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Effects of D-Tagatose on Bacterial Growth of the Genus *Streptococcus*. Systematic Review

Efectos de la D-Tagatosa sobre el Crecimiento Bacteriano del Género *Streptococcus*. Revisión Sistemática

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ABSTRACT: It is currently known that dental caries is one of the most common non-communicable chronic diseases worldwide, whose etiology has been attributed to *Streptococcus*, with the consumption of sweeteners such as D-Tagatose being related to anticariogenic effects. The objective of this study was to analyze the effect of D-tagatose on the proliferation of oral bacteria related to carious lesions. A systematic review of original articles published between 2013 and 2023 in the databases Europe PMC, Medline (PubMed), Cochrane Central, Virtual Health Library and Scopus was carried out, using the following search strategy: "Tagatose OR D-tagatose AND Dental Caries". The quality of the evidence collected being analyzed with the Guidelines for critical review of qualitative studies. The search identified 79 records of which 2 met the eligibility criteria. In general, the selected articles indicate that D-Tagatose in doses between 0.1 to 10 % can inhibit both the bacterial growth of *Streptococcus mutans* and the production of glycosyltransferase-B related to dental biofilm. D-tagatose possibly inhibits the proliferation of oral bacteria related to caries lesions. However, new studies are needed in vivo models that seek to demonstrate these possible anticariogenic effects.

KEY WORDS: tagatose, dental caries, *Streptococcus mutans*, biofilms.

INTRODUCTION

It is currently known that dental caries is one of the most common chronic noncommunicable diseases (NCD) worldwide, defined as a localized process of multifactorial origin that begins after tooth eruption, the result of which determines the softening and formation of cavities in the dental hard tissue, affecting health and quality of life (Palomer, 2006; Moynihan & Kelly 2014; Sheiham & James, 2014; Lamont & Hajishengallis, 2015; Bowel, 2016; Johansson *et al*., 2016; Pitts *et al*., 2017; Hasibul *et al*., 2018; Rossoni *et al*., 2018; Peres *et al*., 2019).

Regarding this pathology, its etiology is commonly attributed to a dysbiosis on the oral biofilm, characterized by the presence of thousands of microorganisms, among which *Streptococcus mutans* stands out as a determining factor of the cariogenic process, both for its adhesion capacity generated from the fermentation of sugars and carbohydrates from the diet and for the demineralization processes caused by low concentrations of hydrogen ions (Palomer, 2006; González Sanz *et al*., 2013; Arweiler & Netuschil, 2016; Giacaman, 2018; Hasibul *et al*., 2018; Chen *et al*., 2019; Nagamine *et al*., 2020). In this context, it is known that an extracellular environment rich in polysaccharides allows the synthesis of glucan polymers related to glucosyltransferase enzymes (GTFs), whose interactions favor of the development of the extracellular matrix, transport capacity and

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carbohydrate metabolism (Lemos *et al*., 2019; Nagamine *et al*., 2020; Sawada *et al*., 2015; Tanner *et al*., 2018; Van Houte *et al*., 1996). In this sense, as D-Tagatose have traditionally been attributed sweetness properties and low or no caloric value, compared to sucrose, in addition to potential effects on the concentration of hydrogen ions related to the prevention of various NCDs (García-Almeida *et al*., 2013; Guo *et al*., 2018; Hasibul *et al*., 2018; Serra-Majem *et al*., 2018), while currently the United States Food and Drug Administration (FDA) has approved since 2003, the use of D-tagatose for daily consumption because it does not generate health complications, This has led the European Union (EU) to designate it as a food ingredient free of restrictions for its use, whose characteristics include an antihyperglycemic potential at postprandial serum level, as well as a preventive capacity on the formation of dental caries and other oral diseases related to the acidogenesis of glucan from the enzymatic process of GTFs in the presence of sucrose (Li *et al*., 2012; Sawada *et al*., 2015; Roy *et al*., 2018; Serra-Majem *et al*., 2018; Nagamine *et al*., 2020; Mayumi *et al*., 2021;). Similarly, D-tagatose, when compared with other sweeteners such as Xylitol, has been shown to be a much more potent anticariogenic as it does not lose its acid suppressive capacity when combined with sucrose (Sawada *et al*., 2015; Ensor *et al*., 2015; Hasibul *et al*., 2018; Nagamine *et al*., 2020; Mayumi *et al*., 2021).

For this reason, in this study we proposed to carry out a systematic review with the aim of analyzing the effect of D-tagatose on the proliferation of oral bacteria related to carious lesions.

MATERIAL AND METHOD

The systematic review was fully conducted according to the ''Cochrane Handbook for Systematic Reviews of Interventions'' and the statement ''Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Liberati *et al*., 2009; Higgins *et al*., 2011). This review is registered in the ''International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY)''. Number: INPLASY2023120121. DOI: 10.37766/inplasy2023.12.0121. Available in https://inplasy.com/inplasy-2023-12-0121.

Eligibility Criteria. Study eligibility included the P.I.C.O. (population, intervention, comparison and outcomes of interest) acronym methodology, considering the following inclusion criteria:

- P: Healthy adults.
- I: D-Tagatose (0,1 %, 0,5 %, 0,8 %, 1 %, 5 % and 10 %).
- C: Sucrose as positive control or water as negative control.
- O: Count of salivary bacteria of the genus *Streptococcus*.

In addition, the phenotype, gene expression and bacterial metabolic profiles over time. This review will only include experimental and/or observational studies applied *in vivo* models. Therefore, they will be excluded; reviews, editorials, books and *in vitro* models among others.

Data Sources and Search. An electronic search of original articles was carried out in the databases Virtual Health Library (https://bvsalud.org/es/), Europe PMC (https://europepmc.org/), Medline / PubMed (https://pubmed.ncbi.nlm.nih.gov/), Scopus (https://www.scopus.com/) and Cochrane Central (https://www.cochranelibrary.com/es/central/about-central) being applied in all the databases as a temporal filter the years 2013 to 2023, while for the Scopus databases the methodological filter ''article'' was applied. The initial search was carried out in April 2023, and was updated on December of the same year, being the strategy constructed based on the terms Medical Subject Headings (MeSH): "Tagatose", "D-tagatose" and "Dental caries" together with the Boolean operator "OR" and "AND" so that the following strategy was used for all searches: "Tagatose OR D-tagatose AND Dental Caries".

Study Selection and Data Collection. The search, review and data extraction process focused on the following information: main author, title, keywords, study design, year of publication, population, intervention, comparison, outcome of interest, ethical considerations and conclusions of the work. The search, review, and data extraction of each article was processed independently by two researchers, and any disagreement over eligibility was determined by a third independent researcher.

Risk of Bias Assessment. The studies included in this review were assessed for risk of bias according to the recommendation of the "Guidelines for the critical review of qualitative studies" (Law *et al*., 1998). These criteria classify the quality of the evidence on a binary scale according to compliance with the criterion (0 = Does not meet / 1 = meets), while if the criterion does not fit the type of work, the option "Not applicable" is selected. Finally, to make a comparison of the methodological quality between different study designs, a percentage score was calculated (total sum of results/number of items evaluated) that allows the methodological quality to be classified as; (A) strong, with a score ≥75 %, (B) moderate, with a score between 51 % and 74.99 % and (C) weak, with a score <50.99 % (Brown *et al*., 2011).

The methodological information of the studies was evaluated by two independent researchers, who blinded the information that could be used to identify the authorship of the articles (authors, affiliations and journals), and discrepancies in risk of bias assessment were resolved by a third independent researcher.

RESULTS

Figure 1, the electronic search identified 78 records in all databases plus 1 record obtained manually, 42 were eliminated in duplicate, where after the screening performed in the reading of the title and abstract, another 33 articles were eliminated because they were not considered relevant to the objective of the study, resulting in 4 potentially eligible articles (Sawada *et al*., 2015; Hasibul *et al*., 2018; Nagamine *et al*., 2020; Mayumi *et al*., 2021). The 4 articles of interest were subjected to a full-text reading, where 2 article was excluded because of *in vitro* design (Sawada *et al*., 2015; Hasibul *et al*., 2018), and the remaining 2 articles were included for qualitative analysis (Nagamine *et al*., 2020; Mayumi *et al*., 2021).

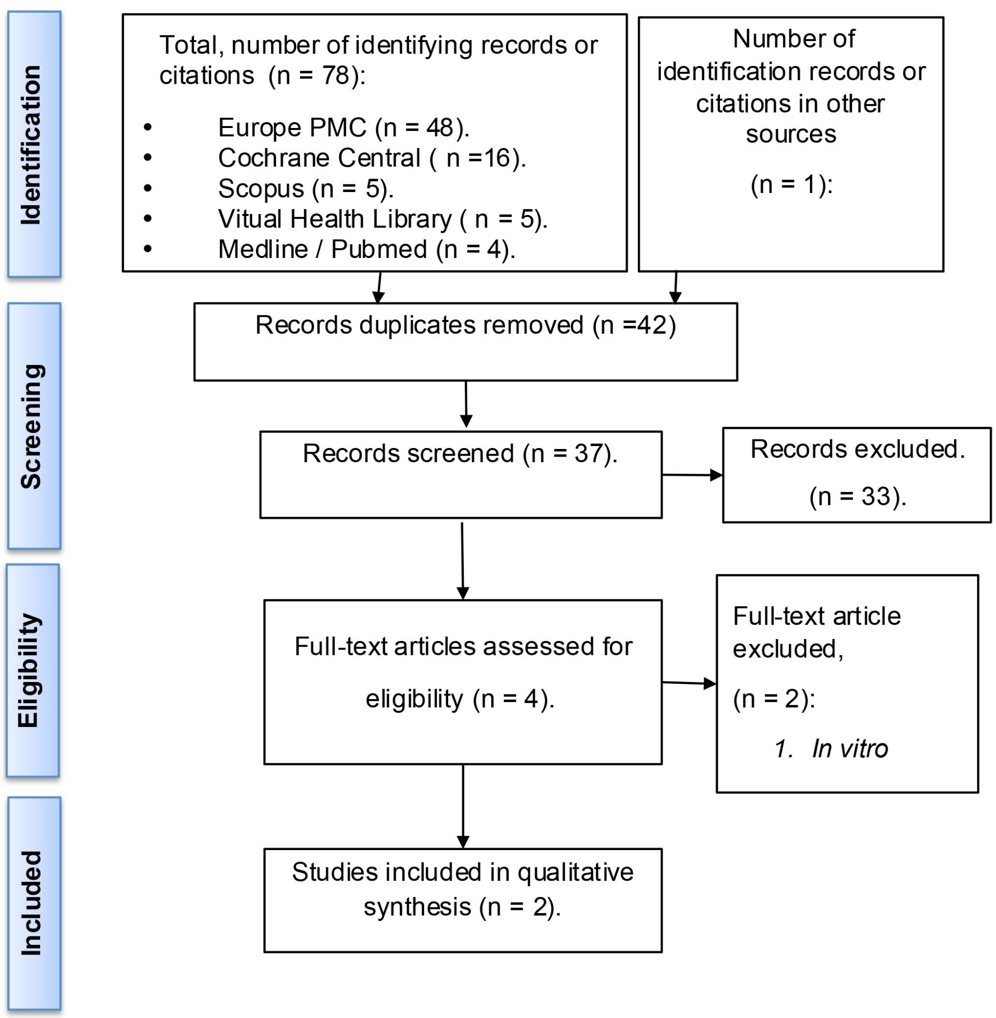

Fig. 1. Flow diagram of the systematic review. Source: Own elaboration based on PRISMA.

Table I appreciated the characteristics of the selected papers related to D-tagatose in humans, where one of the studies corresponds to a randomized clinical trial published in 2020 in the journal Acta Medica Okayama, which involved recruiting humans according to the Helsinki ethical standards (Nagamine *et al*., 2020), while the other article analyzed corresponds to an observational study published in 2021 by the journal Frontiers in Cellular and Infection Microbiology, whose sample included subjects recruited according to Helsinki ethical standards (Mayumi *et al*., 2021).

Table II reports the results related to the specific variables of the subject and quality of the selected documents related to D-tagatose in humans, where the two studies analyzed are of interest for the objectives of the present review, being the methodological quality of both studies "strong" (Mayumi *et al*., 2021; Nagamine *et al*., 2020).

Table I. Characteristics of studies related to D-tagatose delivery in humans.

Reference	Títle	Key words	Design	Ethics	Journal
Nagamine *et al.* 2020	D-Tagatose Effectively Reduces the Number of *Streptococcus mutans* and Oral Bacteria in Healthy Adult Subjects: A Chewing Gum Pilot Study and Randomized Clinical Trial	D-Tagatose; *Streptococcus mutans*; Chewing gum; Oral bacteria; Xylitol	PTE	Yes	Acta Med Okayama.
Mayumi *et al.* 2021	Potential of prebiotic D- tagatose for prevention of oral disease.	D-tagatose; Biofilm; Transcriptomic; Metabolomics; *Streptococcus mutans*; *Streptococcus gordonii*; *Streptococcus oralis*.	DCBA	Yes	Front Cell Infect Micro biol.

PTE: Post-test only, experimental design, DCBA: Descriptive correlation using before- and-after desig.

Table II. Selected documents related to the supply of D-tagatose in humans.

Reference	Population	Interventions	Comparison	Outcome	Conclusion
Nagamine *et al.*, 2020	19 Healthy Adult.	Xylitol gum (5 %) x >10 min for 4 weeks. D-tagatose gum (5 %) x >10 min for 4 weeks. Xylitol gum (2.5 %) + D-tagatose gum (2.5 %) x >10 min for 4 weeks.	Control.	Total salivary bacteria, *Salivary S. mutans* and total, salivary bacteria changes over time.	D-tagatose in combination with xylitol significantly decreased the number of total bacteria and *S. mutans.* However, individually they do not generate significant reductions.
Mayumi *et al*., 2021	18 subjects.	D-tagatose (0.1 %, 0.5 %, 0.8 %, 1 %, 5 % and 10 %). Glucose (0.8 %).	Control.	Bacterial phenotype, gene expression and metabolic profiles.	D-tagatose inhibits the growth of *S. mutans* and *S. gordonii*, while *S. oralis* does not appear to be significantly affected

Table III present the evaluation of the "Guidelines for critical review of qualitative studies" (Law *et al*., 1998; Brown *et al*., 2011), where both studies analyzed present a strong methodological quality (≥75 %) (Mayumi *et al*., 2021; Nagamine *et al*., 2020).

DISCUSSION

In the present systematic review, the objective of analyzing the effect of D-tagatose on the proliferation of oral bacteria related to carious lesions was proposed. In recent years, it has been discovered that the presence of a layer of biofilm generated by cariogenic bacterial communities can trigger the development of dental caries, with the communities of microorganisms and their adhesive interactions providing the resistance and cohesion that make it difficult to eliminate them through biomechanical methods on the dental surface (Kunacheva & Stuckey, 2014; Peterson *et al*., 2015; Harimawan & Ting, 2016). In this sense, it is known that a diet rich in sugars is a fundamental element for the development of cariogenic biofilms, where *Streptococcus mutans* bacteria, characterized by their great virulence, can generate an acidic medium from the fermentation of sugars and carbohydrates from the diet (Palomer, 2006; Adler *et al*., 2013; Nomura *et al*.,

Table III. Critical evaluation of the studies analyzed.

Methodological quality criteria	Naganime *et al.,* 2020.	Mayumi *et al.*, 2022.
Study purpose		
Was the purpose stated clearly?	Yes	Yes
Was relevant background literature reviewed?	Yes	Yes
Design:		
Type	PTE	DCBA
Appropriateness of studies designs?	Yes	Yes
Sample/Methods		
Was the sample described in detail?	Yes	Yes
Was the sample size justified?	No	No
Outcomes		
Were the outcome measures reliable?	Yes	Yes
Were the outcome measures valid?	Yes	Yes
Intervention		
Intervention described in detail?	Yes	Yes
Contamination avoided?	N/A	N/A
Co-intervention avoided?	Yes	Yes
Results		
Results were reported in terms of statistical significance?	Yes	Yes
Were the analysis method(s) appropriate?	Yes	Yes
Clinical importance was reported?	No	No
Drop-outs were reported?	Yes	Yes
Conclusions		
Were conclusions appropriate given the study findings?	Yes	Yes
Average score / methodological quality.	80 % / (A) Strong.	80 % / (A) Strong.

2014; Klein *et al*., 2015; Simón-Soro & Mira, 2015; Jiang *et al*., 2016; Flemming *et al*., 2016; Baker *et al*., 2017; Demonte *et al*., 2017; Bowen *et al*., 2018; Hasibul *et al*., 2018; Nagamine *et al*., 2020). However, there are different types of natural simple sugars such as sucrose, which have also been attributed a certain degree of responsibility in the processes of demineralization and dental caries formation, where the bacterial substrate of sugars is a factor that enhances these pathologies, and research into these interactions is currently being boosted by the appearance of rare sugars known both for emulating flavors and for having a low caloric content compared to sucrose (Chattopadhyay *et al*., 2014; Riley *et al*., 2015; Sheiham & James, 2015; Bowen *et al*., 2018; Giacaman, 2018; Nagamine *et al*., 2020).

This review focused specifically on the effects of D-Tagatose, whose anticariogenic effects seem to be as promising as Xylitol for the prevention of dental caries, even though there is still no consensus on this subject (Nayak *et al*., 2014; Riley *et al*., 2015; de Cock *et al*., 2016; Jayamuthunagai *et al*., 2017). D-Tagatose is known to be a non-fermentable sugar for *Streptococcus mutans*, therefore, it has potential inhibitory effects on bacterial plaque production and its enzymatic processes modulated by GTFs, where *Streptococcus mutans* strains can produce up to three GTFs (-B, -C and -D) from insoluble glucans that in turn help stabilize the oral biofilm by encoding glucan-binding proteins (GBPs-A, -B, -C and-D) (Baker *et al*., 2017). In this context, the inhibitory effect of D-Tagatose on the activity of GTFs leads to a reduced release of D-fructose from sucrose (a powerful inducer of GTF-B expression), thus preventing the formation of dental caries and other oral diseases such as periodontitis (Bowen *et al*., 2018; Guerrero-Wyss *et al*., 2018; Hasibul *et al*., 2018; Nagamine *et al*., 2020; Mayumi *et al*., 2021). Regarding these approaches, Nagamine *et al*. (2020). through their study demonstrated that D-Tagatose generated a decrease in the bacterial growth of *Streptococcus mutans* and the inhibition of the GTF-B enzyme responsible for dental plaque, while Xylitol alone did not generate such a potent effect on oral bacteria and was not very effective in the short term. On the other hand, Mayumi *et al*. (2021), demonstrated that D-Tagatose generated an inhibition on the growth of *Streptococcus mutans* because of an interaction in the glycolysis process, where it is also suggested that D-Tagatose plays an important role in the maintenance of dental plaque by inhibiting the GTF-B enzyme, thus promoting good hygiene in the oral cavity. Similarly, some in vitro studies have concluded that D-Tagatose inhibits acid production, delaying the decrease in salivary pH, as well as bacterial growth and the synthesis of water-insoluble glucan of *Streptococcus mutans* in the presence of sucrose, but not with Xylitol, which loses its anticariogenic effects when in contact with sucrose (Sawada *et al*., 2015; Hasibul *et al*., 2018).

Limitations. This systematic review could have been affected by the assessment made on the quality of the evidence analyzed, since the discrimination of the relevant findings was based on the clinical judgment of each evaluator at the time of applying the data extraction form. In the same way, although the electronic search considered five multidisciplinary databases with wide worldwide recognition, both the number of records recovered and the number of articles analyzed was small, making it possible that part of the gray literature may have been overlooked due to the exhaustiveness of the search strategy despite the fact that it was carried out on two occasions (April and December 2023) considering a period of 11 years (2013 to 2023), where the final analysis of the recent literature reported little available evidence based on previous research, with most of the evidence being *in vitro* studies.

Recommendations for future research. This systematic review has several implications for future research. Firstly, the number of studies analyzed was low (Sawada *et al*., 2015; Hasibul *et al*., 2018; Nagamine *et al*., 2020; Mayumi *et al*., 2021), with a predominance of *in vitro* designs (Sawada *et al*., 2015; Hasibul *et al*., 2018), therefore, future studies should address *in vitro* models, since the main weakness of *in vitro* models designs is the extrapolarity of the results to *in vivo* models. On the other hand, future research should focus on conducting randomized and/or longitudinal clinical studies of greater scope and rigor to determine more precisely the potential effects of D-tagatose on bacterial proliferation related to caries lesions.

Clinical implications. This review was not able to recover any results on specific interventions aimed at the treatment of carious lesions, being the totality of the evidence collected regarding the prevention of pathologies related to biofilms (Sawada *et al*., 2015; Hasibul *et al*., 2018; Nagamine *et al*., 2020; Mayumi *et al*., 2021). Although this is important, it is worth mentioning that dental caries is characterized by high levels of prevalence in all age ranges (Kale *et al*., 2020; Borg-Bartolo *et al*., 2022).

In this context, today obesogenic habits contribute greatly to the generation of favorable conditions for the development of agents that enhance dental caries (González Sanz *et al*., 2013; Moynihan & Kelly, 2014; Sheiham & James, 2014; Giacaman, 2018; Chen *et al*., 2019), with Xylitol and D-tagatose being key considering that today nowadays, sweeteners are highly consumed due to their properties (Nayak *et al*., 2014; Riley *et al*., 2015; Sawada *et al*., 2015; Jayamuthunagai *et al*., 2017; Hasibul *et al*., 2018; Nagamine *et al*., 2020; Mayumi *et al*., 2021).

CONCLUSIONS

D-Tagatose possibly inhibit the proliferation of oral bacteria related to carious lesions, where it is worth mentioning the need to carry out new studies aimed at demonstrating the possible effects of D-Tagatose on oral bacterial proliferation and its associated pathologies. However, because of the small number of articles analyzed in this review, it is necessary to carry out new work aimed at more clearly elucidating the potential effects of D-Tagatose on the bacterial growth of *Streptococcus mutans* and oral biofilms.

INOSTROZA-RIVERA, V.; QUIÑILÉN-COFRÉ, F.; ANGARITA-DAVILA, L.; FUENTES-BARRIA, H.; CARRASCO-HERNÁNDEZ, M. E. & AGUILERA-EGUÍA, R. Efectos de la D-Tagatosa sobre el crecimiento bacteriano del género *Streptococcus*. Revisión sistemática. *Int. J. Odontostomat., 18(4)*:426-432, 2024.

RESUMEN: Actualmente se sabe que la caries dental es una de las enfermedades crónicas no transmisibles más comunes a nivel mundial, cuya etiología se ha atribuido a Streptococcus, siendo el consumo de edulcorantes como la D-Tagatosa relacionados a efectos anticariogénicos. El objetivo de este estudio es analizar el efecto de la D-tagatosa sobre la proliferación de bacterias bucales relacionadas con lesiones cariosas. Se realizó una revisión sistemática de artículos originales publicados entre 2013 y 2023 en las bases de datos Europa PMC, Medline (PubMed), Cochrane Central, Biblioteca Virtual en Salud y Scopus, utilizando la siguiente estrategia de búsqueda: "Tagatose OR D-tagatose AND Caries Dental". La calidad de la evidencia recolectada se analizó con las Guías para la revisión crítica de estudios cualitativos. La búsqueda identificó 79 registros de los cuales 2 cumplieron con los criterios de elegibilidad. En general, los artículos seleccionados indican que la D-Tagatosa en dosis entre 0,1 a 10 % puede inhibir tanto el crecimiento bacteriano de *Streptococcus mutans* como la producción de glicosiltransferasa-B relacionada con el biofilm dental. La D-tagatosa posiblemente inhibe la proliferación de bacterias orales relacionadas con las lesiones de caries, sin embargo, se necesitan nuevos estudios en modelos in vivo que buscan demostrar estos posibles efectos anticariogénicos.

PALABRAS CLAVE: tagatosa, caries dental, *Streptococcus mutans*, biofilms.

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