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ORIGINAL ARTICLE

Research Trends on Preventive and Therapeutic Use of TIF_4 for Dental Caries and Erosion

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ABSTRACT

Objective: To evaluate TIF_4 preventive and therapeutic use in caries and erosive lesions. **Material and Methods:** Searches were performed in six databases. Studies evaluating TiF_4 use *in vitro*, *in situ*, and *in vivo* in caries and erosive lesions were included and imported into VantagePoint™ (VP). Data about publication year, authors, country, journal, study design, outcomes, TIF_4 vehicles, application and intervention time, cariogenic challenge, erosive cycles, effects (positive/ negative /null) and approach (preventive/therapeutic) were analyzed through VP and Excel. **Results:** 93 published studies were included and an increase in publications was observed between 2010 and 2021. Forty-three authors published three or more articles, of which 67.4% were developed in Brazil and published in Caries Research (22.6%). 69.9% were *in vitro* studies with erosion assays (59.1%) and with preventive approaches (67.4%). The principal vehicle was a solution (69.9%) with a 1-min single application (58.0%) and with an intervention time of 5-7 days (22.6%). The principal cariogenic challenge *in vitro* was pH cycling (11.8%); *in situ* was sucrose + biofilm (6.2%); and *in vivo*, biofilm (6.2%). The most used erosive cycle was 4× per day in *in vitro* studies (20.4%) and 1× *in vivo* (2.1%). A positive effect was observed in prevention (41.9%) and treatment (24.7%) studies. **Conclusion:** TIF_4 has shown a positive effect in prevention and therapeutic treatments for dental caries and erosion.

Keywords: Dental Caries; Fluorides; Tooth Erosion.

Introduction

Dental caries is a dynamic process that involves a chemical dissolution brought by biofilm metabolic activity covering the tooth surface in the presence of sugar. As time passes by, these alterations could break the equilibrium in the demineralization/remineralization process between the tooth mineral. So, mineral loss, subsequent enamel lesions, and possible tooth decay formation are symptoms of imbalance in this dynamic process [1].

Another clinical condition that is usually seen in dental practice is dental erosion. It is a tooth lesion caused by exposure to dietary acids, which has been received attention because of its increasing prevalence. This alteration shows two distinct steps: an initial phase classified as "Erosion", where there is only a softening of the tooth enamel and an advanced phase called "Erosive Tooth Wear", where tooth surface loss is due to the successive erosive attacks with a remained softened surface [2].

Dental caries and tooth erosion are the main problems that affect tooth structure [3,4] and are also the conditions that fluoride is widely used for preventive and therapeutic treatments [5,6]. Among the fluorides, titanium tetrafluoride (TIF_4) has first appeared in 1972 as a new type in dentistry [7]. This compound is obtained by a fluoride uptake and a rich titanium coat formation over exposed tooth's substrate. When TIF_4 is applied over the teeth, titanium ions links with oxygen forming a titanium dioxide (TiO_2) alkali insoluble coat [8,9] that is more resistant than any other fluoride agent [10], decreasing enamel solubility [11], reducing caries lesions formation and enhances enamel fluoride concentration [12]. TIF_4 also reduces the progression of erosive/abrasive lesions in the first application and the evolution of the erosive process in multiple applications [13]. These preventive and/or therapeutic effects listed are similar when TIF_4 is applied on enamel, dentine, and cement, independently of the vehicle type, such as solution [14–17], toothpaste [18], gel [19] or varnish [20].

Considering its large application for preventive and therapeutic use in dental caries and erosion and the various published studies with TIF_4, except clinical trials, over the past three decades, it would be meaningful to plot a bibliometric landscape of the history and trends about this compound, supporting researchers about what is necessary to advance in terms of new studies to give scientific evidence about the TIF_4 clinical applicability. Thus, the purpose of the present study was to evaluate TIF_4 applicability and effects, considering its preventive and therapeutic uses for dental caries and erosion treatments, through a bibliometric review.

Material and Methods

Eligibility Criteria

In vitro, *in situ*, and *in vivo* published studies were included. To be eligible, the studies should be performed in human or animal teeth, treated with TIF_4 compared with negative control, placebo or other fluoride treatment to identify its effect and applicability on dental caries and erosion in enamel and dentine. Case reports, literature reviews, editorials, research letters and other studies that did not comply with the inclusion criteria were excluded.

Literature Search Strategy

Two examiners (ABC and KLF), guided by a librarian (DM), independently performed the search process adapted to each database. The following electronic databases were searched: MEDLINE/PubMed, Scopus and Embase/Elsevier, Web of Science/Clarivate Analytics, Cochrane Library, Virtual Health Library -

VHL (Lilacs/BVS). Searches were performed in December 2021 without any restrictions regarding the year or language of publication. The search strategy was created to MEDLINE/PUBMED by using MeSH terms, entry terms and free terms used were included, using the Boolean operators "AND" and "OR" to combine search terms related to the following words: enamel, dentin, dental erosion, dental caries, fluoride, tetrafluoride, and titanium tetrafluoride. The searches were adapted to syntax rules of each database. A manual search was carried out in the reference lists of the articles selected for this bibliometric review to detect relevant publications possibly missed in the databases searched. Articles retrieved from more than one database were computed only once. Databases alerts were set to retrieve newly published articles until November 2020.

Selection Procedures

Articles searched were exported to the Endnote® Web reference management software (www.myendnoteweb.com) and then to the VantagePoint™ software (Search Technology, Inc., Florida, USA) in which two reviewers (ABC and KLF) removed duplicates and performed the screening. Articles in which the title and abstract did not contain sufficient information were analyzed in full to verify their eligibility. When the agreement between the two reviewers was not reached, a third reviewer (LCM) was asked for final a decision.

Data Extraction

The reviewers (ABC and KLF), manually and independently, extracted the main study characteristics and, with the aid of a third reviewer (LCM), organized the data on the VantagePoint™ software (Search Technology, Inc., Florida, USA) in the following categories: year of publication, authors, country, journal title, study design, keywords, outcomes (caries/ erosion), treatment goal (preventive/ therapeutic), TIF_4 vehicles (solution, varnish, gel or toothpaste), dental substrate (enamel/dentine), TIF_4 concentration (%), application time (minutes of TIF_4 application over dental substrate), period of intervention (trial period), cariogenic challenge (sucrose application, bacterial inoculation or pH cycling) or erosion cycles (cycle' times per day) and the application's effect (positive, null or negative in relation to the negative control, placebo or other fluoride treatment).

Regarding the application's effect, a positive effect was observed when TIF_4 had a better effect than the negative control, placebo, or other fluoride; a null effect when TIF_4 had a similar effect than negative control, placebo, or other fluoride; and a negative effect when TIF_4 presented a worst effect than negative control, placebo, or other fluoride.

Data Analyses

Bibliometric data analyzes were carried out in the VantagePoint™ (Search Technology, Inc., Florida, USA) and Microsoft Office Excel 2010 (Microsoft®, USA). The frequency values (absolute and relative) were calculated for all variables.

The articles' publication year was divided into decades since the publications were from 1972 to 2021. The top authors were classified according to the number of published articles (three or more) in TIF_4 subject as experts in this field. The study's country of origin was defined by the address provided in the manuscript, considering the corresponding author. Finally, the most cited 50 keywords, excluding the words from the search strategy, were sorted and mentioned in a word cloud.

The study design was classified as *in vitro*, *in situ*, *in vivo* (animals) and *in vivo* (humans). The *in vivo* (humans) studies were also classified as Non-randomized and Randomized Clinical Trials). The studies' outcomes were considered as dental caries and tooth erosion; trials treatment goals were separated as preventive or therapeutic approaches; TIF_4 vehicles were categorized as a solution, varnish, gel or toothpaste; TIF_4 concentration was the percentage (%) of TIF_4 vehicle; dental substrate was enamel or dentine; the application time was defined as the minutes of TIF_4 applied over the dental substrate; period of intervention was the duration of trial period in hours or days; the cariogenic challenge was determined regarding the method adopted for developing dental caries and was divided as sucrose application, bacterial inoculation or pH cycling); for developing tooth erosion, it was taking account the number of cycle times per day; and application effect (positive, null or negative in relation to negative control, placebo or other fluoride treatment) as explained above.

Results

The electronic search resulted in 4112 articles. After removing the duplicates and screening the titles and abstracts, 137 articles were selected. Of these, 45 were excluded after reading the full text carefully. Thus, a total of 93 articles were selected (Figure 1). Among the excluded articles, four were only about titanium tetrafluoride chemistry; eight articles were about composite microleakage; ten articles were about TIF_4 application in cement; two articles were about toxicity; five studies used TIF_4 as root canal irrigation; one article was about titanium (metal); nine articles were about resin bond strength; five articles were about fluoride uptake after animal's inoculation, and one was sample overlapping.

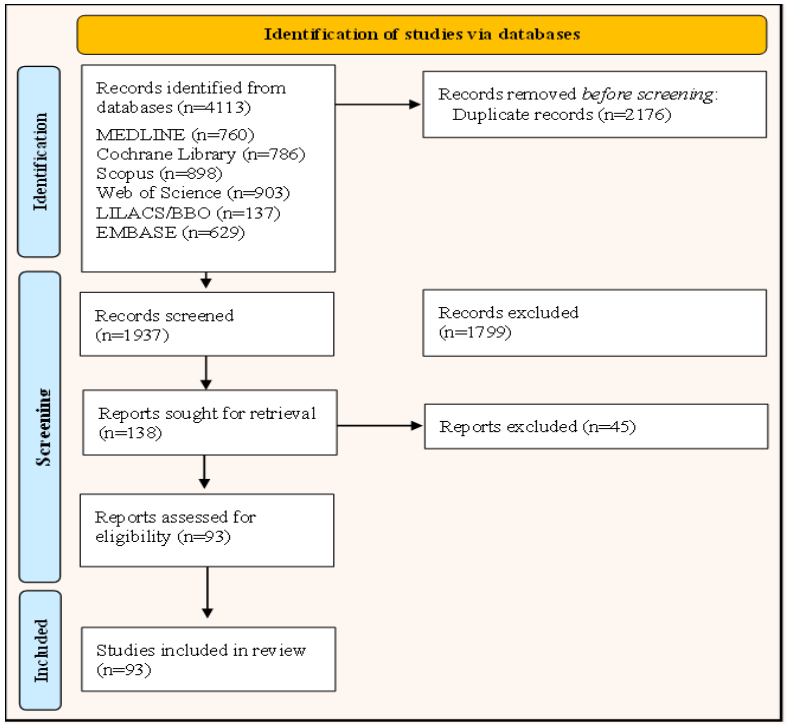

Figure 1. Flowchart considering the search results in databases.

Bibliometric Data for Publication Period and Authors Publications

The oldest study of titanium tetrafluoride was published in 1972. The bibliometric indicators showed an increase in publication rate over time (1972-2021). The period with the greatest number of articles was from

2010 to 2021, with fifty-eight articles published. Bubble charts showed that TIF_4 solution and *in vitro* studies were the vehicle and type of study more frequent among the included articles (Figure 2).

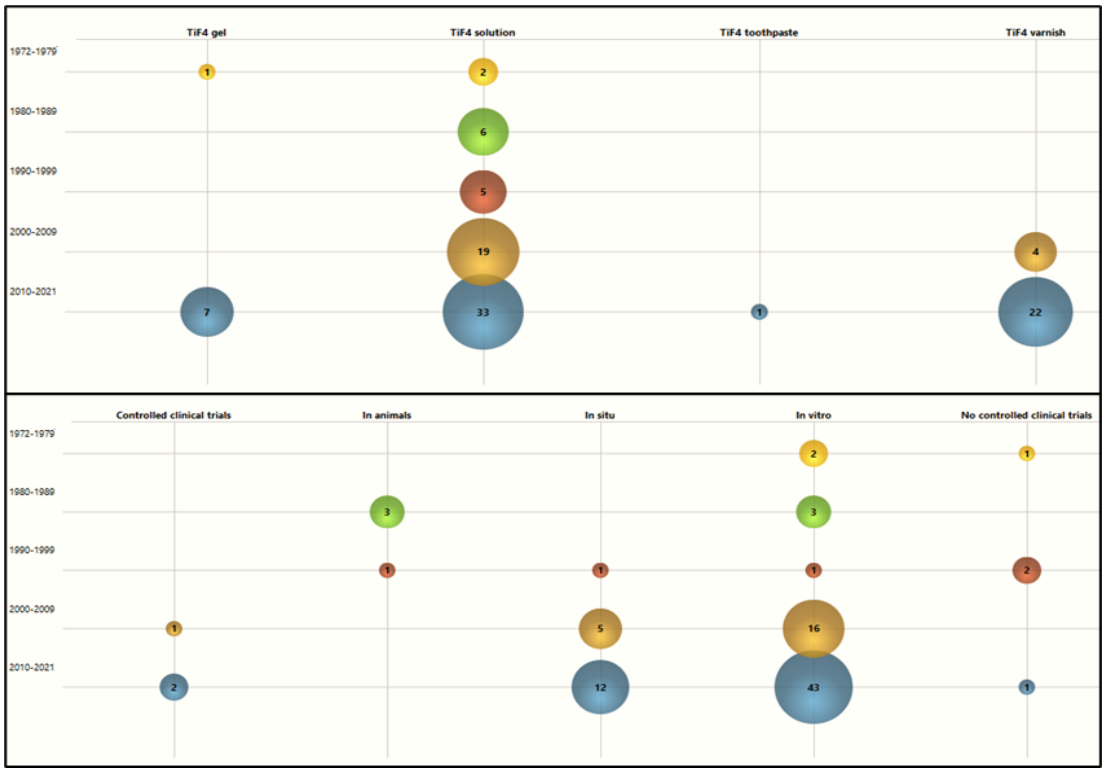

Figure 2. Annual scientific output of the published studies according to the TIF_4 vehicles and study design.

A total of 43 authors (22.8%) with more than three publications contributed to the production of articles about TIF_4 (Figure 3). The journals that published the highest number of articles on TIF_4 were Caries Research (n= 21 / 22.6%), followed by Archives Oral Biology (n= 11 / 11.8%), and Journal of Dentistry (n= 7 / 7.5%) (Figure 4).

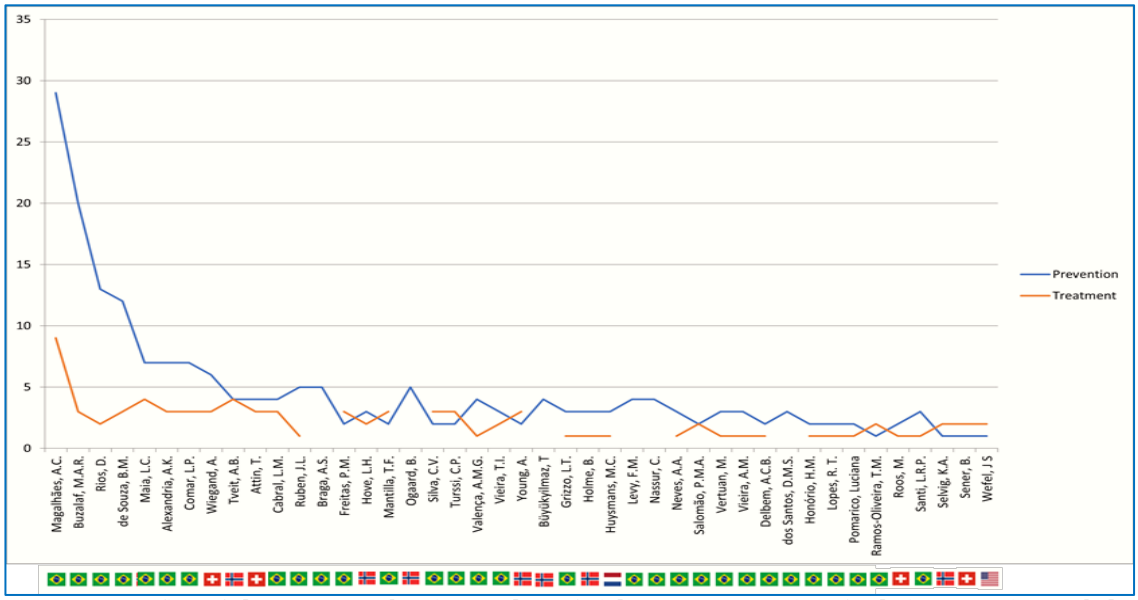

Figure 3. Profile of the most productive authors (with 3 or more articles), their countries and the treatment goal.

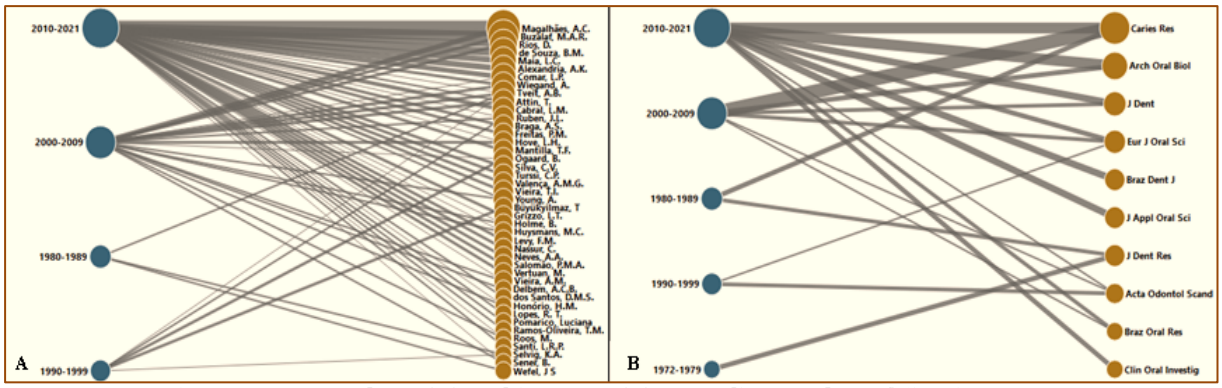

Figure 4. Top authors (A) and journals (B) according to the publication year.

Bibliometric Data by Country and Keywords

The annual number of scientific publications for each country is presented in Figure 5. Among the countries that researched and published articles in TIF$_4$ field, Brazil was the most productive, with more than half of publications worldwide (n= 63 / 67.8%), followed by Norway (n= 19 / 20.4%) and Switzerland (n= 11 / 11.8%). Analysis of the 50 most mentioned keywords showed a different pattern because the most cited ones catered to topics ranging from "animals"/"cattle"/"humans" and outcomes assessment aspects such as "microscopy"/"electron"/"scanning". These studies showed heterogeneity in methodology using different combinations of keywords (Figure 6).

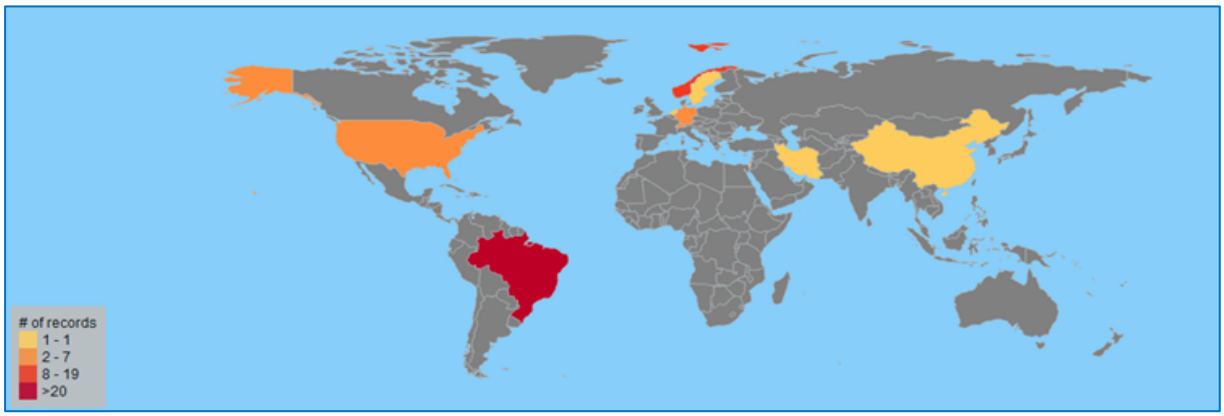

Figure 5. World map of the TIF$_4$ publications' distribution.

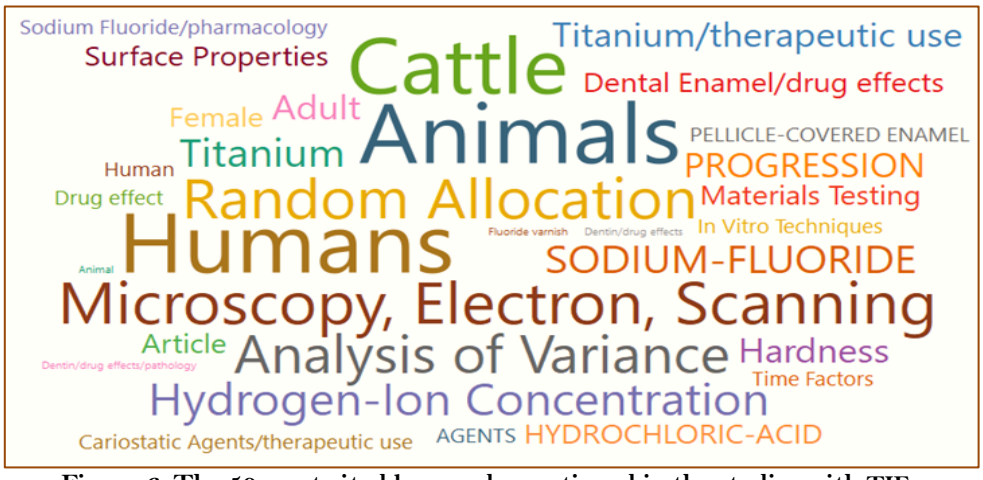

Figure 6. The 50 most cited keywords mentioned in the studies with TIF$_4$.

Bibliometric Data by the Studies' Methods

Preventive treatment was more prevalent among the included studies, especially for tooth erosion outcomes (n=34 / 36.5%) (Figure 7). A number of studies according to variables extracted from the research's methods, such as concentration, application time and intervention period of TIF_4, as well as the outcomes, are shown in Table 1. Overall, articles *in vitro* were the most published (68.8%) and TIF_4 solution was the most vehicle used in the trials (69.9%). Ten studies were carried out *in vivo*, but only three (3.2%) of them were randomized controlled clinical trials (RCT), showing a lack of these trials with TIF_4. Also, the studies that carried out erosion assays (59.1%) were the most frequent, as well as those that presented a prevention treatment goal (66.6%). Regarding dental substrate, studies showed that enamel was more investigated (80.6%) and dentine was studied in 27 (29.0%) articles.

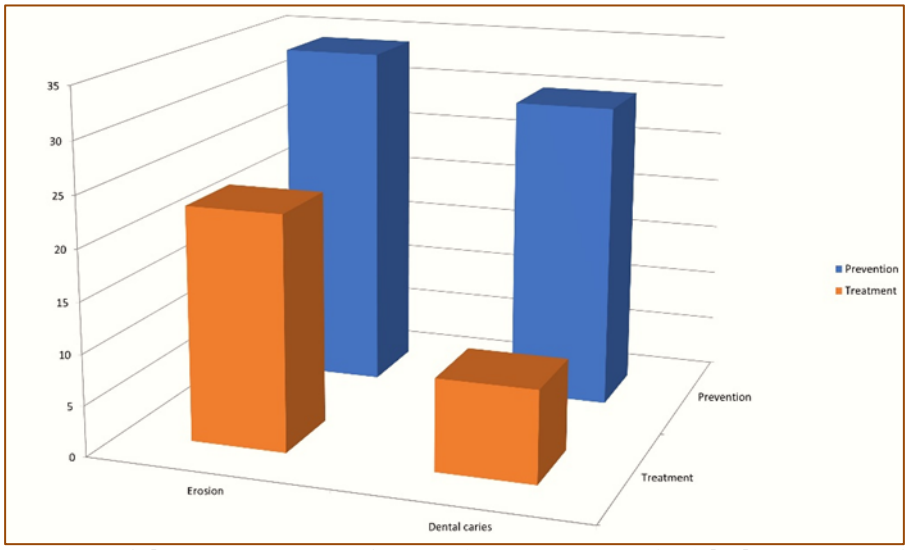

Figure 7. Association of the treatment goal (prevention or treatment) with the outcomes (dental caries and erosion).

Table 1. Distribution of the studies by tooth substrate, TIF_4 vehicle, treatment goal and outcomes investigated.

Variables	Categories	Number of Studies					
		in vitro	*in situ*	*in situ* and animals	*in vivo*		
					Animals	HCT	HRCT
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Substrate	Enamel	42 (45.1)	15 (16.1)	1 (1.0)	2 (2.1)	3 (3.2)	3 (3.2)
	Dentin	15 (16.1)	1 (1.0)	-	2 (2.1)	-	-
	Associated	7 (7.5)	2 (2.1)	-	-	-	-
Vehicles	Solution	38 (40.8)	11 (11.8)	-	4 (4.3)	3 (3.2)	2 (2.1)
	Varnish	15 (16.1)	3 (3.2)	1 (1.0)	-	-	1 (1.0)
	Gel	4 (4.3)	3 (3.2)	-	-	-	-
	Toothpaste	1 (1.0)	-	-	-	-	-
	Solution and Varnish	5 (5.3)	1 (1.0)	-	-	-	-
	Solution and Gel	1 (1.0)	-	-	-	-	-
Treatment Goal	Prevention	40 (43.0)	13 (13.9)	1 (1.0)	2 (2.1)	2 (2.1)	2 (2.1)
	Treatment	22 (23.6)	5 (5.3)	-	2 (2.1)	1 (1.0)	-
	Associated	2 (2.1)	-	-	-	-	1 (1.0)
Outcomes	Caries	21 (22,5)	8 (8.6)	1 (1.0)	3 (3.2)	3 (3.2)	2 (2.1)
	Erosion	42 (45.1)	9 (9.6)	-	1 (1.0)	-	1 (1.0)
	Associated	1 (1.0)	1 (1.0)	-	-	-	-

HCT: Humans Clinical Trial; HRCT: Humans Randomized Controlled Trial; Associated: when different variables were considered at the same time.

The characteristics of the TIF_4 products are observed in Table 2. The concentration of 4% was more frequently used (n= 32 / 32.2%), as well as the application time of 1 min (n= 52 / 55.9%), and the intervention period 5 and 7 days were more frequently observed (n= 35 / 37.6%). The longest trial period was observed for studies *in vivo* with a minimum of 28 days (n=7 / 7,5%). The caries challenge considered for *in vitro* studies was pH cycling (n= 11 / 11.8%), for the *in situ* was sucrose + human dental biofilm (n= 5 / 6.2%) and for *in vivo* was human dental biofilm (n= 5 / 6.2%). The erosion cycles more common was 4 × for *in vitro* studies (n= 19 / 20.4%) and 1 × for *in vivo* (n= 2 / 2.1 %).

Table 2. Number of studies according to the research's variables.

Variables		Categories	Number of Studies					
			in vitro	*in situ*	*in situ* and animals	*in vivo*		
			N (%)	N (%)	N (%)	Animals N (%)	Humans CT N (%)	Humans RCT N (%)
Concentration		< 1 %	6 (6.4)	1 (1.0)	-	-	-	-
		1 %	19 (20.4)	3 (3.2)	-	1 (1.0)	-	2 (2.1)
		1.23 – 3.4 %	22 (23.6)	4 (4.3)	1 (1.0)	3 (3.2)	-	-
		4 %	16 (17.2)	10 (10.7)	-	-	3 (3.2)	1 (1.0)
		> 4 %	1 (1.0)	-	-	-	-	-
Application Time		< 1 min	4 (4.3)	-	-	-	-	-
		1 min	33 (35.4)	10 (10.7)	1 (1.0)	2 (2.1)	3 (3.2)	3 (3.2)
		2 – 5 min	13 (13.9)	6 (6.4)	-	2 (2.1)	-	-
		> 5 min	11 (11.8)	1 (1.0)	-	-	-	-
		Uniformed	3 (3.2)	1 (1.0)	-	-	-	-
Period of Intervention		< 1 day	15 (16.1)	-	-	-	-	1 (1.0)
		1 – 4 days	11 (11.8)	1 (1.0)	-	-	-	1 (1.0)
		5 – 7 days	29 (31.1.5)	6 (6.4)	-	-	-	-
		8 – 21 days	8 (6.8)	9 (9.7)	1 (1.0)	3 (3.2)	-	-
		≥ 28 days	-	2 (2.1)	-	1 (1.0)	3 (3.2)	1 (1.0)
Outcomes	Caries Challenge (n=31)	Sucrose + Bacterial inoculation	4 (4.3)	-	-	1 (1.0)	-	-
		Sucrose + Biofilm human	5 (5.3)	5 (5.3)	1 (1.0)	-	-	-
		Biofilm human	-	1 (1.0)	-	-	3 (3.2)	2 (2.1)
		pH cycling	11 (11.8)	2 (2.1)	-	2 (2.1)	-	-
	Erosion Cycles (n=47)	1 ×	1 (1.0)	-	-	1 (1.0)	-	1 (1.0)
		2 – 3 ×	11 (11.8)	3 (3.2)	-	-	-	-
		4 ×	19 (20.4)	4 (4.3)	-	-	-	-
		> 4 ×	11 (11.8)	2 (2.1)	-	-	-	-
	Associated (n=2)	pH cycling + 4 ×	1 (1.0)	-	-	-	-	-
		Sucrose + Biofilm human + 2 ×	-	1 (1.0)	-	-	-	-

CT: Clinical Trial; RCT: Randomized Controlled Trial; Associated: when different variables were considered at the same time.

The positive effect was found in both prevention (41.9%) and treatment (24.7%) type of therapies (Table 3).

Table 3. Numbers of studies according to the effect of TIF_4 (positive, null or negative) when compared to negative control, placebo or other fluoride treatment.

Variables	Categories	Number of Studies					
		in vitro	*in situ*	*in situ* and animals	*in vivo* animals	*in vivo* humans CT	*in vivo* humans RCT
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Prevention (n=58)	Positive	24 (25.8)	8 (8.6)	-	1 (1.0)	2 (2.0)	1 (1.0)
	Null	9 (9.6)	5 (5.3)	1 (1.0)	1 (1.0)	-	1 (1.0)
	Negative	5 (5.3)	-	-	-	-	-
Treatment (n=32)	Positive	12 (12.9)	5 (5.3)	-	2 (2.1)	1 (1.2)	-
	Null	6 (6.4)	-	-	-	-	-
	Negative	6 (6.4)	-	-	-	-	-
Associated (n=3)	Positive	2 (2.1)	-	-	-	-	1 (1.0)
	Null	-	-	-	-	-	-
	Negative	-	-	-	-	-	-

CT: Clinical Trial; RCT: Randomized Controlled Trial; Associated: when different variables were considered at the same time.

Discussion

Due to the absence of articles showing a review about TIF_4 as a fluoride compound applied in Dentistry, we found that it would be interesting to do a bibliometric review compiling all published articles that used TIF_4 over enamel and dentine for prevention or treatment of caries and tooth erosion. Thus, all *in vitro*, *in situ* and *in vivo* (humans and animals) studies were selected according to an eligibility criterion previously described, amounting to a total of eighty articles that support researchers about what have been studied in the field over time as well as about what is necessary to advance in terms of new studies.

Since the first dentistry publication of TIF_4 in 1972 [7], this fluoride compound has been studied for almost fifty years and many issues have been published on this subject, reaching a peak of TIF_4 trials publication worldwide between 2010 and 2019 [6,12,18,21-28]. This fact led us to think that authors have seen TIF_4 as a promising fluoride compound and tried to investigate all preventive and therapeutic effects to use it in clinical routine for dental caries and tooth erosion.

Among the nineteen authors that were considered the most productive with more than three published articles on this field, almost half of them were Brazilians, highlighting Magalhães, AC; Buzalaf, MAR; Rios, D and Comar, LP that have published over ten articles each, corroborating to the institutional collaboration networks, in which the Brazilian institutions were the most productive in worldwide. The high Brazilian productivity is expected since Brazil is the 13th in the world in terms of the number of peer-reviewed papers and its research output grows annually [29].

Regarding the source, Caries Research was the journal with the greatest number of published TIF_4 articles. Concerning that Caries Research has a great reputation and a good impact factor of 2.186 (2019) in Dentistry, this led us to believe that these articles have a high standard of methodological protocol quality.

Analyzing the word cloud, keywords most cited in articles (excluding keywords of data search) were "animals"/"cattle"/"humans" and outcomes assessment aspects as "microscopy"/"electron"/"scanning". Probably, the words animals/cattle/humans have been shown because of the bovine teeth commonly used in several *in vitro* [30,31] and *in situ* [11,32] studies. Also, the words microscopy/electron/scanning are due to the most common outcomes assessment for study analysis in this field [11,19,32-38].

Regarding the type of articles published, the most found were *in vitro* studies that have a lower hierarchical position in scientific evidence, followed by *in situ* studies, compared to the smallest amount of clinical trials [16,33,34] and RCT [20,39,40], but besides this lower hierarchical position, they have a great importance to produce trials research hypothesis. The largest number of in vitro studies found is probably due to ethical reasons such as safeguarding patients from deleterious effects during the trials, the convenience of selecting a sample for a survey, and the guarantee the researcher has more control of study variables too [41].

The prevention goal was more prevalent among the studies approach and it was performed especially for tooth erosion [15,19-21,38,42-46]. Regarding that public politics are focused on prevention and TIF_4 has a preventive approach by forming a Ti-coat over enamel, maybe this material could have a greater response in prevention than in therapeutical manners for both dental caries and erosion. Although there are more articles about tooth erosion prevention, researches using TIF_4 to prevent dental caries has achieved results as good as on the erosive process [11,33-39,47].

When analyzing TIF_4 vehicles, it could be found that TIF_4 solution [18,32-38,42,43,48] was the most used vehicle in the studies, followed by varnish [12,18-20,28] and gel [13,19] with 4% concentration and 1 minute of application time. These were found to agree with the majority of studies of TIF4 that uses different types of vehicles over the dental substrate but with the same concentrations and a short application time to create a standardized protocol use of this fluoride compound.

The frequency and duration of the intervention, as well as the washout period in crossover studies, varied according to the type of treatment and outcome assessed. This variability is also due to the different objectives and protocols of the studies evaluated. The outcome that has a longer time of intervention and follow-up was dental caries ranging from 3-years [39] to a month [34]. For tooth erosion, this period varied from 2-weeks [45] to 1-day [40,49] and washout duration was much longer to cariogenic challenge (10-days) [11,20,47], while the short term (3-days) was regarding tooth erosion [15]. Although it is well known that intervention adherence and subjects' follow-ups in long-term studies can be difficulted and unexpected confounding factors may occur during the trials, it is welcoming when new studies help researchers in choosing a clinical protocol that achieves the best outcome with the shortest intervention time.

Observing conducted studies with TIF_4, the majority of them supports that this compound had positive effects for both prevention or treatment outcomes, when compared with other fluoride compounds or no treatment, suggesting that this fluoride would be a good choice to be use in clinical trials.

Concerning its clinical use, only a few studies reported some information regarding the possible side effects of TIF_4 application over enamel. Pedro et al. [50] and Pomarico et al. [16] reported a yellowish-brown pigment, suggesting a possible reaction between this fluoride compound and white spotted lesion in the enamel. One hypothesis is that the interaction between TIF_4 and the proteins on the tooth's surface influences the incorporation of fluoride and changes the constitution of this glaze, resulting in this unexpected stain. Although, the authors suspect that, as there was no food restriction, it could be possible that the patient's diet may also have been responsible for this glaze's pigmentation and raised another hypothesis related to the titanium reaction with phosphate groups on the tooth's surface with the oxygen atoms, forming a stable titanium dioxide [51]. Corroborating with these authors, Mosquim et al. [52] observed that both TIF_4 varnish and TIF_4/NaF solutions have demonstrated a staining potential with the same magnitude as commercially available NaF varnishes and Elmex® solution when applied over sound or eroded enamel.

Regarding the TIF_4 low pH and probably its toxicity, studies of Huggins and Froehlich [53], Shrestha and Olsen [54] and Shrestha [55] inoculated rats with TIF_4 and observed no toxic effect in their works. These

results were corroborated by Alexandria et al. [47], which verified that TIF_4 showed no oral toxicity and was effective in preventing caries in rats. Although no microbiological changes occurred in the biofilm adhered to the enamel surface treated with TIF_4 varnish, a decrease in caries lesion depth was observed, probably because of enamel fluoride uptake after TIF_4 application. Both TIF_4 and NaF varnishes were able to reduce the progression of the lesions under high cariogenic activity *in situ*. Therefore, studies development aiming at other fluoride compounds such as TIF_4, which possibly have at least the same efficacy than NaF against tooth demineralization, is very meaningful [47]. Vieira et al. [56] also reported that hydroxypropyl-β-cyclodextrin/γ-cyclodextrin with TIF_4 did not induce critical cytotoxic effects and did demonstrate bactericidal potential against S. mutans, inhibiting enamel mineral loss; highlighting that these results encourage the performance of clinical trial to test the efficacy of these new agents for dental caries control.

Another fact that could compromise the clinical use of TIF_4 is its instability. Dutra [57] observed problems with TIF_4 solution storage and due to this, Morais et al. [58] compared two TIF_4 solutions (a new brand and the other was an old one – with 8 months after manipulation) that were applied before acid etch to put brackets bonded on enamel. The authors found better results with the fresh TIF_4 solution. Probably when there is a loss of titanium in TIF_4, titanium dioxide (TiO_2) is formed as a final product and could impair the absorption of free fluoride by the dental substrate. It would undermine the remineralization of the structure of the final formed product [59]. In an attempt to develop a novel TIF_4 fluoridated nanocomplex, which shows greater stability, Vieira's research [56] with β-cyclodextrins (βCDs) demonstrated that, among all-natural CDs, β-CD is the most available, lowest-priced and generally the most useful. The use of β-CD can increase the pH of the TIF_4 nanosystems allowing its professional use and improving thermal stability.

Finally, in this bibliometric review, we could show a great panorama about the therapeutic and preventive use of TIF_4 in carious and erosive lesions since we did the search at a considerable number of databases, showing a strong amount of papers to be compared and analyzed. However, one limitation of this work is that our analysis of countries or institutions was based only on the corresponding authors' countries and not took account the international institutional exchanges.

Conclusion

Studies with TIF_4 have been increased as years gone by, mainly in the last decade. This fluoride compound was more used at *in vitro* trials, with the solution as the major vehicle used by the researchers for 5-7 days. It has showed a positive effect in both prevention and therapeutic treatments for dental caries and erosion. However, more clinical trials are needed to confirm these effects since most studies have been carried out by *in vitro* models.

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Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

This study is part of the principal author's PhD thesis. The data used to support the findings of this study can be made available upon request to the corresponding author.

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