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ORIGINAL ARTICLE

The Xylitol Applicability and its Effects in Health Area Worldwide: A Bibliometric Analysis Based on Randomized Controlled Trials

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ABSTRACT

Objective: To describe and evaluate the xylitol products' applicability and its effects in the health area worldwide utilizing a bibliometric analysis from randomized controlled trials (RCT) with humans. **Material and Methods:** Electronic searches were carried out in Medline/PubMed, Scopus, Cochrane Library, Web of Science, and VHL databases. The main data extracted were: year, area of applicability, type of treatment, country, journal, xylitol posology and concentration, presentation form, outcomes, and effects. **Results:** From 1476 studies, 257 were included. These studies were published between 1973-2021. The majority was carried out in dentistry (73.9%) and under preventive treatment (67.4%). These studies were developed in the USA (15.4%) and published in Caries Research (6.6%). The posology and concentration ranged between 0.004-67 g/day and 0.002-100%, respectively. The xylitol is usually used in the chewing gum form (44.0%), and for antimicrobial activity evaluation (38.5%). A positive effect was observed in 204 studies (79.3%) and was associated with xylitol concentration ≥ 15% (p=0.007). Side effects were reported in 8.2% and were associated with posology ≥ 5 g/day (p=0.03). **Conclusion:** Most studies with xylitol were conducted to prevent diseases in the dentistry field. The chewing gum form and antimicrobial activity evaluation were more frequent. Most xylitol products have a positive effect, and few studies report side effects.

Keywords: Xylitol; Therapeutics; Randomized Controlled Trials as Topic; Bibliometrics.

Introduction

Xylitol is a sugar alcohol (or polyol) found in fruits and vegetables and exhibits the same sucrose sweetness [1]. Its consumption has no physiological requirement and can be considered a sucrose substitute [2]. This product is found in various formulations, including chewing gum, tablet, candy, toothpaste, mouthwash, gel, and spray [3-5]. It can be used to prevent and / or treat diseases of different areas, such as dentistry, medicine, and nutrition [6-9].

In dentistry, the xylitol is used as an adjuvant method to dental caries prevention and is recommended as part of oral health promotion programs. It is a non-cariogenic sugar due to its inability to be metabolized by oral microorganisms [5]. The xylitol can also be used in medicine to treat, for example, acute otitis media (AOM) because of its antibacterial properties against *Streptococcus pneumoniae* [10,11] and to facilitate gastric emptying after surgical procedures [7,12]. In nutrition, solutions with xylitol can be used to control blood glucose levels [13,14], and malnutrition in postoperative patients [15,16].

Due to its obtention and purification processes, the use of xylitol products is relatively expensive as a sweetener compared to sucrose. In addition, because it is poorly hydrolyzed and absorbed by the small intestine, it can cause osmotic diarrhea to flatulence when consumed in high amounts [10,13,17,18]. Simultaneously, there are controversies in the literature regarding the applicability, efficacy, and possible side effects arising from the use of xylitol in different health areas.

Therefore, the present study aimed to describe the published studies profile on this topic and evaluate the xylitol products' applicability and its effects in the health area worldwide through a bibliometric analysis based on randomized controlled trials with humans.

Material and Methods

Eligibility Criteria

Randomized controlled trials (RCT) in humans (P) treated with xylitol (I) compared to control treatment (negative or gold standard) or without receiving the intervention (C) to evaluate the effect on health (O) were included.

In vitro, *ex vivo*, and *in situ* studies, no randomized or no controlled studies *in vivo*, studies involving animals, case reports, literature reviews, observational studies, research protocols, and other studies that did not comply with the inclusion criteria were excluded.

Literature Search Strategy

Two examiners (MLM and MBM), guided by a librarian (DM), independently performed the search without restrictions on year nor language. The following electronic databases were searched: PubMed, Scopus, Cochrane Library, Web of Science, and VHL (Latin American and Caribbean Health Sciences Literature - LILACS / Brazilian Dentristy Bibliography - BBO). MeSH terms, free terms, and Boolean operators (OR, AND) were used, organized according to the PICO search strategy (Table 1), and following each database's syntax rules. Alerts were created in the databases to indicate new searches, including articles published no later than August 2021.

Reference management software (Online version of EndNote™, version X7, Thomson Reuters, Philadelphia, USA) was used to organize references and to read titles and abstracts. Then, examiners MLM and AF removed duplicates and performed the screening in the VantagePoint™ software (Search Technology,

Inc., Florida, USA). Finally, articles in which the title and abstract did not contain sufficient information were analyzed in full by two independent examiners to verify their eligibility.

Table 1. Search strategy according to the different databases used in this study.

Database	Strategy
PubMed	((((Xylitol[MeSH Terms] OR Xylitol[Title/Abstract] OR Xylose[MeSH Terms] OR Xylose[Title/Abstract] OR D-Xylose[Title/Abstract] OR D Xylose[Title/Abstract] OR Xylose Reductase[Title/Abstract] OR Engineered Xylitol[Title/Abstract])))) AND ((((Prospective Studies[MeSH Terms] or Prospective Stud*[Title/Abstract] OR Clinical Trial[Publication Type] OR Clinical Trial[Title/Abstract] OR Controlled Clinical Trial[Title/Abstract]) AND Randomiz*[Title/Abstract]) OR (Random Allocation[MeSH Terms] OR (Random Allocation[Title/Abstract]) OR Randomized Controlled Trial[Title/Abstract] OR Randomized Controlled Clinical Trial[Title/Abstract] OR Randomized Clinical Trial[Title/Abstract]))
Scopus	TITLE-ABS-KEY(Xylitol) OR TITLE-ABS-KEY(Xylose) OR TITLE-ABS-KEY(D-Xylose) OR TITLE-ABS-KEY("D Xylose") OR TITLE-ABS-KEY("Xylose Reductase") OR TITLE-ABS-KEY("Engineered Xylitol") AND ((TITLE-ABS-KEY (prospective AND stud*) OR TITLE-ABS-KEY ("Clinical Trial") OR TITLE-ABS-KEY ("Controlled Clinical Trial")) AND (TITLE-ABS-KEY (randomiz*))) OR (TITLE-ABS-KEY ("Random Allocation") OR TITLE-ABS-KEY ("Randomized Controlled Trial") OR TITLE-ABS-KEY ("Randomized Controlled Clinical Trial") OR TITLE-ABS-KEY ("Randomized Clinical Trial"))
Web of Science	(TS=(Xylitol OR Xylose OR D-Xylose OR "D Xylose" OR "Xylose Reductase" OR "Engineered Xylitol") AND ((TS=(Prospective Stud* OR "Clinical Trial" OR "Controlled Clinical Trial") AND TS=(Randomiz*)) OR (TS=("Random Allocation" OR "Randomized Controlled Trial" OR "Randomized Controlled Clinical Trial" OR "Randomized Clinical Trial"))))
Cochrane Library	ID Search Hits #1 MeSH descriptor: [Xylitol] explode all trees 243 #2 xylitol 664 #3 MeSH descriptor: [Xylose] explode all trees 45 #4 xylose 130 #5 D-xylose 67 #6 "D xylose" 69 #7 "xylose reductase" 0 #8 "engineered xylitol" 0 #9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 793 #10 MeSH descriptor: [Prospective Studies] explode all trees 94900 #11 prospective stud* 229350 #12 "clinical trial" 680099 #13 "controlled clinical trial" 266341 #14 randomiz* 1154711 #15 #10 OR #11 OR #12 OR #13 795048 #16 #15 AND #14 643308 #17 MeSH descriptor: [Random Allocation] explode all trees 20643 #18 "random allocation" 26782 #19 "randomized controlled trial" 920248 #20 "randomized controlled clinical trial" 12856 #21 "randomized clinical trial" 56742 #22 #17 OR #18 OR #19 OR #20 OR #21 947793 #23 #16 OR #22 1003071 #24 #9 AND #23 443
VHL (LILACS/BBO)	((mh:(xylitol)) OR (tw:(xylitol)) OR (mh:(xylose)) OR (tw:(xylose)) OR (tw:(D-xylose)) OR (tw:("D xylose")) OR (tw:("xylose reductase")) OR (tw:("engineered xylitol"))) AND ((mh:("random allocation")) OR (tw:("random allocation")) OR (tw:("randomized controlled trial")) OR (tw:("randomized controlled clinical trial")) OR (tw:("randomized clinical trial"))) OR (((mh:("prospective studies")) OR (tw:(prospective stud*)) OR (tw:("clinical trial")) OR (tw:("controlled clinical trial"))) AND (tw:(randomiz*)))

Data Extraction

Examiners MLM and KLFL performed complete reading and extraction of the data. A spreadsheet was created to standardize the data to be extracted, containing the following information: year (grouped into decades); age group of participants (infant – 0 to 1 year; child – 2 to 9 years; adolescent – 10 to 19 years; adult – 20 to 60 years; elderly – up to 60 years); area of applicability, type of treatment (preventive, therapeutic, and indirect); country (in which the study was developed); journal; frequency and duration of the intervention and washout; xylitol posology and concentration; associated products; presentation form; outcomes; effect (positive, null or negative); and possible side effects. The indirect treatment was considered when it was applied to a mother, but the effect was investigated in her child.

In case of studies in which additional data were required or classified as a summary of the congress presentation, their authors were contacted by email to clarify doubts. Disagreements between the authors were settled by discussion, with a third author (AF) when necessary.

Data Analyses

Data analyses were carried out in the VantagePoint™ software (Search Technology, Inc., Florida, USA), Microsoft Office Excel 2010™, and SPSS software version 21.0 (SPSS Inc., Chicago, USA). Descriptive and inferential data analyses were performed. For descriptive analyses, the same study could contain one or more classification options in the same variable (age group, area of applicability, type of treatment, xylitol concentration, associated products, presentation form, outcomes, effect, and possible side effects). This could become a total frequency value of these variables greater than the number of RCT included. For inferential data analyses, the Chi-square test was used to observe a possible association between the xylitol effect and data of the frequency of use (< 3 / ≥ 3 times/day), time of intervention (< 5 / ≥ 5 minutes per intervention; < 28 / ≥ 28 days considering the total period of treatment), posology according to the presentation form (< 3 / ≥ 3 daily use of pieces; < 10 mL / ≥ 10 mL or < 5 / ≥ 5 g/day), xylitol concentration (< 15 / $\geq 15\%$), other active compounds in the same product containing xylitol (yes or no) and other interventions (yes or no). The level of significance considered was 5% ($p<0.05$).

Results

Initially, the authors identified 1476 studies. After removing duplicates, 890 studies remained. Of these, 593 were excluded after reading the titles and abstracts, and 297 were selected for reading the full text carefully. After this step, 40 studies were excluded because they did not meet the eligibility criteria, and 257 were selected and progressed to the quantitative synthesis and data extraction stages (Figure 1).

Year of Publication and Age Groups

The RCT included in this bibliometric study were published between 1973 and 2021. The production was higher between 2011-2021 (n=119; 46.3%), and 2001-2010 (n=67; 26.1%), follow by 1991-2000 (n=45; 17.5%), 1981-1990 (n=15; 5.8%), and 1973-1980 (n=11; 4.3%). Distribution of age groups, areas of applicability, and types of treatment over the years are represented in Figures 2, 3, and 4.

Most studies were conducted with adults (n=162; 63.0%), and a minor number were carried out with infants (n=7; 2.7%). One study did not report the age group and was not included in this analysis. On the other hand, some authors included different age groups (Figure 2).

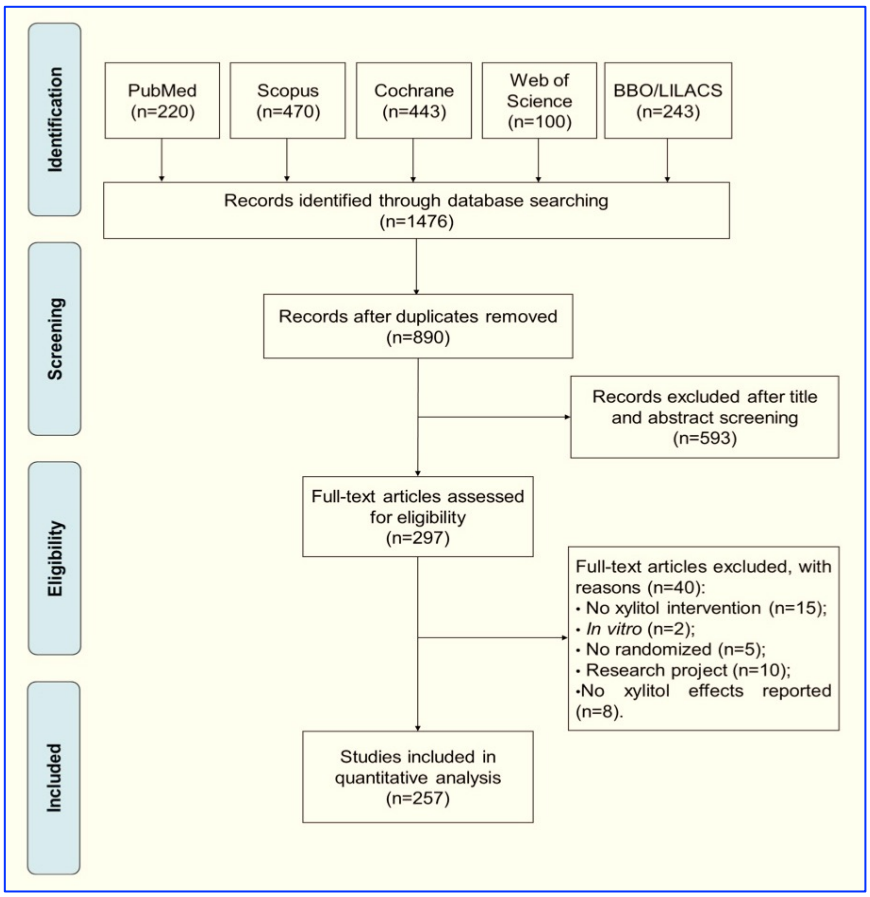

Figure 1. Flowchart of search results in databases.

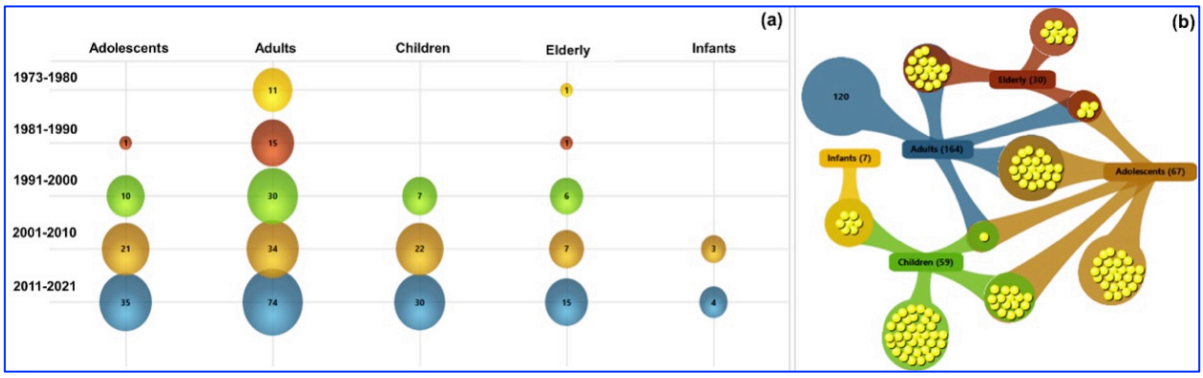

Figure 2. Bubble chart of the studies distribution over the years by age group (a) and cluster map of the age groups (the intersection among them indicates the number of studies with different age groups simultaneously) (b). There is no correspondence between the colors in figures 2a and 2b.

Area of Applicability, Type of Treatment, Countries, and Journals of Publication

The more frequent health area was dentistry (n=190; 73.9%), followed by medicine (n=38; 14.8%). Some studies were included in different areas simultaneously (Figure 3).

The preventive treatment management (n=160; 62.3%) was the most frequent and also was evaluated simultaneously with therapeutic treatment in 13 studies (5.1%) (Figure 4). The type of intervention was classified as main (n=250; 97.3%) or complementary (n=7; 2.7%). Other interventions, such as dental restorative treatments performed simultaneously with xylitol-containing products, were carried out in 36 studies (14.0%).

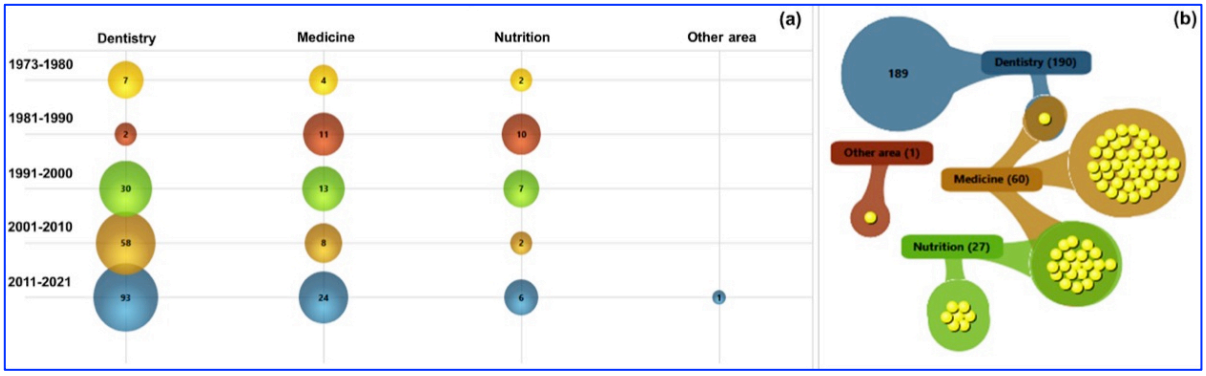

Figure 3. Bubble chart of the studies distribution over the years by area (a) and cluster map of the areas of applicability (the intersection among them indicates the number of studies about different areas simultaneously) (b). There is no correspondence between the colors in figures 3a and 3b.

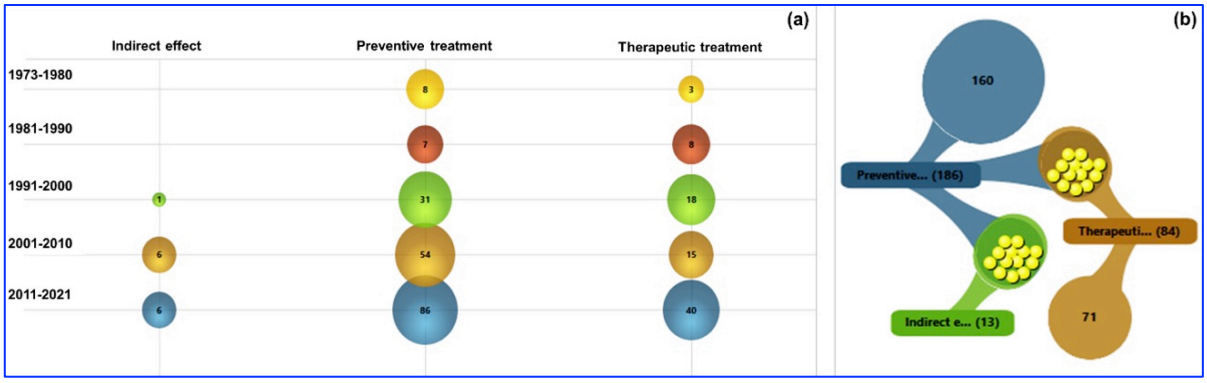

Figure 4. Bubble chart of the studies distribution over the years by treatment (a) and cluster map of the types of treatment (the intersection among them indicates the number of studies with different types of treatment simultaneously) (b). There is no correspondence between the colors in figures 4a and 4b.

The papers originated from 39 countries and were published in 143 journals, with a more significant number of studies from the United States of America (USA) (n=39; 15.4%) (Figure 5).

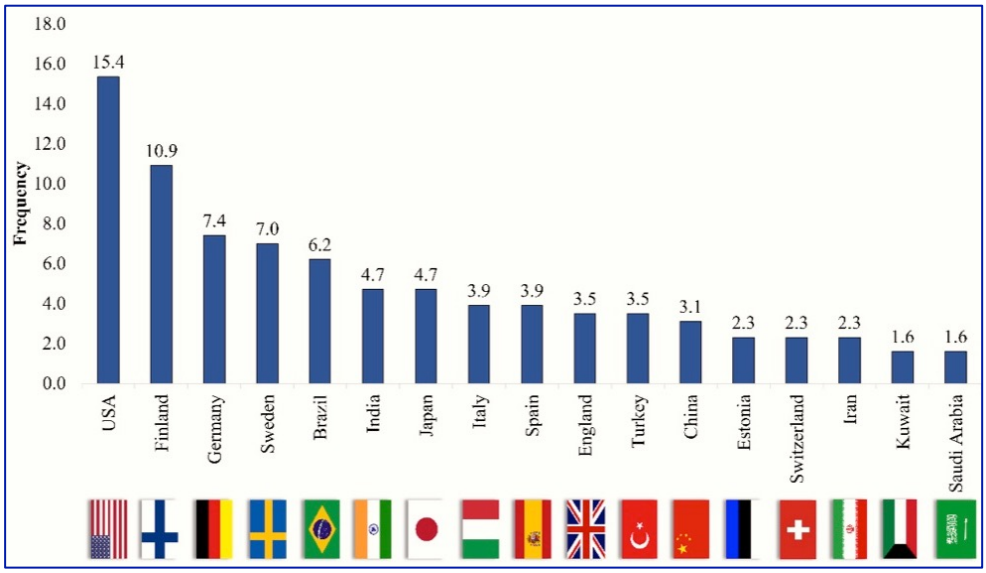

Figure 5. Frequency of countries with five or more randomized clinical trials in humans with xylitol worldwide.

Among journals with four or more publications, 12 were from the dentistry area, and one was from the nutrition area. The journal with the highest number of published RCT about xylitol was Caries Research (n=17; 6.6%), and the Journal of Clinical Periodontology presented the highest impact factor (IF=5.24) (Table 2).

Table 2. Frequency of journals with four or more randomized clinical trials published about xylitol over the years.

Journal	Years					Total	IF*
	1973-1980	1981-1990	1991-2000	2001-2010	2011-2021		
Caries Research	0	1	4	5	7	17	2.18
Acta Odontologica Scandinavica	4	0	3	3	1	11	1.57
Clinical Oral Investigations	-	-	0	2	7	9	2.81
Journal of Dental Research	0	0	3	2	2	7	4.91
Oral Health and Preventive Dentistry	0	0	0	3	4	7	0.92
Infusionstherapie und Klinische Ernährung	1	5	0	0	0	6	-
Journal of Clinical Periodontology	1	0	2	3	0	6	5.24
Community Dentistry and Oral Epidemiology	0	0	1	1	2	4	2.13
European Journal of Oral Sciences	0	0	2	2	0	4	2.22
Indian Journal of Dental Research	0	0	0	0	4	4	0.37
International Journal of Paediatric Dentistry	-	-	0	2	2	4	1.99
Journal of Clinical Pediatric Dentistry	-	-	0	0	4	4	0.94
Journal of Dentistry for Children	-	-	-	1	3	4	0.66

*IF: Impact Factor. (-) Clinical Oral Investigations, International Journal of Paediatric Dentistry, Journal of Clinical Pediatric Dentistry, and Journal of Dentistry for Children started their publications in 1997, 1991, 1990, and 2002, respectively. The Infusionstherapie und Klinische Ernährung was discontinued and has no IF.

Xylitol Concentration, Frequencies of Dosage and Washout Period

In studies that presented more than one xylitol concentration tested, the mean value was considered. Among the studies that reported the xylitol posology, 78 (58.6%) used products with a dosage < 5 g/day and 55 (41.4%) used it ≥ 5 g/day, while among the studies that reported the xylitol concentration, 23 (41.1%) used a xylitol concentration < 15% and 33 (58.9%) tested it ≥ 15%. The highest frequencies of dosage were 2 pieces/day (n=17; 6.6%), 6 pieces/day (n=15; 5.8%), and 10 mL/intervention (n=11; 4.3%). Most crossover studies considered a washout period of 7 (n=16; 40.0%) or 14 days (n=6; 15.0%) (Table 3).

Table 3. Characteristics of the RCT included in the bibliometric analysis.

Variables	Studies N (%)	Mean (SD)	Range
Frequency (Daily)	170 (66.1)	3.3 (1.8)	1-15
Intervention Time			
Minutes	91 (35.4)	8.7 (8.1)	0.25-35
Days	239 (93.0)	173.4 (312.9)	1-1461
Xylitol Concentration			
%	56 (21.8)	32.0 (33.0)	0.002-100
Dosage			
Gram/Day	133 (51.8)	6.4 (10.6)	0.004-67
Pieces/Day	61 (23.7)	4.6 (3.2)	1-14
mL/Intervention	20 (7.8)	36.0 (69.3)	0.25-300
Washout (Days)	40 (15.6)	11.9 (14.5)	0.007-84

Presentation Form and Other Active Compounds

Some studies included in this bibliometric analysis tested more than one xylitol presentation form, associated products, and/or outcomes. The products exhibited a several presentation form, among them the

more common are chewing gum (44.0%), tablet (10.9%), parenteral nutrition solution (10.5%), mouthwash (9.3%), and toothpaste (7.0%) (Table 4).

Products containing xylitol as a single active compound were reported in 160 studies (62.3%) and they were associated with other active compounds in 90 studies (35.0%). Seven studies did not report the compounds (2.7%). The main associations were with sorbitol (10.1%), fluoride (8.5%), glucose (3.5%), and chlorhexidine (2.3%), respectively (Table 4).

Outcomes and Effects

The main outcomes evaluated were antimicrobial activity (39.3%), dental biofilm (plaque and calculus) (26.1%), dental caries (DMF-T, ICDAS, white spots lesions) (19.8%), salivary parameters (salivary flow, pH and buffer capacity) (13.2%), periodontal condition (10.9%), blood glucose levels (9.7%), xerostomia (5.0%), gastric emptying (3.1%), nasal symptoms (nasal obstruction, sneezing, rhinorrhea, snoring, headache, facial pain, and olfactory changes) (3.1%), quality of life (QoL) (3.1%), and acute otitis media (AOM) (2.7%) (Table 4).

A positive effect was observed in 204 studies, a null effect in 63 studies, and a negative effect in 27 studies (10.5%). Among the outcomes in which xylitol had a negative effect, dental caries was the most frequent (25.9%). A statistically significant difference regarding the xylitol products' effect was observed only for the xylitol concentration variable, since 90.0% of the products that presented xylitol concentration ≥ 15% exhibited a positive effect for the evaluated outcome (p=0.007) (Table 5).

Possible side effects associated with the use of xylitol products were reported in 21 (8.2%) studies, which were gastrointestinal effect as bloating, flatulence, bowel sounds, nauseas, vomiting, and diarrhea (n=14; 5.4%), oral burning (n=2; 0.8%), and atopic eczema (n=2; 0.8%). Eighty-three studies (32.3%) did not find any adverse effect, and the majority of the studies did not mention about side effects (n=153; 59.5%). Products in solution (n=3; 75%) and tablet forms (n=5; 45.5%) demonstrated a higher frequency of possible side effects. Among these, the gastrointestinal side effects were associated with a xylitol concentration ≥ 5 g/day (n=10; 83.3%) (p=0.03).

Table 4. Frequency of the presentation form, association with active compounds, and main outcomes of the RCT with xylitol intervention.

Variables	N	%
Presentation Form		
Chewing Gum	113	40.9
Tablet	28	10.1
Parenteral Nutrition Solution	27	9.8
Mouthwash	24	8.7
Toothpaste	18	6.5
Oral Solution	17	6.2
Nasal Irrigation Solution	9	3.3
Candy	8	2.9
Spray	6	2.2
Wipe	5	1.8
Varnish	5	1.8
Gel	4	1.4
Sweetener	3	1.1
Syrup	3	1.1
Powder	2	0.7
Others	4	1.5
Total	276	100.0

Associated Products		
Isolated Xylitol	158	61.5
Sorbitol	26	10.1
Fluoride	22	8.5
Glucose	9	3.5
Chlorhexidine	6	2.4
Fructose	4	1.6
Malic Acid	4	1.6
Probiotic	3	1.1
Bicarbonate	3	1.1
Green Tea	2	0.8
Funoran Extract	2	0.8
Magnolia	2	0.8
Others	9	3.5
Not Informed	7	2.7
Total	257	100.0
Main Outcomes		
Antimicrobial Activity	101	26.5
Dental Biofilm	68	17.9
Dental Caries	51	13.4
Salivary Parameters	34	8.9
Periodontal Condition	28	7.4
Blood Glucose Levels	25	6.6
Xerostomia	12	3.1
Gastric Emptying	9	2.4
Nasal Symptoms	8	2.1
Quality of Life	8	2.1
Acute Otitis Media	7	1.8
Malnutrition	6	1.6
Halitosis	4	1.0
Respiratory Tract Infections	4	1.0
Salivary/Biofilm Xylitol Concentrations	3	0.8
Others	13	3.4
Total	381	100.0

Table 5. Association between the xylitol products effect and data of frequency, time of intervention, dosage, concentration, composition, and other interventions in the RCT included in the bibliometric analysis.

Variables	Xylitol Products Effect		p-value*
	Positive N (%)	Null / Negative N (%)	
Frequency of Xylitol Use (Daily)			
< 3 times	38 (66.7)	19 (33.3)	0.630
≥ 3 times	140 (70.0)	60 (30.0)	
Time of Intervention (min)			
< 5 min	16 (69.6)	7 (30.4)	0.923
≥ 5 min	155 (68.6)	71 (31.4)	
Time of Intervention (Total Period of Treatment)			
< 28 days	78 (70.9)	32 (29.1)	0.620
≥ 28 days	100 (68.0)	47 (32.0)	
Number of Pieces (daily)			
< 3 pieces	20 (83.3)	4 (16.7)	0.106
≥ 3 pieces	150 (67.3)	73 (32.7)	
Dosage (mL)			
< 10 mL	3 (100.0)	0 (0.0)	0.241

≥ 10 mL	167 (68.4)	77 (31.6)	
Dosage (gram/day)			
< 5 g/day	46 (59.0)	32 (41.0)	0.063
≥ 5 g/day	41 (74.5)	14 (25.5)	
Xylitol (%)			
< 15%	11 (47.8)	12 (52.2)	0.007
≥ 15%	27 (81.8)	6 (18.2)	
Other Active Compounds			
Yes	63 (70.0)	27 (30.0)	0.759
No	109 (68.1)	51 (31.9)	
Other Interventions			
Yes	25 (69.4)	11 (30.6)	0.979
No	153 (69.2)	68 (30.8)	

*Statistical analyses were performed using the Chi-Square test, and the significance level was considered as $p<0.05$.

Discussion

Bibliometrics is a method used to draw the panoramic view and the current state of research on a given subject. This method consists of descriptive and quantitative analyses that aim to identify the characteristics of publications in a specific field of study, providing information for developing health research strategies [19]. Thus, in this study, the profile of clinical trials with xylitol and its applicability were described to inform healthcare professionals about the possible benefits of using products containing xylitol in different clinical conditions and assisting in the development of future research on the topic.

In the present bibliometric analysis, the studies selected were limited to RCT, which are characterized as the most relevant primary studies when considering the production of scientific evidence in the face of interventions [20]. So, two hundred fifty-seven RCT were included, and their data were extracted to evaluate the xylitol applicability and its effects worldwide.

Over the years, there has been an increase in the number of RCT with xylitol, which may suggest a large search and use for alternative products instead of conventional therapies for different clinical outcomes. This increase was greater in dentistry, which also grouped most studies. This can be justified due to the large number of clinical outcomes related to dentistry and, consequently, their greater applicability in this area.

In order to standardize the classification of the age groups between different studies, the World Health Organization criteria were considered [21]. Adults were more common in the present study, probably because the included studies with elderly (70%) and adolescents (31.3%) also incorporated adults in their sample, and by the facility in carrying out studies with this population compared to children.

Preventive treatment prevailed among studies and was performed to evaluate especially antimicrobial action [22-30], dental biofilm control [23,25,28,31] and blood glucose levels [9,13,14,32], while the therapeutic treatment was tested mainly for xerostomia [33-36], halitosis [35,37-39], gastric emptying [7,8,40,41], and respiratory tract infections [11,42]. The studies cited above showed a positive effect, which suggests that xylitol can be used for such outcomes if it follows the other characteristics of the studies' interventions.

The indirect treatment was observed in only 13 studies, all about dentistry [43-55]. In these studies, the mother-child transmission and the effect of products containing xylitol against dental caries, periodontal conditions, and /or counts of oral microorganisms in mother and child were assessed. Although some of these studies have shown a positive effect, this may be associated with non-evaluated confounding factors, such as the bias in the measurement of outcomes due to the lack of blinding and calibration of the examiners. It is known

that this type of indirect effect is no longer considered due to the change in paradigms related to the etiology of dental caries [56,57].

Industrialized products containing xylitol have been used in several countries, especially by the food and pharmaceutical industries [58]. The significant number of countries included in this research reflects the global use of xylitol. The USA contributed most to the overall production of xylitol studies, followed by Finland and Germany. The high number of studies in these countries may be due to the greater consumption and addition to the population's diet. Brazil appeared among the top 10 countries with the largest production of studies on the subject, despite the fact that the Brazilian population did not frequently consume xylitol products due to their high cost. This finding can be justified because it is one of the countries with the most publications in dentistry [59].

The Caries Research was the journal with the largest number of publications, which can be justified by the most significant number of dentistry studies and due to the scope of the journal, as well as the relationship between xylitol and this topic. Although the studies have not been evaluated for their methodological quality, it is assumed that, as Caries Research is one of the leading journals with an excellent impact factor in the area, the investigated dentistry studies probably have a good methodological rigor [60]. Besides, the journal with the highest impact factor was the Journal of Clinical Periodontology, also of dentistry area.

The frequency and duration of the intervention and the washout period in crossover studies vary according to the type of treatment, outcome assessed, and also due to the different objectives and protocols among the studies evaluated. The greater frequency daily (10 and 15×) was observed for preventive treatment [61,62]. Dental caries was the outcome that presented a longer time of intervention (4-year) probably because some clinical changes in this outcome can be better observed in the long term [47], while some interventions that evaluated blood glucose levels, salivary parameters, halitosis, and urinary effects, for example, were performed only once [14,63-67], considering that variations in these outcomes may occur in the short term. The washout was longer to gastric emptying (12-week) [68], while the short term (1 day) was regarding salivary parameters [69] and halitosis [64]. It is expected that the longer the frequency and duration of interventions, the results would be more favorable [70]. However, it becomes more difficult the treatment adherence and follow-ups of participants, besides the possibility of unforeseen confounding factors in long-term studies.

The lowest daily xylitol posology (0.004 g/day) was used for two weeks as a therapeutic treatment to nasal symptoms, in the form of a nasal irrigation solution (0.002%) [71], and as an indirect treatment to reduce the colony count of *Streptococcus mutans*, in saliva and biofilm, for 9 months, in chewing gum form [48]. The highest daily xylitol posology (67 g/day) was also tested for 2 years as an indirect treatment against the colony count of *S. mutans* in saliva and dental caries in chewing gum form [43]. The highest xylitol concentration (100%) was tested as a preventive treatment in adolescents to control the colony count of *S. mutans* in saliva for 1 month, also in chewing gum form (2.56 g/day) [22]. Despite the variability of the studies, an overview about the potential of chewing gums in oral health suggested that a dosage of 5-10 g/day xylitol divided into 3 or more times of consumption are needed for therapeutic effects [72].

Most of the tested products presented xylitol as the only active compound in the formulation. Regardless of this result, it is known that most commercially available products have, in their composition, other polyols or associated active compounds, to enhance the effect of this product or as a blend body agent to reduce the product cost. Besides, it can also be justified by the high cost of xylitol compared to other sugars [73]. Among the studies, products that contained xylitol as a sweetener or as a secondary compound were also

observed, as in probiotic formulations [74]. Furthermore, other products, also related to dentistry, showed a combination of xylitol and sorbitol or fluoride to control dental biofilm, white spot lesions and improve salivary parameters [23,30,75-81]. However, there was no statistical difference between studies regarding the effect of products with isolated xylitol compared to xylitol associated with other active compounds in the present review.

The presentation form of the products varied according to the clinical outcome evaluated. Chewing gum was the most common form among studies and may have been chosen due to its greater acceptance by the general population. The more recent studies exhibited a positive effect of xylitol gums for antimicrobial activity [22,23,25,26,30,82], dental caries [30,82], dental biofilm [23,31,82], periodontal condition [23,30,31], salivary parameters [26,30,67], and gastric emptying [12]. The presentation forms less common are aerosol, tested for treat acute rhinopharyngitis in children, but without positive effect [83]; cream to treat atopic dermatitis and *Staphylococcus aureus* in the skin of adults [84], and milk to control *S. mutans* in children's biofilm and saliva [18,85]. It is believed that these products' presentation forms were less used among the studies because they have a more restricted applicability, as the aerosol and cream, or because they are more perishable, as the milk.

The main outcome assessed was the antimicrobial activity, in which only three studies were not in dentistry [84,86,87]. Regarding to oral health, the mechanism of action of xylitol is to inhibit the growth and production of acids by microorganisms present in the biofilm, such as *S. mutans*, in the glucose exposure; facilitate the remineralization of the initial dental caries and arrest the progress of dental caries; and stimulate the production of saliva to neutralize acids, providing the necessary ions for remineralization [88]. In addition, the forms of chewing gum and tablets presentation increase the salivary flow, pH, and buffer capacity of products containing xylitol. Therefore, these products can also be indicated for patients with xerostomia, as is the case of those undergoing chemotherapy / radiotherapy [89,90].

Xylitol has also been used to regulate blood glucose levels, as this sucrose substitute has a low absorption rate in the gastrointestinal tract [1,13,32,75]. For the same reason, xylitol can be used for gastric emptying [7,12,40,68,91].

The evaluation of these products' antimicrobial effects becomes more complicated when xylitol is associated with other compounds, resulting in major or minor positive effects. The minor effect may be due to an interaction in which one of the active compounds nullifies the other's effect. Therefore, we suggest that further studies should be carried out with isolated xylitol as well as with the chemical composition of the tested product to identify more precisely the interaction among the compounds present in these products.

Most studies showed a positive effect in relation to the evaluated outcome; however, the concentration was the only variable that showed a statistical difference. The dosage in grams per day showed a tendency for the same result, but the absence of statistical difference may have been due to the low number of studies that provided this information. The same can be applied to the other parameters, possibly because not all studies provided the necessary data for statistical analyses.

Few studies reported information related to possible side effects. Among these studies, a minority exhibited these effects (especially gastrointestinal side effects), which generally occurred mildly and in few study participants. These side effects can be justified due to low xylitol absorption in the gastrointestinal tract, which consequently results in increased bowel movement, nausea, flatulence, bloating, stomachache, diarrhea, and vomiting [13,41,92-96]. One study reported more complicated side effects (deep vein thrombosis, bronchospasm, and hemoptysis); however, the participants of this study presented a critical health condition

since they were hospitalized with a pulmonary exacerbation of cystic fibrosis [42]. Nevertheless, the reporting of side effects is a relevant information that should be presented in future studies to alert about possible undesirable effects resulting from the use of products containing xylitol.

This bibliometric analysis presents limitations inherent to the primary studies. Several data, such as xylitol concentration, product composition, daily frequency, and intervention times, were not provided in some studies. Given these findings, further RCT with better intervention descriptions are needed to evaluate the proposed criteria. Further, the variability among the studies makes the comparison with other products problematic. Furthermore, it is impossible to conclude certainty of evidence since the methodological quality and the risk of bias of the studies were not evaluated.

However, this is the first study about the xylitol applicability and effect in different areas of health, worldwide, specifically with bibliometric approaches. In addition, the authors believe that these findings provide useful information for researchers and health professionals, especially to design new studies. Therefore, with the present results, it was possible to view that the studies about xylitol have been developed over the years and applied in different areas of health for different clinical conditions.

Conclusion

The studies with xylitol have increased worldwide, with the majority carried out with adults, in the dentistry field, and under preventive treatment. The largest number of these studies were developed in the United States and published in Caries Research. The chewing gum form is the most common, with antimicrobial activity as the main outcome. Most xylitol products presented a positive effect, and few studies reported side effects.

Authors' Contributions

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All authors declare that they contributed to critical review of intellectual content and approval of the final version to be published.

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Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

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