Probiotic Streptococcus A12 Strain in Caries Prevention: A Systematic Review

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Abstract

Background: Dental Caries is a biofilm-mediated multi factorial disease affecting around 5 billion people worldwide. A consensus is now emerging that caries preventive measures should not only correct the environmental pressures responsible for the plaque biofilm dysbiosis, but also help to maintain a healthy resident microbiome which plays a crucial role in preventing caries and promoting oral health. This PROSPERO registered review (registration no 166695) aimed to examine the evidence on the role of probiotic Streptococcus A12 in caries prevention.

Objectives: To know the effectiveness of A12 strain in caries prevention in early stages of disease onset.

Intervention: Streptococcus A12 strains.

Results: A preliminary search yielded a total of 2630 studies recorded through database searching and 23 additional records were identified through manual search. From 2653 articles, 2504 were excluded based on screening through review of titles. 8 articles were included for qualitative synthesis. Streptococcus A12 strains demonstrates antimicrobial efficacy by neutralization of the environment by arginine metabolism.

Conclusion: Streptococcus A12 strains demonstrates antimicrobial efficacy by neutralization of the environment by arginine metabolism, which leads to the reduction in Streptococcus mutans count and helps in lowering the acidic nature of saliva is the potential strength of A12 strain. Due to a lack of controlled clinical studies on probiotics for caries prevention, evidence on their caries-preventive potential is weak. Future studies are needed to examine the probiotics as a potential agent against cariogenic pathogens.

Keywords: *Dental caries, Probiotics, Probiotic Streptococci, Streptococcus A12, caries prevention.*

Introduction

Dental Caries belongs to a group of diseases that are considered "complex" or multifactorial, with no single causation pathway, and therefore are not amendable to simplistic preventive solutions such as the elimination of one type of organism.[1] Microbial culture techniques have demonstrated that Mutans Streptococci or Lactobacilli, can contribute to the caries process at different stages[2] and Candida Albicans can significantly enhance the cariogenic virulence of plaque biofilm.[3] Although many preventive and interceptive treatments are available, dentalcaries is still a constant concern in children. "Fluorides" being highly effective and economicalmay not be sufficient alone to prevent dental caries. Even with regular use of fluoride, carieslesions can still develop when there are more than 6 dietary exposures per day.[4] A consensus is now emerging that caries preventive measures should aim not only to correct the environmental pressures of the plaque biofilm but also help maintain a healthy microbially diverse, resident

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microbiota.[5] Preventive and restorative products should target only cariogenic bacteria without effecting the resident oral microflora or they should inhibit only the virulence factor.[6] A healthy oral microbiome is important in preventing dental caries and understanding it has become mandatory. The oral cavity is composed of a diverse group of microbial species that are harmful as well as healthy.[7] Probiotics are strains of live microorganisms which when administered in adequate amounts provides a health benefit on the host. Most probiotics are Gram-positive bacteria that belong to the genera Lactobacillus or Bifidobacterium. Studies based on the use of the intestinal probiotics Lactobacillus Rhamnosus GG, Lactobacillus Reuteri, and Bifidobacterium have each reported achieving reduced levels of Streptococcus mutans. However, these strains have limitations in terms of their colonization of oral tissues.[8] However very recently, two natural oral commensal species Streptococcus Dentisani and Streptococcus A12 Strains have demonstrated promising probiotic effects against dentalcaries.[9] They not only inhibit growth of mutans streptococcus but also moderate plaque pH through their arginolytic actions.[10] Streptococcus A12 competes with the dental pathogen Streptococcus mutans using various gene products with diverse functions. A12 displayed enhanced competitiveness by (i) disrupting intercellular communication pathways of S. mutans, (ii) sensing and resisting antimicrobial peptides, and (iii) producing factors involved in theproduction of a putative antimicrobial compound. The rationale of this systematic review is toreview the published literature with the purpose of knowing the importance of using streptococcus A12 as a preventive method for dental caries management.

Method

The present study is reported as per PRISMA-ScR guidelines.

Study Protocol: The study protocol was prepared prior to conducting the study selection and registered on PROSPERO with registration no.166695. The protocol was drafted using PRISMA-ScR guidelines and included the following sections–study aim, search strategy, eligibility criteria, outline for data summary charting as per consensus by all the contributors of the study.

Inclusion Criteria: Any in vitro study, clinical trial, systematic review with/without meta-analysis, umbrella review/meta-evaluation, narrative review addressing the role of streptococcus A12 in caries prevention were included in the review.

Exclusion Criteria: Studies with no keywords, specific components, commentaries, opinions, and articles in languages other than English were excluded from the review.

Database Search Strategy: A search strategy was developed using keywords related to role of probiotic Streptococcus A12 strain in caries prevention. Data was searched through the database, PubMed, and Google scholar from 1st January 2001 till 31st December 2019. Further, references of the identified articles were hand searched prior to initiating the screening process to identify potential records for inclusion in the review. All possible search using the search strategy was conducted until December 2019. The search strategy included the use of the keyword “Probiotics” whereby “probiotic” was limited and the wild card specified any further number of characters for search by the databases. Then, a Boolean operator “AND” was incorporated in the database search to connect the keyword “caries”. The keyword “prevention” was not included in the search to identify a larger number of records on probiotic and caries using the most significant keywords.

Study selection and data charting: Irrespective of the study design, peer-reviewed articles in English that fulfilled the inclusion/exclusion criteria, addressing the role of probiotic Streptococcus A12 strain in caries prevention were eligible for inclusion. The base map for final inclusion was—Population (Any),Intervention-(Probiotic Streptococcus A12),Outcome- (Caries prevention)

The study selection and data charting process were performed by two independent reviewers (NQ and MP). Disagreements in the process were resolved by seeking expert advice from two other reviewers (APTand PP). The articles for final inclusion in the review were as per the consensus of all the reviewers. The data charted for the included studies was as per the pre-approved registered protocol. The variables extracted to chart the data were author (year), location, study type and objectives, results and conclusion, and inferred limitations. The charted data was approved and confirmed by all the reviewers prior to summarising the results. Finally, the search yielded 8 studies to be included in the systematic review.

Data Collection Process: The reviewers extracted the data separately from the selected papers. This

information was transferred to a data extraction sheet. Data items that were included for extracting the data were:

1. Author's name- Name of the author
2. Year of publication- Year in which the study was published
3. Purpose of the study- Aim and objectives of the study
4. Study design- Whether the study was in vitro, in vivo, clinical trial, randomized controlled trial
5. Sample size- Sample size for that study
6. Duration of the study- The time for which the study was conducted
7. Study setting- The place where the study was conducted
8. Intervention- Probiotic intervention against cariogenic pathogen.
9. Probiotic Strain - Streptococcus A12 used as a probiotic Strain
10. Adverse effects- Any complications reported
11. Inference- The conclusion of the study
12. Result- Outcome of the study
13. Remark- The remarks by the authors

Results

Evidence Selection: In the evidence selection of this present review, 2630 no of records were identified from databases and 23 additional records were identified through manual searches. From the search of reference lists of identified records, one additional study was identified for possible inclusion. The study was retrieved for screening and eligibility assessment. Therefore, a total of 2653 records were identified. 149 records were screened for title and abstract content; of which 2504 were excluded. Fulltexts of 10 articles were reviewed for eligibility assessment and eventually 8 were included in the review based on the inclusion/exclusion criteria. Since streptococcus A12 was not used as a probiotic in two of the articles. It was the main reason for excluding the min this review.

Evidence insights on Streptococcus A12 for caries prevention: Eight articles that met the inclusion criteria reported to have shown that the strain specific Streptococcus A12 can express high ADS activity under environmental conditions commonly occurring in oral biofilms. It can directly inhibit growth of S. mutans by producing H_2O_2 and can disable bacteriocin production via interference with the CSP-ComDE pathway which may provide substantial protection to a human host against dental caries.[10] Streptococcus dentisani and Streptococcus A12 are two species which show particular promise as potential probiotics. Both species are active colonizers of the tooth surface, increase the pH of dental plaque through the arginolytic pathway and inhibit the growth of mutans streptococci. In addition, Streptococcus A12 produces a challisin-like protease that disrupts pheromone signalling.

Discussion

As per WHO, probiotics are defined as "live micro-organisms which when administered in adequate amounts confer a health benefit on the host".[11] Several invitro studies examining the effect of probiotics on caries prevention have been conducted in the last two decades using different probiotics strains and species; however, probiotic colonization in the oral cavity is transient. Therefore, formulations enhancing probiotics survival are needed to impart long-standing caries-preventive benefits.

Summary of evidence: This systematic review tries to report the role of A12 strain in caries prevention in early stages of disease onset. Baker, J.L discussed the development of novel modalities to prevent caries. The author provided an insight of most promising methodologies in development that exploit the exclusive nature of the healthy oral microbiome. It was concluded that probiotics derived from the dental plaque of healthy individuals sharply antagonize cariogenic species, such as Streptococcus mutans. Meanwhile, targeted antimicrobials allow for the killing of specific pathogens, allowing reestablishment of a healthy microbiome, presumably with its protective effects. The author also stated that the prohibitive cost associated with sufficiently rigorous clinical trials, and the status of dental caries as a non-life-threatening condition would likely to impede the advancement of new therapeutics to market.[12] Lee, K. conducted an in vitro study to explore the ability of a novel oral bacterial isolate, Streptococcus A12, to compete with the dental pathogen Streptococcus mutans using various gene products with diverse functions. Results showed that commensal oral streptococci, like A12, could express high ADS activity under environmental conditions commonly occurring in

oral biofilms. They could also directly inhibit growth of S. mutans by producing H_2O_2 and disable bacteriocin production via interference with the CSP-ComDE pathway.[7] Zaura, E. and Twetman, S. discussed the role of oral pre- and probiotics in caries prevention and caries management. The authors suggested the possibility of prebiotic arginine and arginolytic probiotics as a future synbiotics for caries prevention and management of dental caries and need for the development and evaluation of such a combination was highlighted by the author[13].Poorni et al discussed the importance of using various probiotic Streptococcus strains as a preventive and therapeutic method for dental caries management. The oral probiotic S. salivarius JH produced important in vitro inhibitory activity toward strains of S. mutans and Streptococcus sobrinus, the principal species of MS associated with human dental caries. However, the author stated the lack of clinical research pertaining to the use of probiotic streptococcal strains in caries prevention[8] Philip, Nemphasised the importance of maintaining a healthy diverse oral microbiome for long-term caries control. The authors stated that natural oral commensal species had double probiotic action, as they could not only inhibit the growth of major oral pathogens but also moderate plaque pH through their arginolytic actions. Given the polymicrobial nature of dental caries, it was predicted that diagnostic, preventive, and treatment strategies directed toward specific bacterial species would not be universally effective.[9]Burne, R.Areviewed a healthy microbiome and the mechanisms by which beneficial bacteria promote health is that an inherent characteristic of the most abundant members of the oral flora, those that potentially play the greatest roles in health and disease. The authors stated thatt he microbiome colonizing a healthy tooth actively generated alkaline products from salivary and dietary substrates, neutralizing plaque acids and creating a resting plaque pH that was favourable for remineralization.[14] Elevated resting plaque pH had been correlated with ammonia levels, and a higher resting plaque pH meant that an equivalent amount of acid production from ingestion of fermentable carbohydrates would result in a higher terminal pH in tooth biofilms.[15] Thus,one-way commensals were actively beneficial to dental health was through alkali generation.[16] It was also concluded that the commensals had other active mechanisms to interfere with the growth and/or expression of virulence of S. mutans.[17] About 5 genetic lociof Streptococcus A12 had been identified that influence the competition of A12 with S. mutans. Haung et al. conducted an in vitro study to explore the microbiological, molecular, and genomic basis for the desirable properties of streptococcus A12. In light of the strong correlation between the absence of dental caries and high dental plaque ADS activity, results showed that oral bacteria with constitutionally high ADS expression levels might have significant potential for applications in probiotic therapies to prevent and control dental caries.[10] Laleman et al. evaluated the effect of probiotics in the prevention of caries. The results showed that the probiotic and control group were compared after treatment, significantly more patients in the probiotic group had low mutans streptococci (<105 CFU/ml) counts and significantly less patients had high (>106 CFU/ml) counts. Regarding the Lactobacillus counts, comparing the probiotic and control group at the end of the probiotic use, no significant differences could be observed, neither in low (<104 CFU/ml) nor in high Lactobacillus (>106 CFU/ml) counts. Within the limitations of the available data, authors concluded that probiotics might decrease the mutans streptococci counts suggesting that probiotics could have a positive effect in the prevention of caries.[18]

The results described by various research groups were encouraging, but the scientific evidence is still unclear, and the level of evidence is only moderate. The current systematic review has shown the lack of clinical research pertaining to the use of probiotic streptococcal strain A12 in caries prevention. As there is paucity of clinical research in this field, and the focus of future studies should be on the evaluation of the effect of streptococcal strain A12 on plaque formation, on modulation of the composition of the oral microbiota and their influence on caries risk. Further clinical research is vital to determine the exact dose, treatment time, and ideal vehicles for specific strain of probiotic Streptococcus A12.

Future Recommendations: The Research on probiotic mechanisms employed by Streptococcus A12 provided essential insights into how beneficial bacteria may help maintain oral health, thereby aiding in the development of therapeutics which can improve the practice of clinical dentistry. It can be very well utilized as a preventive routine in paediatric practice under dentists or parents' supervision. Moreover, it can be incorporated in any form like probiotic drinks, pills, tablets or added to existing products like gum, mouthwash, toothpaste etc. Administering probiotic in candies and lollipop can be well accepted by the children.

Conclusion

Based on the findings of our review, it can be concluded that there is insufficient evidence that probiotics can prevent caries, but they can reduce the mutans streptococci counts. Arginine-based probiotics, especially Streptococcus A 12 have been proposed for caries prevention; however, its eligibility for classification as true probiotic needs to be carefully addressed. Due to a lack of clinical studies on probiotics for caries prevention, evidence on their caries-preventive potential is weak. Our review clearly identifies the need to further explore the caries-preventive effects of probiotic to optimize their use in clinical dentistry.

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References

1. Fejerskov O. Changing paradigms in concepts on dental caries: consequences for oral health care. Caries research. 2004;38(3):182-91.
2. Tanner AC, Kressirer CA, Rothmiller S, Johansson I, Chalmers NI. The caries microbiome: implications for reversing dysbiosis. Advances in dental research. 2018 Feb;29(1):78-85.
3. Koo H, Bowen WH. Candida albicans and Streptococcus mutans: a potential synergistic alliance to cause virulent tooth decay in children. Future microbiology. 2014 Dec;9(12):1295-7.
4. Van Loveren C, Duggal MS. The role of diet in caries prevention. International dental journal. 2001 Dec;51(S6):399-406.
5. Devine DA, Marsh PD, Meade J. Modulation of host responses by oral commensal bacteria. Journal of oral microbiology. 2015 Jan 1;7(1):26941.
6. Philip N, Suneja B, Walsh L. Beyond Streptococcus mutans: clinical implications of the evolving dental caries aetiological paradigms and its associated microbiome. British dental journal. 2018 Feb;224(4):219.
7. Lee K, Walker AR, Chakraborty B, Kaspar JR, Nascimento MM, Burne RA. Novel probiotic mechanisms of the oral bacterium Streptococcus sp. A12 as explored with functional genomics. Applied and environmental microbiology. 2019 Nov 1;85(21):e01335-19.
8. Poorni S, Srinivasan MR, Nivedhitha MS. Probiotic Streptococcus strains in caries prevention: A systematic review. Journal of conservative dentistry: JCD. 2019 Mar; 22(2):123.
9. Philip N, Suneja B, Walsh LJ. Ecological approaches to dental caries prevention: paradigm shift or shibboleth?. Caries research. 2018;52(1-2):153-65.
10. Huang X, Palmer SR, Ahn SJ, Richards VP, Williams ML, Nascimento MM, Burne RA. A highly arginolytic Streptococcus species that potently antagonizes Streptococcus mutans. Applied and environmental microbiology. 2016 Apr 1;82(7):2187-201.
11. Bijle MN, Ekambaram M, Lo EC, Yiu CK. Synbiotics in caries prevention: A scoping review. PloS one. 2020 Aug 12;15(8):e0237547.
12. Baker JL, Edlund A. Exploiting the oral microbiome to prevent tooth decay: Has evolution already provided the best tools?. Frontiers in microbiology. 2019 Jan 11;9:3323.
13. Zaura E, Twetman S. Critical appraisal of oral pre-and probiotics for caries prevention and care. Caries Research. 2019;53(5):514-26.
14. Burne RA. Getting to know "The Known Unknowns": heterogeneity in the oral microbiome. Advances in dental research. 2018 Feb;29(1):66-70.
15. Burne RA, Marquis RE. Alkali production by oral bacteria and protection against dental caries. FEMS microbiology letters. 2000 Dec 1;193(1):1-6.
16. Zheng L, Itzek A, Chen Z, Kreth J. Environmental influences on competitive hydrogen peroxide production in Streptococcus gordonii. Applied and environmental microbiology. 2011 Jul 1;77(13):4318-28.
17. Son M, Ahn SJ, Guo Q, Burne RA, Hagen SJ. Microfluidic study of competence regulation in Streptococcus mutans: environmental inputs modulate bimodal and unimodal expression of comX. Molecular microbiology. 2012 Oct;86(2):258-72.
18. Laleman I, Detailleur V, Slot DE, Slomka V, Quirynen M, Teughels W. Probiotics reduce mutans streptococci counts in humans: a systematic review and meta-analysis. Clinical oral investigations. 2014 Jul 1;18(6):1539-52.