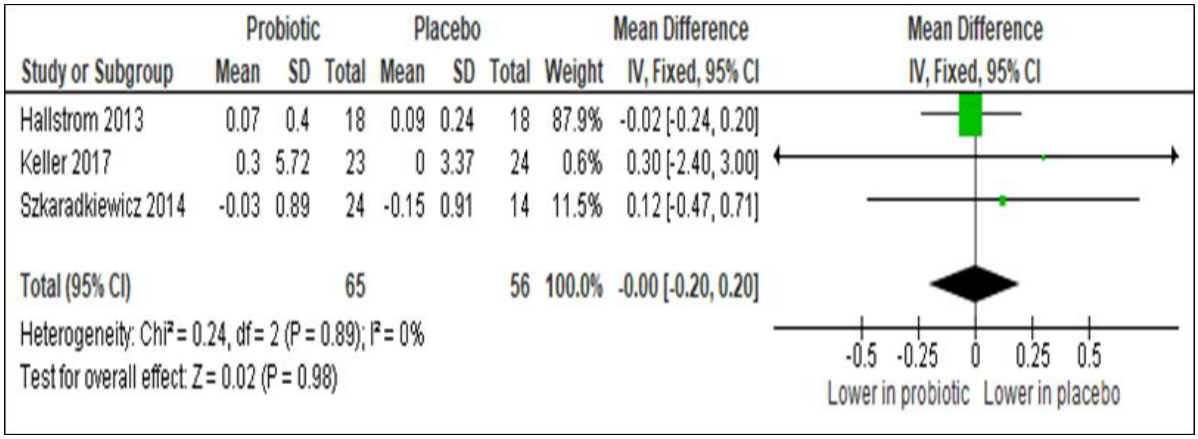

Figure 4: Forest plot presenting concentration of TNF-α. The comparison was made between the probiotic and placebo group. CI; confidence interval, SD; standard deviation

Publication Bias

The visual inspection of the funnel plot for all four studies included in the meta-analysis to assess the influence of probiotics on IL-1β concentration showed partially symmetrical, indicating no obvious evidence of asymmetry and, therefore, did not suggest the presence of any publication biases (Figure 5A) clear analysis of the absence of potential publication bias cannot be made due to a limited number of studies.

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eISSN: 2600-8173
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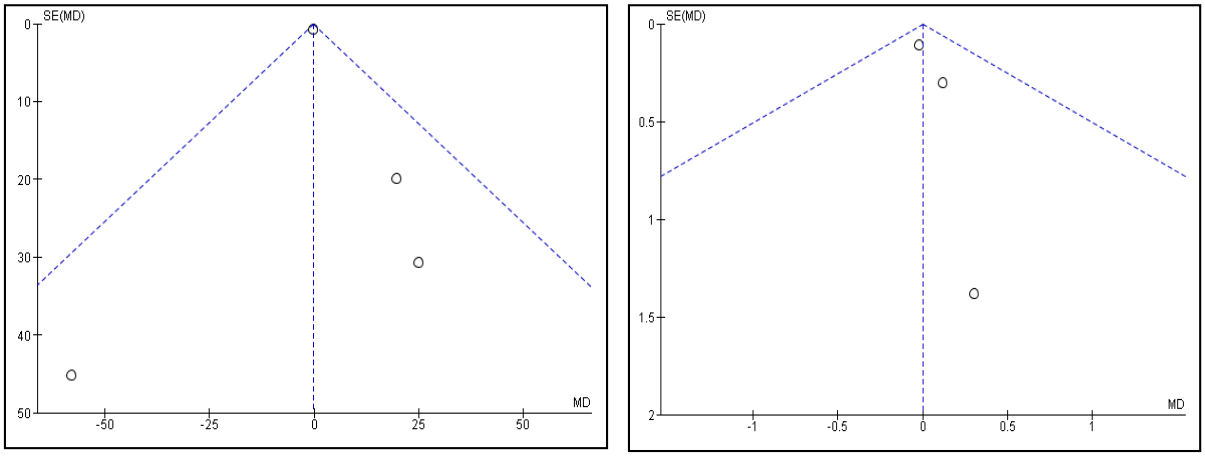

(A) (B)

Figure 5: Funnel plot analysis for studies that assessed the concentration of IL-1β (A). The analysis presented low heterogeneity among the studies and no evidence of publication bias—funnel plot analysis for studies that assessed the concentration of TNF-α (B). The research presented very little heterogeneity among the studies and no evidence of publication bias.

The visual inspection of the funnel plot for all three studies included in the meta-analysis; that assessed the effect of probiotics on TNF-α concentration showed partially symmetrical, indicating no obvious evidence of asymmetry and, therefore, no evidence of publication biases (Figure 5B)

Discussion

Periodontal disease affects approximately 743 million people worldwide, with the global prevalence rising by 57.3% from 1990 to 2010. Periodontitis, a severe periodontal disease, causes tooth loss among adults worldwide. The likelihood of these people suffering from toothlessness and masticatory impairment became higher. As a result, their diet, health, and self-confidence are impacted and impose significant socioeconomic effects and healthcare costs [13]. Besides, antibiotic resistance and the possibility of adverse allergic reactions due to antibiotics or chlorhexidine usage, apart from recolonization of periodontal pathogens following mechanical removal procedures such as scaling and root planning to cure the periodontal infection, might worsen the condition. Moreover, it became economically burdensome for the disease retreatment. Therefore, using probiotics to control and treat periodontal disease gained interest among researchers in recent decades while searching for effective treatment options that offer long–term benefits with minimal risk [14]. Moreover, probiotics were used widely in the medical field and have proven effective in treating inflammatory bowel disease, cancer, liver disease, and genitourinary tract infections [15].

In recent years, several animal studies using *Lactobacillus* spp. and *Bifidobacterium* spp. were conducted, resulting in a reduction of periodontal disease following the administration of probiotic bacteria in these studies [7]. Moreover, numerous clinical research has presented that using probiotics in chewing gums or tablets daily had a lower prevalence of gingivitis and periodontitis along with better clinical indices such as plaque index and probing pocket depth [16].

Probiotics are suggested to modify the systemic immunological parameters in subjects with periodontal disease, resulting in altered inflammatory metabolites in the serum transudate of the gingival sulcus [12]. Therefore, many placebo-controlled trials were conducted to investigate the impact of probiotics on the inflammatory response as gingival crevicular fluid is considered to demonstrate elevated cytokine levels

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with inflammation in gum disease [16]. In one of the previous studies, a significant decrease in the inflammatory cytokines was observed among moderate gingivitis patients following the temporary use of probiotics [16]. Meanwhile, another study demonstrated a higher level of anti-inflammatory cytokines in periodontitis rats treated with probiotics than in control groups [17]. The effectiveness of probiotics to counteract the periodontal pathogen, specifically through host immune modulation, is a potential choice for treating periodontal disease.

Analysis Evaluation

The cytokines analyzed in this study were pro-inflammatory cytokines such as IL-1β and TNF-α. No anti-inflammatory cytokines are evaluated due to limited clinical studies presenting a significant change in the concentration of cytokines after the probiotic administration. This is due to probiotics' uncertain efficacy in performing immunomodulation by increasing the concentration of anti-inflammatory cytokines such as IL-10 in some of the probiotics' strains and dosage [18]. Meanwhile, pro-inflammatory cytokines demonstrated a significant change in the concentration due to multidirectional interaction with the NF-κB pathway, whereby a direct inhibition of transcription factor by probiotics occurs [18]. After probiotic consumption, the current meta-analysis showed no significant reduction in salivary IL-1β and TNF-α concentrations in periodontal disease patients. These findings were against previous clinical research presenting a substantial cytokine reduction in the saliva [10, 19]. Moreover, another study showed a significantly lower level of IL-1β and ratio of IL-1β/IL-10; after topical administration of probiotic bacteria from the genus *Bifidobacterium* [20]. In contrast with this finding, some studies presented a substantial increase in the concentration of IL-1β following probiotics administration [12]. Meanwhile, some researchers could not discover any significant impact on the concentration of cytokines in the saliva between the probiotic and placebo interventions [9, 21].

IL-1β and TNF-α are pro-inflammatory cytokines that can cause tissue damage and bone loss in periodontal disorder. According to the previous study, both were pivotal cytokines in this disease [22]. Therefore, it became one of the reasons for accessing their concentration after probiotic intervention in the current study. TNF-α is the first cytokine produced in all species, followed by IL-1β and IL-6, and IL-8 during inflammation [22]. Both IL-1β and TNF-α are synergistic in many activities, such as enhancing movement to invade interstitial connective tissue from the vascular lumen by inducing the expression of adhesion particles in endothelial cells and leukocytes, increasing the phagocytic activity and osteoclast formation, stimulating the synthesis of lysins in various type of cells, and promoting the upregulation of chemotactic mediators [23].

The mechanisms by which probiotic administration can affect the salivary cytokines remain inconclusive. However, some studies suggested that probiotics suppress the nuclear factor kappa B (NF-κB) pathways and promote the accumulation of T regulatory cells to reduce the secretion of pro-inflammatory cytokines or chemokines [24]. As a result, the concentration of anti-inflammatory metabolites, including IL-4, IL-10, and TGF-β are elevated [25]. These metabolites will then induce the expression of other co-stimulatory surface molecules and soluble cytokines and inhibit IL-12 and other pro-inflammatory cytokines from phagocytic cells. As a result, the proliferation and differentiation of T and B cells and the production of IL-2, IFN-γ, and TNF- α, will be suppressed [25]. As for the present meta-analysis, several limitations must be considered. First, we could not conduct a meta-analysis on other cytokines or chemokines due to a lack of publications. Secondly, most studies did not appropriately report the effect sizes, contributing to fewer included studies. Besides that, the study population of one of the included studies consisted of healthy female adults with no clinical signs of periodontal diseases. The probiotic effect on IL-1β and TNF-α was evaluated using experimental teeth with gingivitis [12]. Although the study fulfilled the selection criteria, this clinical scenario was unlikely to be accurate as it did not represent the population associated with the pathogenesis of the disease. The short period of the intervention and frequency of probiotic intake in the

included studies must also be highlighted, as the ability of probiotics to have a favorable impact on oral health is not excluded.

Conclusion

The increasing prevalence of periodontal disease worldwide has underscored the imperative for using probiotics to mitigate the extent of inflammation associated with this condition, given that conventional periodontal therapies have demonstrated diminished efficacy in halting the progression of periodontal disorders. The beneficial impact of probiotics in the context of periodontal disease arises from their capacity to modulate the immune response by reshaping the equilibrium between pro-inflammatory and anti-inflammatory cytokines. While prior clinical investigations have appraised various concentrations of inflammatory cytokines among individuals afflicted with periodontal disease, this meta-analysis study selectively focuses on examining pro-inflammatory cytokine concentrations, specifically IL-1β and TNF-α. These cytokines are emphasized due to their prominent roles as primary targets influenced by probiotics in patients with periodontal disease across all the studies in this analysis. Conversely, the impact of probiotics on other cytokines appears to be less pronounced and inconsistently observed in the included studies. Nevertheless, it is noteworthy that the administration of probiotics orally did not yield a statistically significant reduction in IL-1β and TNF-α concentrations in individuals with periodontal disease. This outcome may be attributed to the relatively modest sample sizes and the limited availability of pertinent data within the existing body of research. Consequently, it is imperative that additional clinical trials, characterized by sound methodological design, be conducted to comprehensively evaluate the effect of probiotics on a broader spectrum of pro-inflammatory and anti-inflammatory cytokines. Finally, this study might enrich the current literature by providing a consolidated view of the impact of probiotics on periodontal inflammation. Its findings contribute to ongoing discussions and research efforts in the field, highlighting the potential benefits and the need for further investigation in this area of dental health.

Funding

The author(s) received no specific funding for this work.

Conflict of Interest Disclosure

None to declare

References

1. Nazir, M. A. Prevalence of periodontal disease, its association with systemic diseases and prevention. International Journal of Health Sciences 2017; 11(2), 72–80. http://www.ncbi.nlm.nih.gov/pubmed/28539867
2. Ji, S., Choi, Y. S., & Choi, Y. Bacterial invasion and persistence: Critical events in the pathogenesis of periodontitis? In Journal of Periodontal Research 2015; Vol. 50, Issue 5, pp. 570–585. Blackwell Munksgaard. https://doi.org/10.1111/jre.12248
3. Kassebaum, N. J., Smith, A. G. C., Bernabé, E., Fleming, T. D., Reynolds, A. E., Vos, T., Murray, C. J. L., & Marcenes, W. Global, Regional, and National Prevalence, Incidence, and Disability-Adjusted Life Years for Oral Conditions for 195 Countries, 1990-2015: A Systematic Analysis for the Global Burden of Diseases, Injuries, and Risk Factors. Journal of Dental Research 2017; 96(4), 380–387. https://doi.org/10.1177/0022034517693566
4. Gupta, G. Probiotics and periodontal health. *Journal of Medicine and Life* 2011; *4*(4), 387–394. https://doi.org/10.9790/0853-13853740
5. Chatterjee, A., Bhattacharya, H., & Kandwal, A. Probiotics in periodontal health and disease. In *Journal of Indian Society of Periodontology*. Wolters Kluwer Medknow Publications 2011; Vol. 15, Issue 1, pp. 23–28. https://doi.org/10.4103/0972-124X.82260
6. Mahasneh, S., & Mahasneh, A. Probiotics: A Promising Role in Dental Health. *Dentistry Journal* 2017; *5*(4), 26. https://doi.org/10.3390/dj5040026
7. Jayaram, P., Chatterjee, A., & Raghunathan, V. Probiotics in the treatment of periodontal disease: A systematic review. In Journal of Indian Society of Periodontology 2016; Vol. 20, Issue 5, pp. 488–495. Medknow Publications. https://doi.org/10.4103/0972-124X.207053

8. Teughels, W., Loozen, G., & Quirynen, M. Do probiotics offer opportunities to manipulate the periodontal oral microbiota? Journal of Clinical Periodontology 2011; 38(SUPPL. 11), 159–177. https://doi.org/10.1111/j.1600-051X.2010.01665.x
9. Keller, M. K., Brandsborg, E., Holmstrøm, K., & Twetman, S. Effect of tablets containing probiotic candidate strains on gingival inflammation and composition of the salivary microbiome: A randomised controlled trial. Beneficial Microbes 2018; 9(3), 487–494. https://doi.org/10.3920/BM2017.0104
10. Kuru, B. E., Laleman, I., Yalnızoğlu, T., Kuru, L., & Teughels, W. The Influence of a Bifidobacterium animalis Probiotic on Gingival Health: A Randomized Controlled Clinical Trial. Journal of Periodontology 2017; 88(11), 1115–1123. https://doi.org/10.1902/jop.2017.170213
11. Szkaradkiewicz, A. K., Stopa, J., Tomasz, •, Karpin´ski, M., & Karpin´ski, K. Effect of Oral Administration Involving a Probiotic Strain of Lactobacillus reuteri on Pro-Inflammatory Cytokine Response in Patients with Chronic Periodontitis 2014. https://doi.org/10.1007/s00005-014-0277-y
12. Hallström, H., Lindgren, S., Yucel-Lindberg, T., Dahlén, G., Renvert, S., & Twetman, S. Effect of probiotic lozenges on inflammatory reactions and oral biofilm during experimental gingivitis. *Acta Odontologica Scandinavica* 2013; *71*(3–4), 828–833. https://doi.org/10.3109/00016357.2012.734406
13. Tonetti, M. S., Jepsen, S., Jin, L., & Otomo-Corgel, J. Impact of the global burden of periodontal diseases on health, nutrition and wellbeing of mankind: A call for global action. Journal of Clinical Periodontology 2017; 44(5), 456–462. https://doi.org/10.1111/jcpe.12732
14. Eke, P. I., & Genco, R. J. CDC Periodontal Disease Surveillance Project: Background, Objectives, and Progress Report. Journal of Periodontology 2007; 20078(7s), 1366–1371. https://doi.org/10.1902/jop.2007.070134
15. Mohanty, R., Nazareth, B., & Shrivastava, N. The potential role of probiotics in periodontal health. RSBO. 2012.
16. Twetman, S., Derawi, B., Keller, M., Ekstrand, K., Yucel-Lindberg, T., & Stecksén-Blicks, C. Short-term effect of chewing gums containing probiotic Lactobacillus reuteri on the levels of inflammatory mediators in gingival crevicular fluid. Acta Odontologica Scandinavica 2009; 67(1), 19–24. https://doi.org/10.1080/00016350802516170
17. Ricoldi, M. S. T., Furlaneto, F. A. C., Oliveira, L. F. F., Teixeira, G. C., Pischiotini, J. P., Moreira, A. L. G., Ervolino, E., Oliveira, M. N. de, Bogsan, C. S. B., Salvador, S. L., & Messora, M. R. Effects of the probiotic Bifidobacterium animalis subsp. lactis on the non-surgical treatment of periodontitis. A histomorphometric, microtomographic and immunohistochemical study in rats. PLOS ONE 2017; 12(6), e0179946. https://doi.org/10.1371/JOURNAL.PONE.0179946
18. Shadnoush, M., Hosseini, R. S., Mehrabi, Y., Delpisheh, A., Alipoor, E., Faghfoori, Z., Mohammadpour, N., & Moghadam, J. Z. Probiotic yogurt affects pro- and anti-inflammatory factors in patients with inflammatory bowel disease. Iranian Journal of Pharmaceutical Research 2013; 12(4), 929–936. https://doi.org/10.22037/ijpr.2013.1351
19. Kim, J. W., Jung, B. H., Lee, J. H., Yoo, K. Y., Lee, H., Kang, M. S., & Lee, J. K. Effect of Weissella cibaria on the reduction of periodontal tissue destruction in mice. Journal of Periodontology 2020; 91(10), 1367–1374. https://doi.org/10.1002/JPER.19-0288
20. Oliveira, L. F. F., Salvador, S. L., Silva, P. H. F., Furlaneto, F. A. C., Figueiredo, L., Casarin, R., Ervolino, E., Palioto, D. B., Souza, S. L. S., Taba, M., Novaes, A. B., & Messora, M. R.. Benefits of Bifidobacterium animalis subsp. lactis Probiotic in Experimental Periodontitis . Journal of Periodontology 2017; 88(2), 197–208. https://doi.org/10.1902/jop.2016.160217
21. Jørgensen, M. R., Keller, M. K., Kragelund, C., Hamberg, K., Ericson, D., Nielsen, C. H., & Twetman, S. Lactobacillus reuteri supplements do not affect salivary IgA or cytokine levels in healthy subjects: A randomized, double-blind, placebo-controlled, cross-over trial. Acta Odontologica Scandinavica 2016; 74(5), 399–404. https://doi.org/10.3109/00016357.2016.1169439
22. Howells, G. Cytokine networks in destructive periodontal disease. Oral Diseases 1995; 1(4), 266–270. https://doi.org/10.1111/j.1601-0825.1995.tb00192.x
23. Graves, D. T., Delima, A. J., Assuma, R., Amar, S., Oates, T., & Cochran, D. Interleukin-1 and Tumor Necrosis Factor Antagonists Inhibit the Progression of Inflammatory Cell Infiltration Toward Alveolar Bone in Experimental Periodontitis. Journal of Periodontology, 1998; 69(12), 1419–1425. https://doi.org/10.1902/jop.1998.69.12.1419
24. Balta, M. G., Papathanasiou, E., Blix, I. J., & Van Dyke, T. E. Host Modulation and Treatment of Periodontal Disease. In *Journal of Dental Research*. SAGE Publications Inc. 2021; https://doi.org/10.1177/0022034521995157
25. Donkor, O. N., Ravikumar, M., Proudfoot, O., Day, S. L., Apostolopoulos, V., Paukovics, G., Vasiljevic, T., Nutt, S. L., & Gill, H. Cytokine profile and induction of T helper type 17 and regulatory T cells by human

https://doi.org/10.37231/ajmb.2023.1.S.693
https://journal.unisza.edu.my/ajmb

peripheral mononuclear cells after microbial exposure. Clinical and Experimental Immunology, 2011; 167(2), 282–295. https://doi.org/10.1111/j.1365-2249.2011.04496.x