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Review Article

Dentistry Section

Association between Oral Probiotic Streptococcus Supplements and Salivary *Streptococcus mutans* Count in Human Study: A Systematic Review

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ABSTRACT

Introduction: Probiotics in caries prevention is a subject of growing interest due to their specific activities and inhibitory effects on the cariogenic organisms. Though numerous reviews have evaluated the effect of probiotics in caries prevention, very few have focussed on the probiotic streptococcus strains, none of them have emphasised on the effect of probiotic Streptococcus strains on the salivary *Streptococcus mutans (S. mutans)* count.

Aim: To evaluate the current literature on the association between oral probiotic Streptococcus supplements on the *S. mutans* level.

Materials and Methods: In the present systematic review a focused PICO question was formulated. Comprehensive literature searches were independently performed by two reviewers in various electronic databases. Randomised control trials in humans in which oral probiotic Streptococcus supplements were used to alter the salivary *S. mutans* count were included. Risk of bias and data extraction of the included articles was performed.

Results: Five studies were included in the qualitative synthesis. The quality of the included studies was quite low as only one among the five studies had moderate risk of bias while all others had a high risk of bias.

Conclusion: Within the limitations of the available data, it can be concluded that probiotic Streptococcus supplements have a positive effect on reducing the *S. mutans* levels as long as they are being used.

Keywords: Dental caries prevention, Oral health, Probiotic supplements

INTRODUCTION

Dental caries is one of the most common microbial diseases in industrialised countries and has an enormous social impact [1]. The disease is elicited over time by the interaction among cariogenic microorganisms, a diet rich in fermentable carbohydrates and a range of host factors like saliva secretion rate, buffer capacity and pH [1,2]. The role of microbes in the aetiology of dental caries is well defined and it plays a fundamental role in the onset of the disease [3]. Research in the literature has proved the presence of microbial biofilms which is a well-organised microbial community that is attached to the tooth surface and is the main cause of various pathological processes [4].

Studies have shown oral cavity to have its own ecosystem with intricate ecology of microbial species [5-8]. Changes in the oral cavity caused by a variety of factors like increased consumption of fermentable carbohydrates can shift the homeostasis of this ecosystem to particularly acidophilic bacteria known to be damaging to the tooth surface resulting in caries formation [9]. *Mutans Streptococci* (MS), a cluster of acidogenic plaque inhabiting species, are recognised as a major constituent of most active dental caries lesions. Among these, *S. mutans* have been principally responsible in dental caries development in humans [10].

Preventive strategies for dental caries predominantly focus on controlling the various caries risk factors mainly based on dietary modifications and enhancing host resistance [11,12]. Though in some cases, antibacterial agents are administered to reduce the cariogenic microflora, yet a complete eradication of the caries associated microorganisms is impossible to attain [13]. An emerging preventive strategy for dental caries is the use of probiotics. Probiotics are by definition, "Live microorganisms which, when administered in adequate amounts, confer a health benefit to the host" as described by World Health Organisation (WHO) [14]. The most utilised probiotic strains belong to *Lactobacillus, Bifidobacterium* and Streptococcus genera [15].

Literature shows numerous studies that have researched the effect of *Lactobacillus* and *Bifidobacterium* probiotic species on dental caries, but these species have their own limitations in terms of colonisation on oral tissues [13-16]. Over the recent years, there is an emerging interest in various probiotic streptococcus strains as a caries preventive strategy. Although there are numerous systematic reviews that evaluate the effect of probiotics on caries prevention, very few have focussed on the probiotic streptococcus strains [17-19]. Furthermore, none of them have emphasised on the effect of probiotic streptococcus strains on the salivary *S. mutans* count. Thus, this review aimed at systematically evaluating the current literature on the association between oral probiotic streptococcus supplements on the *S. mutans* level. The hypothesis of the systematic review was that the administration of probiotic streptococcus supplements might play a role in altering the salivary *S. mutans* levels in humans. The primary outcome variable of interest was *S. mutans* colony count.

MATERIALS AND METHODS

The protocol of the systematic review was registered on the PROSPERO database (Reg No. CRD42021255880). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement recommendations for reporting the systematic review were followed.

Focused PICO question: What is the association between oral probiotic *Streptococcus* supplements on the salivary *S. mutans* levels, in healthy humans?

Literature Search Strategy

The review was conducted during March 2021 to June 2021. Two reviewers (first and second author) performed a comprehensive

literature search for studies evaluating the effect of probiotic streptococcus strains on the *Mutans Streptococci* count in the oral cavity according to specific search terms until Dec 2020 using the electronic databases: Pubmed, Google Scholar, Trip medical data base and Ebsco. Grey literature (OpenGrey) was also searched. Additional manual search was performed that includes the bibliographies of previous reviews on the subject and bibliographies of all publications cited in these articles.

Search terms: MeSH Browser was accessed to identify entry terms and compose the final Boolean searches. The following search terms or equivalent were used: dental caries, dental plaque, *streptococcus sobrinus*, *S. mutans*, probiotics, randomised controlled trial. The search terms were adapted for each database.

Eligibility criteria: Studies that focused on the use of probiotic streptococcus supplements which directly or indirectly alter the salivary *S. mutans* level were included for the review. Only randomised control trials and clinical studies published in journals were included. Articles published in English alone were included, due to the virtual absence of research published in other languages.

Inclusion and Exclusion criteria: All in-vitro studies and in-vivo studies that did not focus on administration of probiotic streptococcus supplements for caries prevention and studies where probiotic streptococcus supplements were administered for other reasons were excluded from the review process. Systematic reviews and meta-analysis, in vitro studies and studies not involving human participants were excluded from the review.

Study selection: Abstracts of all selected papers were by the two evaluators (first and second author) independently. When information present in the title and abstract was insufficient, the full text version was retrieved for further assessment. A comparison of 19 different searches was carried out to delete the repeated entries. Full text format was obtained for all the articles that met with the inclusion and exclusion criteria.

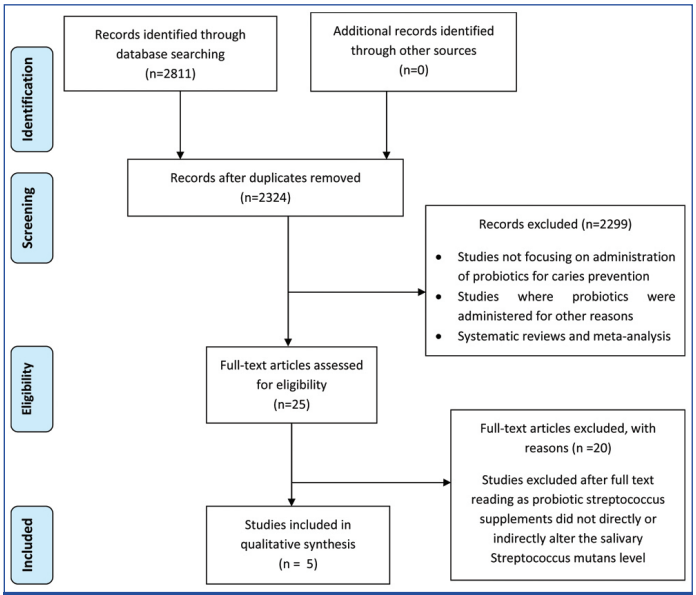
Data extraction: Data extraction form was created using Microsoft Excel and two independent reviewers extracted the data from all the selected articles. Disagreements between the reviewers were solved by consulting a third reviewer (third author). The data extraction form contained the following details: author and year, design, probiotic strains, form of probiotic, sample size, population, control, trial period, primary outcome, results and conclusion. Data extracted from each article was tabulated using Microsoft Excel version 2016.

Quality and risk of bias assessment: The quality assessment of included studies was carried out by two independent reviewers (first and second author) using the Cochrane assessment tool for assessing risk of bias in randomised control trials [20]. All assessments were done at the individual study level. The assessments were done based on the seven criteria which included random sequence generation, generation, allocation concealment, blinding of participants and professionals, blinding of outcome assessment, incomplete outcome data, selective reporting and other possible sources of bias. During this assessment process, any disagreements were resolved by an expert in the field (fourth author).

Assessment of risk of bias for each domain was scored following the handbook for systematic reviews of interventions [21]. Each included study was evaluated individually for each domain and recorded as '+' for low risk of bias, '-' for high risk of bias and '?' representing unclear risk of bias. When all these domains had a low risk of bias, the article was classified as low risk of bias. When one or two of these domains were assessed as high risk or unclear risk, the study was regarded to have a moderate potential risk of bias. The risk of potential bias was high when three or more domains had a high or unclear risk of bias independently. No restrictions were made to exclude papers from qualitative analysis based on risk of bias. The risk of bias graphs was plotted using RevMan 5.4® (Cochrane Collaboration, Oxford, UK).

RESULTS

Study selection: The complete search process that was applied in the systematic review is illustrated in [Table/Fig-1]. Screening of the database identified 2811 records as shown in [Table/Fig-2] and 2324 records remained after removing duplicates. After reading the title and abstract further 2299 records were removed and 25 remained. The full text of these 25 studies was assessed thoroughly for eligibility and 19 were further excluded as they did not meet the eligibility criteria. Thus, five studies were included in this qualitative synthesis [6,17-20].



[Table/Fig-1]: Showing the PRISMA Flow Diagram for the search process.

Keywords	PubMed	Google Scholar	Trip	Ebsco	Open Grey	Manual Search
Dental caries, Dental plaque, *Streptococcus sobrinus*, *S. mutans*, Probiotics randomised controlled trial	17	145	2523	126	0	0

[Table/Fig-2]: Shows the keywords used to search the databases and the number of articles retrieved from the databases.

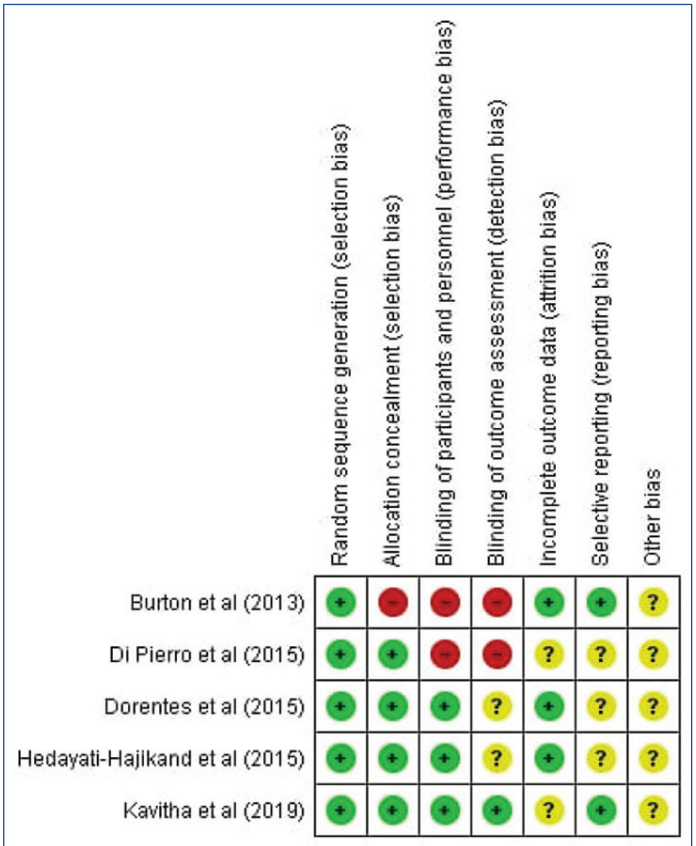
Characteristics of the included studies: The characteristics of the five included studies are listed in [Table/Fig-3] [10,21-24]. Parallel study design was predominantly used in all five studies. Double blinding was done in only one study [6,20] among the five trials included for the review. Among the five studies two of them tested the *Streptococcus salivarius* M18 [10,21] while the others used more than one species of Streptococcus. Three studies used lozenges form of probiotics [10,21] while the other two studies used the tablet form [10,22-24]. Four studies used a placebo for control [22-24] while one study used an untreated group as the control [20].

The number of participants in these studies ranged from 40 [10,24] to 138 [21,22] and the age of the participants ranged from two years [22] to 17 years [21,22]. The intervention period ranged from two weeks [23,24] to one year [22,24]. In two studies, outcome was assessed immediately after the intervention period [21,22] while the other three studies had a follow-up period ranging from two weeks [23] to five months [10].

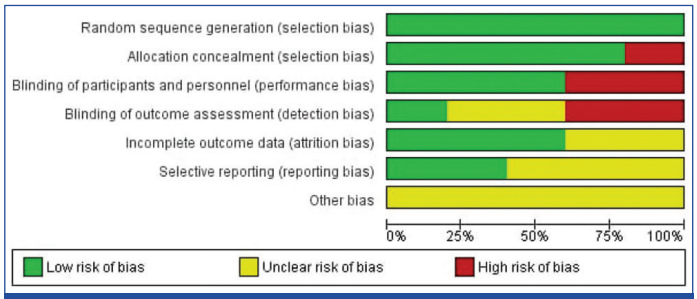
Risk of bias: The assessment of risk of bias within the selected studies is presented in [Table/Fig-4,5]. Four studies among the five included studies were considered to have a high risk of bias as three or more domains had a high or unclear risk of bias [10,21-23]. One study among them was considered to have a moderate risk of bias as only two of the domains were assessed as high risk or unclear risk [24].

Author	Year of study	Design	Probiotic strains	Form of probiotic	Sample size	Age	Control	Intervention period	Follow-up period	Primary outcome	Results and conclusion
Kavitha M et al., [24]	2019	Double blind randomised controlled trial	• *Streptococcus faecalis* T 1110 (30 million) • *Clostridium butyricum* TO A (2 million) • *Bacillus mesentricus* TO A (1 million) • *Lactobacillus sporogenes* (50 million)	Lozenge	60	6-12 year	Placebo	4 week	6 month	Analysis of *S. mutans* and serotypes e, f, and k level	A significant reduction of *S. mutans* was seen after 1-month intervention and 6 months follow-up
Cortés-Dorantes, N et al., [23]	2015	Randomised controlled trial	• *Streptococcus uberis* KJ2TM • *Streptococcus oralis* KJ3TM • *Streptococcus rattus* JH145TM (ProBiora3)	Oral tablets	40	4-6 year	Tablets without probiotics	2 week	2 week	Change in Relative Light Units (RLU)	Reduction of RLU values
Pierro FD et al., [21]	2015	Randomised controlled study	*Streptococcus salivarius* M18 (BLIS M18)	Lozenges	76	6-17 year	Untreated	3 month	-	Cariogram change in chances of avoiding new dental caries development	Chances of avoiding new dental caries development increased
Hedayati-Hajikand T et al., [22]	2015	Randomised controlled trial	• *Streptococcus uberis* KJ2TM • *Streptococcus oralis* KJ3TM • *Streptococcus rattus* JH145TM (ProBiora3)	Tablets	138	2-3 year	Placebo	1 year	-	Prevalence and increment of initial and manifest caries lesions	Reduced early childhood caries development could
Burton JP et al., [10]	2013	Randomised double-blind, placebo-controlled	*Streptococcus salivarius* M18	Lozenges	100	5-10 year	Placebo	3 month	4 month	• Changes to their plaque score and gingival and soft-tissue health • Salivary levels of *S. salivarius, S. mutans, lactobacilli*, β-haemolytic streptococci and Candida species	Reduced *S. mutans* counts

[Table/Fig-3]: Shows the characteristics of the five studies included in the systematic review [10,21-24].



[Table/Fig-4]: Assessment of risk of bias within the selected studies [10,21-24].



[Table/Fig-5]: Illustrating the risk of bias among the included studies.

Outcome assessment: [Table/Fig-3] depicts all relevant primary outcomes assessed in the studies included. The studies were heterogeneous with regards to the outcomes assessed. The parameters evaluated were reduction in *S.mutans* [10,24], reduction in relative light units [23], chance of avoiding new caries development [21,22] and reduction in early childhood caries [18]. Two of the included studies showed a reduction of *S.mutans* [10,24] while one study showed a reduction in the chance of developing new caries [21] and new childhood caries [22] due to the reduction in the *S.mutans* count and one study showed a reduction in relative light units [23].

DISCUSSION

The purpose of this systematic review was to investigate the association between oral probiotic supplements and salivary *S. mutans* levels in the human population. Probiotics act by replacing and displacing the cariogenic bacteria, mainly *S. mutans* [25]. Several mechanisms of action have been described in the

literature, some fully not understood. Several local and systemic effects that include adhesion, co-aggregation, competitive inhibition, production of organic acids and bacteriocin-like compounds and immune modulation [26]. One such mechanism is that oral probiotics potentially reduce oral *S. mutans* levels by either directly out- competing *S. mutans* for their favoured ecological niche or by producing extracellular substances that diffuse or kill *S. mutans* within the plaque [27]. Thus elevated levels of the *S. mutans* have always been an index for cariogenic activity [28,29]. Hence in this systematic review, change in the salivary *S. mutans* levels was the outcome that was assessed.

Assessing the risk of bias is very relevant as it evaluates important aspects of the study design, corresponding to the internal validity of the studies included. Seven domains were chosen to evaluate the quality of the studies. Among these, four domains including random sequence generation, generation, allocation concealment, blinding of participants and professionals, and blinding of outcome assessment are considered very essential. This is due to the fact that correct randomisation guarantees the chance of being allocated in either the test or the control group. In addition to this, allocation concealment is also equally important as it protects the randomisation procedure. Both the blinding process is important parts of the scientific method, used to prevent research outcomes from being influenced by the placebo effect or observer bias [18].

Inexorably, there was variability among the studies included in the systematic review. This heterogeneity may be related to methodology, clinical factors like specific interventions or patient characteristics and the statistical methods used [18]. Among the five clinical trials included, differences were observed that included the patient characteristics, Streptococcus species used as probiotics, the form of probiotics used, duration of treatment and evaluation time points.

Results described by various clinical trials included in this review were encouraging but the scientific evidence is still unclear and often not very high [10,21-24]. Most clinical trials that were reviewed had a very small sample size and have reported the ability to reduce the *S. mutans* count regardless of the streptococcus strain used and the duration of use [21,23,24]. However, probiotic bacteria are not able to colonise the oral cavity permanently [30], hence a continuous daily intake is required. Almost all the included studies demonstrated a daily intake of the streptococcus supplements. This may have been a compliance aspect in these studies that needs to be considered.

Two of the included studies tested only the effect of *streptococcus salivarius* M18 supplements [10,21]. The results of these trials have demonstrated that *streptococcus salivarius* M18 supplements reduced the *S. mutans* counts [10] thereby reducing the chance to develop new carious lesions [21]. The outcome of this study is considered to be attributable to the specific anticariogenic property of this strain, which after colonising the oral mucosa, is able to release bacteriocins, limiting the growth of *S.mutans* and *S. sobrinus* and the enzyme dextranase and urese, catalysing the breakdown of dextran and hydrolysis of urea [21]. If these preliminary results can be confirmed by long-term clinical studies with a larger number of subjects, the practical application of strain M18 could be proposed in future as an effective tool for caries prevention.

Theoretically, increased use of probiotics should lead to an increase in the caries risk due to biofilm formation and resulting increased acid production [14]. Thus, this aspect was analysed in one of the included studies [21] and the results showed that the among children, the chance to avoid new caries formation increased with the use of salivarius M18. Among the included studies, another study by Hedayati-Hajikand T et al., demonstrated a significant reduction of early childhood caries following daily intake of oral probiotic tablets [22].

Limitation(s)

Limitations of this study were that due to the heterogeneity of the included studies, pooling of data was not possible. Though three among the five included studies have employed different measures to evaluate the effect of the probiotic streptococcus supplements, they were a direct or indirect effect of reduction in the salivary *S. mutans* count [21-23]. Hence, those studies were also included in the systematic review though they did not directly measure the reduction in the *S. mutans* count. Validity of the studies and the interpretation of the results are reduced by the methodological weakness and this may lead to biased findings. In general, the quality of the included studies was quite low as only one among the five studies had moderate risk of bias while all others had a high risk of bias. There is a demand for progressive improvement in the scientific evidence concerning the effect of oral probiotic streptococcus supplements on the salivary *S. mutans* levels which is a factor contributing to the chance to develop new carious lesions. Future studies need to focus on the design of clinical research to improve the level of evidence in the most appropriate species of streptococcus to be used as probiotic, its optimal concentration, ideal vehicle, the dosage and intervention period.

CONCLUSION(S)

Within the limitations of the available data, it can be concluded that probiotic streptococcus supplements have a positive effect on reducing the *S. mutans* levels as long as they are being used. This may indicate a positive possible effect on the chance to develop new carious lesions. There is a need for well-designed long term trials to examine the effect of these products on the caries development.

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- iThenticate Software: Mar 09, 2022 (25%)

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