

Effects of D-tagatose on cariogenic risk. A systematic review

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Aguilera-Eguía, R; Alarcón-Rivera, M; Guzmán-Muñoz, E.**ADMINISTRATIVE INFORMATION****Support** - None.**Review Stage at time of this submission** - Preliminary searches.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY202510002**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 2 January 2025 and was last updated on 2 January 2025.**INTRODUCTION**

Review question / Objective How effective is D-tagatose, alone or in combination with other non-caloric sweeteners, compared to a control group without sweeteners, in reducing cariogenic risk?

Condition being studied Since 2003, the Food and Drug Administration (FDA) has approved the use of D-tagatose for daily consumption, as it poses no health risks. This led the European Union (EU) to designate it as an unrestricted food ingredient, highlighting features such as its potential antihyperglycemic effect at the postprandial serum level and its preventive capacity against dental caries formation. This is attributed to its ability to maintain its glucan acid-suppressing effect, linked to the enzymatic process of glycosyltransferases (GTF), even when combined with sweeteners like xylitol and sucrose. D-tagatose has gained significant relevance in preventing non-communicable chronic diseases, such as dental caries, which have a high prevalence across all age.

METHODS

Search strategy The search strategy will consider Medical Subject Headings (MeSH) terms combined with Boolean operators (AND/OR) to construct the following query across all databases: "Tagatose OR D-tagatose AND Dental Caries." Results will subsequently be filtered by methodological design, specifying "Article" in Scopus and Web of Science, "Research Articles" in Europe PMC and Springer Link, and "Randomized Controlled Trial" in Medline/PubMed. In all searches, articles published until 2024 are considered.

Participant or population In this systematic review, we will include clinical studies in which adults present a state of oral health that includes the absence of active cavities, advanced periodontitis or significant oral lesions related to habits such as smoking, excessive alcohol consumption, or diets extremely high in sugars simple.

Intervention The intervention will include any form of D-tagatose in isolation.

Comparator RCTs that include a control group with any form of non-caloric sweetener other than D-tagatose (e.g. Sucrose, Stevia or Xylitol) will be included.

Study designs to be included Only randomized clinical trials (RCTs).

Eligibility criteria This systematic review focused exclusively on randomized controlled trials (RCTs) with variable intervention durations written in English, Spanish, and Portuguese will be included.

Information sources The databases consulted included: Web of Science, Europe PMC, Scopus, Medline/PubMed, CENTRAL, Dentistry & Oral Sciences Source, Springer Link (<https://link.springer.com/>), and the Virtual Health Library. Grey literature was also included, with searches conducted in bioRxiv (<https://www.biorxiv.org/>) and <https://www.preprints.org>.

Main outcome(s) The primary outcome in our review is cariogenic risk.

Measurements: This could be reported as either a dichotomous or a continuous outcome (number or percentage change of colony-forming units). If available, data on the time-to-event following the administration of the non-caloric sweetener were also included. Since cariogenic risk can be associated with various factors, studies were considered eligible only if they used a predefined criterion to establish cariogenic risk, which was based, at least in part, on an objective assessment. This included measurements of Streptococcus genus colony-forming units. Consequently, studies evaluating interventions based solely on a cariogenic risk assessment performed by a healthcare professional were not included.

Additional outcome(s) Hydrogen potential (pH), which must be evaluated using a calibrated digital meter.

Quality assessment / Risk of bias analysis The methodological quality of the included studies was evaluated using the Risk of Bias 2 (ROB 2) tool, developed by the Cochrane Collaboration. This tool assesses and classifies potential biases in randomized controlled trials across five key domains: (D1) random sequence generation process, (D2) deviations from assigned interventions, (D3) missing outcome data, (D4) outcome measurement, and (D5) selection of reported outcomes [16]. The risk of bias was conducted independently by two researchers. Discrepancies regarding the inclusion of specific

articles were resolved by a third reviewer, who acted as an arbitrator.

Strategy of data synthesis Information extracted from included studies will be used to make a descriptive summary analysis, following systematic review guidelines. Studies having homogeneous experimental variables will be meta analyzed through Revman (Review Manager). Heterogeneity will be assessed using the I^2 test: values above 75% indicate substantial heterogeneity, between 40%-75% is moderate, and below 40% is low. Data will be analyzed using a random effects model. Should there be moderate heterogeneity, we will conduct a subgroup analysis to identify the sources of heterogeneity.

Subgroup analysis In this systematic review, all forms of non-caloric sweeteners will be considered.

If there is moderate heterogeneity and sufficient data available, a subgroup analysis will be conducted based on the type of non-caloric sweetener and Colony Forming Units.

Sensitivity analysis A sensitivity analysis will be conducted only if a sufficient number of studies are found, aiming to assess the robustness of the results by repeating the analysis with the following adjustments:

Limit the analysis to studies showing low risk of bias.

Analyze the results as standardized mean differences (SMD) across all scales, or as mean differences (MD) for each individual scale.

Country(ies) involved Chile.

Keywords Tagatose; Dental caries; Streptococcus mutans; biofilms.

Contributions of each author

Author 1 - Lissé Angarita-Davila - Conceptualization, investigation, data curation, writing—original draft preparation, writing—review and editing, visualization, supervision, and project administration.

Author 2 - Héctor Fuentes-Barría - Conceptualization, methodology, investigation, data curation, writing—original draft preparation, writing—review and editing, visualization, supervision, and project administration.

Author 3 - Diana Rojas-Gómez - Data curation, writing—original draft preparation, writing—review and editing, and visualization.

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