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REVIEW ARTICLE

What is the effectiveness of titanium tetrafluoride to prevent or treat dental caries and tooth erosion? A systematic review

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ABSTRACT

Objectives: Answer the question: What is the effectiveness of titanium tetrafluoride (TiF_4) when compared to other fluorides, placebo solution or a negative control to prevent or treat dental caries and tooth erosion?

Materials and methods: This review is in accordance with PRISMA guidelines. *In vivo* and *in situ* studies that used TiF_4 over enamel or dentine were included. Electronic searches were conducted on MEDLINE, Scopus, Embase, WOS, Cochrane Library, VLH, Clinical Trials and OpenGrey. Risk of bias (ROB) assessments used RoB2 and ROBINS-I for randomized and non-randomized controlled trials (RCTs and on-RCTs); Syrcle's ROB tool for animal studies; and a modified tool proposed by Hollanders for *in situ* studies.

Results: A total of 28 studies met the eligibility criteria. From these, 6 were in humans (3 RCT and 3 Non-RCT); 4 were in animals and 18 were *in situ*. For *in vivo* studies, all RCTs have some concerns related to ROB and all of the non-RCT studies were classified as with serious risk. One animal study had a low and three a high ROB. Regarding *in situ* studies, seven had a low, ten had an average and only one had a high ROB. The certainty of the evidence (GRADE) ranged from moderate to very low.

Conclusions: Although most of the results suggest a positive effect of TiF4 on the prevention and treatment of caries and dental erosion, it is not possible to have definitive conclusions due to the high studies' methodological heterogeneity, and the low quality of evidence for most outcomes.

Registration: The protocol of this syste. atic review was registered in the OPEN SCIENCE FRAMEWORK database (osf.io/6dgs9) DOI:10.17605/OSF.IO/KUZA7 on 6 August 2020.

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Introduction

Among all disorders that affect oral cavity, dental caries and tooth erosion are very common findings seen in dentistry practice. The first one is considered to be a dysbiosis that promotes a demineralization by metabolic activity in a microbial deposit (biofilm) covering a tooth surface at any given time [1]. Over time, the outcome of this dynamic process may result in an imbalance between the tooth mineral and the surroundings, developing mineral loss, subsequent lesion formation and possible cavity formation in teeth [1]. On the other hand, tooth erosion is usually seen in clinical aspects associated with dietary acid [2] and eating disorders [3]. It is a lesion caused by exposure to non-bacterial acids, which has been received attention from researchers and clinicians by its increasing prevalence and clinical detection [3].

In order to prevent or to treat these disorders, fluorides have been widespread used in dentistry as for dental caries [4] as for tooth erosion [5]. Among fluoride compounds, titanium tetrafluoride (TiF_4) was first appeared in 1972 as a new type of fluoride in dentistry [6].

TiF_4 has a preventive and treatment effect that is achieved by fluoride uptake and a rich titanium coat formation over exposed tooth's substrate [7]. When this compound is applied over the enamel, dentine or cement, titanium ions links with oxygen forming a titanium dioxide (TiO_2) coating that is more resistant than any other fluoride agent [7], decreasing enamel solubility [8], reducing caries lesions formation and enhance enamel fluoride concentration [9] and it cannot be removed of enamel surface by potassium hydroxide (KOH) [10] or hydrochloric acid (HCl) [7]. This Ti-coat can be verified over enamel until a year after its first application [11] and it was observed that titanium could also penetrate into the enamel subsurface [12].

Although TiF_4 has been studied for almost 50 years showing good results when compared with other fluoride compounds, the literature did not show a consensus about its application benefits in Dentistry. Based on this, the aim of the present review was to systematically assess the whole existing literature to answer the following focussed question: What is the effectiveness of TiF_4 when compared to other

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fluorides, placebo solution or a negative control to prevent or treat dental caries and tooth erosion?

Materials and methods

Protocol and registration

This systematic review was conducted following the Cochrane Handbook for Systematic Reviews of Interventions [13], reported according to the PRISMA statement guideline [14] and registered in the Open Science Framework database under protocol (https://osf.io/kuza7) DOI:10.17605/OSF.IO/KUZA7 available on line on 6 August 2020.

Eligibility criteria

The eligibility criteria were defined based on the PICO research strategy for clinical practice based on scientific evidence and their adaptations considering the different types of studies:

1. **Participants:** Human of any age and gender with sound teeth and/or incipient caries lesions or dental erosion (randomized and non-randomized controlled trial [RCT and Non-RCT studies]); any kind of animal species such as hamsters, rats or dogs (animal studies); and dental enamel or dentine blocks fixed into oral appliances (*in situ* studies).
2. **Intervention:** Use of TiF_4 in solution, varnishes or gels over tooth enamel and dentine surfaces.
3. **Comparison:** Other fluorides (NaF, SnF_2, APF, CuF_2, AmF, HF_4, etc.), placebo solution (distilled or deionized water) or a negative control.
4. **Outcome:** The primary outcomes were those that evaluated the TiF_4 effectiveness to prevent or treat caries or dental erosion such as: presence/absence of caries or erosion (clinical assessment), surface hardness, mineral density profiles, lesion depth, white spots prevention/remineralisation, elements permeability in tissue, chemical elements weight percent, tooth wear, smooth-surface, fissure caries scores, severity of lesions or others. Secondary outcomes were percentage of the degree of patient satisfaction after the products' applications, counts of colony-forming units, animal's growth conditions (weight gain after treatment, plaque scores and the bone loss score).

Thus*, in situ* or *in vivo* (humans) studies including syndromic or systemically compromised patients, or individuals using antibiotics or other medications interfering in the salivary flow, and in animals' studies when TiF_4 was inoculated (since it was not topically used). As well as case reports, case series, observational studies, review articles, conference or congress/meeting abstracts, discussions, interviews, letters, book chapters, reviews, editorials or experts' opinions were excluded.

Information sources

The electronic search was performed in December 2021 and alerts were set to retrieve new published articles. Searches were made on MEDLINE (PubMed); Scopus and Embase (Elsevier); Web of Science (Clarivate Analytics); Cochrane Library (www.cochranelibrary.com) LILACS/BBO and Clinical Trials. Grey literature was also consulted through OpenGrey.

Search strategy

The search strategy included Medical Subject Headings (MeSH) terms, entry terms, free terms and keywords related to the aim of this systematic review, with no restrictions on language or date.

The search was developed using the Boolean operators AND/OR, first applied for PubMed and then adapted to each database according to their syntaxes rules (Table1), with the guidance of a senior health science's specialized Librarian (DFM).

Filters regarding the subject area of Dentistry were applied at the Scopus and Web of Science databases. LILACS and BBO database were consulted in VHL collections with entry terms in Portuguese. Experts in the field were identified and contacted for ongoing studies or unpublished results regarding the focussed question, using e-mail contact up to five attempts.

An additional hand search was conducted to identify additional relevant publications in Caries Research (https://www.karger.com) and Journal of Dental Research (https://journals.sagepub.com/). A manual search was carried out in the reference lists of the articles selected for the systematic review to detect relevant publications possibly missed in the database searches.

Articles retrieved from more than one database were computed only once. Authors and co-authors of studies that were not retrieved in full text were contacted by e-mail up to five attempts, from June to December 2021. Articles published in other languages that authors did not have knowledge were translated using the Google® Translate Tool (https://translate.google.com).

Selection process

The studies identified on the searches were exported to the Endnote® Web (www.myendnoteweb.com) reference management software, organized and duplicates were removed. Two reviewers (A.B.C and K.L.F.) independently read the titles and abstracts to determine whether the articles met the inclusion criteria. Articles that did not meet the eligibility criteria were excluded at this stage. Selected articles were read in full to confirm eligibility. If a study had sample overlapping with other study and the same methodology criteria assessed, the most complete and recent study was included. If the two reviewers become unsure about the inclusion/exclusion of any article, a discussion meeting was held with a third senior reviewer (L.C.M.) to reach a final decision. Reasons for exclusion of articles after full-text examination were registered.

Data collection process/data items

Two reviewers (A.B.C and K.L.F.) independently performed the data extraction manually. The main study characteristics such as author's name, year of publication, study design, sample size, subjects/age, animals' characteristics, substrate, pathological condition, type of TiF_4, application methods, intervention time, outcomes assessed, outcome evaluation, periods of evaluation and conclusions were identified and organized on spreadsheets (Excel®, Microsoft®, USA). Outcomes reported at a single period of assessment or assessed at different follow-up periods were assessed.

Quality assessment

The risk of bias (ROB) evaluation through the following tools:

- Revised Cochrane risk-of-bias tool for randomized trials in humans (RoB 2) [15]. This instrument has five domains: bias due to the randomization process; bias due to deviations from the intended interventions; bias due to lack of outcome data; bias in measuring the result; and bias in the selection of the reported result. The questions for each domain can be answered with yes, probably yes, no, probably no and no information. The final ROB judgement can be: ''Low Risk of bias' or 'High Risk of bias' or can express 'Some concerns'.
- The ROB In non-randomized Studies of Interventions (ROBINS-I) [16] for non-randomized human studies. This instrument has seven domains: ROB due to confusion; ROB in the selection of study participants; ROB in the classification of interventions; Partiality risk due to deviations from the intended interventions; ROB due to lack of data; ROB in measuring results; and ROB in the selection of the reported result. The questions for each domain can be answered with yes, probably yes, no, probably no and no information. The final ROB judgement can be: 'Low risk of bias' or 'Moderate risk of bias' or 'Serious risk of bias' or 'Critical risk of bias' or 'lack of information'.
- SYRCLE's ROB tool for animal studies [17]. This instrument has 10 domains: sequence generation; baseline characteristics; allocation concealment; random housing; performance bias blinding; random outcome; detection bias blinding; incomplete outcome data; selective outcome reporting; and other source of bias. These 10 domains generate 22 questions that can be answered with yes, no and unclear. The final ROB judgement were scored as 'Low Risk' or 'Average Risk' or 'High Risk', according with the number of answers yes, no or unclear were more prevalent.
- A modified tool by Hollanders et al. [18] for *in situ* studies. This instrument has ten questions to be answered (Table 6). The questions for each domain can be answered with yes or no. At the end, all answers 'no' were count one point. The final ROB judgement can be: 'Low Risk' (1–3 'no') or 'Average Risk' (4–6 'no') or 'High Risk' (7-more points 'no').

Disagreements between the two reviews authors on the ROB in studies were solved by a third reviewer. In case of missing data, the authors were contacted for unreported data or additional details.

Synthesis methods

Initially, the characteristics of the included studies were summarized and tabulated using spreadsheets (Excel®, Microsoft, USA). First, the articles were divided according to the type of study (*in vivo* or *in situ* studies); the *in vivo* studies were also divided in experimental studies in animals and RCTs and non-RCTs in humans; after this, the studies were categorized regarding approach they have (prevention or therapeutic goal); and finally, they were divided considering their outcome (caries or erosion).

The studies were grouped for the narrative synthesis based on the outcomes related to the caries assessment, clinical examination, mineral content, chemical evaluation, CFU, surface topography and patient's satisfaction, considering their similarities between control and interventions groups, in attempt to separate them according to their similarity. However, due to the samples heterogenicity, the final synthesis was done based on (1) caries prevention, (2) caries treatment, (3) erosion prevention and (4) erosion treatment.

Subsequently, the studies characteristics were screened to determine which were similar enough to be grouped within each comparison, exploring and comparing the PICO elements across the studies. Data were analysed and interpreted aiming to integrate the reported information and present the synthesis results.

As pre-established in the protocol, a quantitative synthesis was planned in the dependence on the clinical and/or methodological heterogeneity of the included studies. Random effects meta-analyses would be performed to estimate mean differences or standardized mean differences for the outcomes reported as continuous data, or the relative risk of presenting certain outcome reported as categorical data, between the TiF_4 intervention groups and the specific comparator groups. Additionally, it was planned to evaluate the publication bias for those quantitative syntheses that include more than ten data sets.

Certainty of evidence assessment

The certainty of evidence was evaluated using the Grading of Recommendations, Assessment, Development and Evaluation Pro software [19]. ROB, inconsistency, indirectness, imprecision, suspicion of publication bias, presence of large effect, dose–response gradient and plausible confounders were the items considered to rate the overall certainty of evidence from both human and animal studies [20–22]. All the judgments were adapted to qualify the evidence synthesized in a narrative way [23].

Results

Study selection

Identified records from the main databases (4112), were exported to Endnote Web® software and organized in the groups: Pubmed – 760; Cochrane Library – 786; Scopus – 898; Web of Science – 903; VHL – 137 and EMBASE – 629. Regarding the records identified *via* other sources, 395 records in Opengrey, 29 found in reference lists of the included studies and 01 in Clinical Trials were found (Figure 1). After duplicate removal, 2175 remained for title and abstract reading. Based on the eligibility criteria, 1808 records were excluded and, after that, only 31 studies were assessed for eligibility and for full-text reading. Three reports were excluded following the exclusion criteria: two because the animals were inoculated with TiF_4 [24,25] and one had an overlapping sample [26]. Twenty-eight records [27–53] were selected and included from the main databases. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the study selection process is presented in Figure 1.

Twelve new articles [32,53–63] were notified by alerts, but they have not fulfilled the eligibility criteria to be included in this review because they are *in vitro* studies.

Study characteristics

All include articles retrieved were written in English. The main characteristics of the included studies were reported in Tables 2–4. Among the 28 articles included: six were *in vivo* (humans) where half of them were RCT [26,30,31] and other half were non-RCT [27–29]; four were *in animals* [32–35]; and 18 were *in situ* [8,36–52].

One article [30] was published from 1972 to 1979; two from 1980 to 1989 [34,35]; four from 1990 to 1999 [11,27,28,33]; six from 2000 to 2009 [30,36,39,46,47,51] and 15 from 2010 to 2021 [8,26,29,32,37,40–45,48–50,52]. Worldwide overall, 10 studies were conducted in Europe [11,27–30,33–35,48,49,51]; 17 in South America [8,26,28,32,36,37,39–47,50,52] and one in North America [31]. It was observed that same authors conducted some studies assessing outcomes through the same methodological criteria but with different samples, characterizing that these works did not present sample overlapping [27,28,33–35,37,41–44,46,47], except two articles of Souza et al. [26,32] that used the same sample. In this particular case, we considered and included the more complete and recent study for qualification [32] and excluded the article of Souza et al. [26].

In vivo (humans) studies with TiF_4

In vivo trials showed that three studies had caries prevention approach [27,28,31], two were about caries treatment [26,29] and one was an erosion treatment trial [30].

All volunteers received a 1-min single application of TiF_4 solution varying from 0.31% to 4%, except one trial that used a 4% TiF4 varnish in a protocol once a week for 4 weeks [26]. The control groups were other fluorides (NaF and SnF_2)

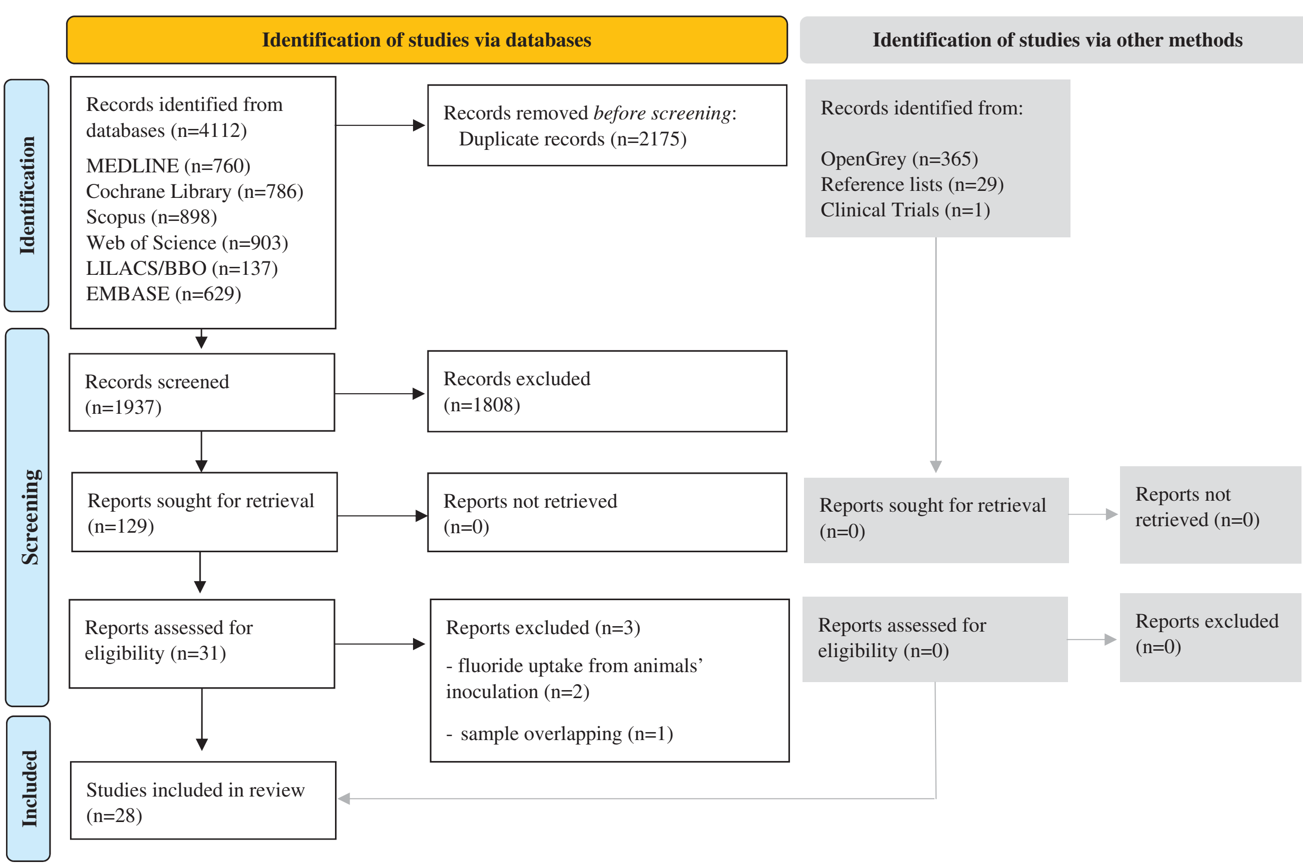

Figure 1. Flow diagram of November 2021 review (PRISMA model).

Table 1. Search strategy according to the different information sources.

MEDLINE www.ncbi.nlm.nih.gov/sites/pubmed. . .	('Dental Caries' [mh] OR 'Dental Caries' [tiab] OR Carie* [tiab] OR Decay [tiab] OR 'DMF Index' [Mh] OR 'DMF INDEX' [Tiab]) OR ('tooth erosion' [Mh] OR Tooth erosio* [Tiab] OR Dental Erosion* [Tiab] OR 'Erosions Dental' [Tiab] OR 'Erosions Teeth' [Tiab] OR 'Eroded enamel' [Tiab] OR Erosive lesio* [Tiab] OR Erosive Loss* [Tiab]) AND ('titanium tetrafluoride' [Supplementary Concept] OR 'titanium tetrafluoride' [Tiab] OR titaniumtetrafluoride [Tiab] OR TiF4 [Tiab] OR 'Titanium fluoride' [Tiab] OR topical fluoride* [Tiab])
COCHRANE LIBRARY www.cochranelibrary.com. . .	ID SearchHits #1 MeSH descriptor: [Dental Caries] explode all trees #2 (Carie* OR Decay) #3 MeSH descriptor: [DMF Index] explode all trees #4 'DMF Index' #5 #1 OR #2 OR #3 OR #4 #6 MeSH descriptor: [Tooth Erosion] explode all trees #7 (Tooth erosion* OR Dental Erosion* OR 'Erosions Dental' OR 'Erosions Teeth' OR 'Eroded Enamel' OR Erosive lesion* OR Erosive Loss*) #8 #6 OR #7 #9 ('Titanium tetrafluoride' OR titaniumtetrafluoride OR TiF4 OR 'Titanium fluoride' OR topical fluoride*) #10 #5 OR #8 #11 #9 AND #10
SCOPUS www.scopus.com. . .	(('Dental Caries' OR Carie* OR Decay OR 'DMF Index') OR ('Tooth erosion' OR 'Tooth erosions' OR 'Dental erosion' OR 'Dental erosions' OR 'Erosions Dental' OR 'Erosions Teeth' OR 'Eroded enamel' OR 'Erosive lesion' OR 'Erosive lesions' OR 'Erosive Loss' OR 'Erosive losses') AND ('titanium tetrafluoride' OR titaniumtetrafluoride OR TiF4 OR 'Titanium fluoride' OR 'topical fluoride' OR 'topical fluorides'))
WOS www.webofknowledge.com. . .	('Dental Caries' OR Carie* OR Decay OR 'DMF Index') OR ('Tooth erosion' OR 'Tooth erosions' OR 'Dental erosion' OR 'Dental erosions' OR 'Erosions Dental' OR 'Erosions Teeth' OR 'Eroded enamel' OR 'Erosive lesion' OR 'Erosive lesions' OR 'Erosive Loss' OR 'Erosive losses') AND ('titanium tetrafluoride' OR titaniumtetrafluoride OR TiF4 OR 'Titanium fluoride' OR 'topical fluoride' OR 'topical fluorides')
LILACS / BBO www.bvsalud.org. . .	tw:((mh: 'Dental Caries' OR 'Cárie dentária' OR carie* OR cárie* OR decay OR mh: 'DMF Index' OR 'Índice CPO' OR 'DMF Index' OR 'Índice CPO') OR (mh: 'Tooth erosion' OR 'Erosão dentária' OR 'Tooth erosion' OR 'Tooth erosions' OR 'Erosão dentária' OR 'Erosões dentárias' OR 'Dental Erosion' OR 'Dental erosions' OR 'Erosão dental' OR 'Erosões dentais' OR 'Erosions Dental' OR 'dentárias erosões' OR 'dentais erosões' OR 'Erosions Teeth' OR 'dentes erosões' OR 'Eroded enamel' OR 'esmalte erodido' OR 'Erosive lesion' OR 'Erosive lesions' OR 'lesão erosiva' OR 'lesões erosivas' OR 'Erosive Loss' OR 'Erosive losses' OR 'perda erosiva' OR 'perdas erosivas') AND ('Titanium tetrafluoride' OR 'tetrafluoreto de titânio' OR titaniumtetrafluoride OR tif4 OR 'Titanium fluoride' OR 'fluoreto de titânio' OR topical fluoride* OR 'fluoreto tópico' OR 'fluoretos tópicos')) AND (db:('LILACS' OR 'BBO' OR 'BINACIS' OR 'IBECS'))
EMBASE www.embase.com. . .	('dental caries':ti,ab,kw OR carie*:ti,ab,kw OR decay:ti,ab,kw OR 'dmf index':ti,ab,kw OR 'tooth erosion':ti,ab,kw OR 'tooth erosions':ti,ab,kw OR 'dental erosion':ti,ab,kw OR 'dental erosions':ti,ab,kw OR 'erosions dental':ti,ab,kw OR 'erosions teeth':ti,ab,kw OR 'eroded enamel':ti,ab,kw OR 'erosive lesion':ti,ab,kw OR 'erosive lesions':ti,ab,kw OR 'erosive loss':ti,ab,kw OR 'erosive losses':ti,ab,kw) AND ('titanium tetrafluoride':ti,ab,kw OR titaniumtetrafluoride:ti,ab,kw OR tif4:ti,ab,kw OR 'titanium fluoride':ti,ab,kw OR 'topical fluoride':ti,ab,kw OR 'topical fluorides':ti,ab,kw)
CLINICAL TRIALS www.clinicaltrials.gov. . .	Titanium tetrafluoride
OPENGREY www.opengrey.eu. . .	Titanium tetrafluoride

and no intervention groups and the studies duration were from 1 d to 3 years. The outcomes assessed were mineral content, surface topography, caries assessment, chemical evaluation and patient's satisfaction to determine if TiF_4 was effective in caries or erosion preventive/therapeutic goal (Table 4).

In vivo *(animals) studies with TiF_4*

Regarding animals' studies, it could be observed that all of them researched about preventive caries approach. Two used beagle dogs [34,35] and two worked with rats [32,33] and streptococcus inoculation. The studies compared TiF_4 (varnish and solution) with other fluorides (NaF and SnF_2) and no intervention groups [32–35]. The fluorides concentration varied between 1% and 4% with an application time of 1 and 4 min and the study duration was from 19 d to 21 weeks. The outcomes assessed were microbiological analysis, caries assessment and mineral content to determine if TiF_4 was effective in dental caries prevention (Table 2).

In situ *studies with TiF_4*

For *in situ* studies, the patients' ages ranged from 18 years [45] to 64 years [49] and the sample size ranged from five patients [36,39] to 20 volunteers [42] with a period of evaluation varying from 2 d [44] to 96 d [8] (Table 3).

Regarding TiF_4 outcomes, 10 articles (55.56%) [8,36–39,43–47] evaluated its preventive potential and eight (44.44%) [40–42,48–52] its treatment effect when applied over enamel and dentine for caries and dental erosion. Regarding the method used to evaluate TiF_4 outcomes, 14 studies [8,36–41,43,44,46,48–51] analysed surface topography by scanning electron microscope (SEM), confocal laser scanning microscopy (CLSM), profilometer, white light interferometry (WLI); 10 [8,36–42,46,47] evaluated mineral content by CSMH, micro-CT, microradiography, TRM, SMHC and 04 [8,40,46,52] measured chemical evaluation through energy dispersive spectrometry (EDS), histochemical colouring method (HCM), atomic absorption spectrometer (AAS). Also, patients' satisfaction was researched in one issue by an application of Wong–Baker Visual Scale (WBPS) [26] (Table 3).

Table 2. Data extraction of *in vivo* (randomized and non-randomized studies).

		Sample-related information		Experimental intervention		Comparison interventions		Outcomes			
Authors/country	Study design	Subjects/ age	Sample size/ substrate	Type of TiF4	Application method details	Intervention type	Application method details	Outcomes assessed	Outcomes evaluation methods	Periods of evaluation	Conclusions
[11] Norway	Split-mouth non-randomized clinical trial	07 Volunteers (mean 12.9 years)	$n = 20$/ Human enamel	1% TiF4 solution	1 min single application	no intervention was made	———	Mineral content/ surface topography	Microradiography (TRM)/SEM	4 weeks	Topical application of 1% TiF4 solution for 60 s reduced lesion depths by 37% and the mineral loss by about 14% during a 4-week experimental period.
[38] Norway	Split-mouth non-randomized clinical trial	07 Volunteers (mean 8.9 years)	$n = 28$/ Human enamel	4% TiF4 solution	1 min single application	no intervention was made	———	Surface topography	SEM	3 months; 6 months; 1 year	Compared with other pit and fissure sealant materials TiF4 appears to be an acceptable, less costly preventive option.
[30] Norway	Randomized, single-blind	67 Volunteers (16–69 years)	$n = 255$/ Human enamel	0.31% TiF4 solution	6 ml for 60 s	0.78% SnF2; 0.2% HF and 0.42% NaF solutions	6 ml for 60 s	Chemical evaluation	Atomic absorption spectrometer	One day application	Treatment with either HF or SnF 2 was significantly more effective in reducing calcium dissolution than the corresponding treatments with NaF or TiF 4
[29] Brazil	Single-blind, non-randomized split-mouth clinical trial	08 Volunteers (6–12 years)	$n = 18$/ Human enamel	4% TiF4 solution	1 min single application	MFP dentifrice with 1.450 ppm of fluoride	Daily use	Caries assessment/ surface topography	Clinical examination and digital photographs/ epoxi resin replicas for SEM	4 weeks	A single application of TiF4 with toothbrushing with a fluoride-containing dentifrice was no more effective than the use of dentifrice alone for treating incipient carious lesions
[31] USA	Randomized, controlled, double-blind, split-mouth clinical trial	204 Volunteers (11–13 years)	$n = 144$ Test group $n = 60$ control group	1% TiF4 solution	1 min single application	APF	4 min single application	Caries assessment	Clinical examination	3 years	An annual, single, 1 min application of 1% TiF4 had a large protection against caries
[32] Brazil	Randomized three-armed controlled clinical trial	60 Children (6–8 years)	$n = 40$ Test group $n = 20$ control group	4% TiF4 varnish	once a week for four weeks	5% NaF varnish and control (placebo varnish)	Once a week for 4 weeks	Caries assessment/ patient's satisfaction	Clinical examination/ quantitative light-induced fluorescence (QLF)/Wong–Baker Visual Scale (WBPS)	18 months	TiF4 had a similar ability to control caries lesions as NaF; however, only TiF4 differed from the placebo. The acceptability of TiF4 varnish was similar to that of NaF varnish.

Table 3. Data extraction of *in animals'* studies articles.

		Sample-related information			Experimental intervention		Comparison interventions		Outcomes			
Authors/ country	Study design	Sample size	Animals characteristics	Development of the pathological condition	Type of TiF4	Application method details	Intervention type	Application method details	Outcomes assessed	Outcomes evaluation methods	Periods of evaluation	Conclusions
[33] Brazil	Crossover, randomized, and double-blinded *in vivo*	$n=48$	Female wistar rats	Overnight culture of *Streptococcus* sobrinus 6715	2.26% TiF4 varnish	1 min topical application	2.26% NaF varnish (Duraphat®)	Topical application	Microbiological analysis/caries assessment	Histopathological analysis/count of *S. sobrinus*/clinical examination (Ds/Dm)	4 weeks	The tested TiF4 varnish showed no oral toxicity and was effective in preventing caries in rats.
[34] Norway	Crossover, randomized, and *in vivo*	$n=60$	Male sprague-Dawley rats	*Streptococcus mutans* (twice weekly)	1% TiF4 solution	1 min topical application	1.3% NaF (acidulated and neutral) and distilled water	1 min topical application	Caries assessment	Clinical examination	19 d	TiF4 caries-inhibitory effect is at least as good as that of NaF in rats
[35] Norway	Crossover, randomized, and *in vivo*	$n=5$	Beagles dogs	___	3.4% TiF4 solution	4 min topical application	0.05% NaF solution ___ 0.7% NaF varnish ___ 2.26% NaF varnish	4 min topical application	Mineral content	Electron microprobe	3 weeks	TiF4 may be an efficient anti-caries topical agent for application to exposed dentine surfaces
[36] Norway	Crossover, randomized, and *in vivo*	$n=2$	Beagles dogs	___	3.4% TiF4 solution	1 and 4 min topical application	SnF2 solution	1 and 4 min topical application	mineral content	Electron microprobe	21 weeks	A brief application of TiF4 resulted in the same increase of fluoride that a 4 min application of SnF2, however surface demineralisation is less with TiF4.

Comparing application time of TiF_4 over the tooth substrate, 13 articles [8,36–40,42,45–47,49,50,52] showed that 1-min single application has goal its preventive or treatment purposes, contrasting with two studies [48,51] that used a 2-min single application and two [43,44] that tested a 4-min single application time.

Regarding tooth substrate, among *in situ* studies, in 14 [8,36–42,46–48,50–52] researches TiF4 was applied over enamel and in four [43–45,49] was over dentine, showing good results in both surfaces. Among the TiF_4 vehicles, the most used was solution (66.67%), followed by varnish (27.78%) and gel (16.67%).

Risk of bias in the included studies

Among *in vivo* studies, all RCT were classified as having some concerns related to the ROB [26,30,32] (Figure 2), while all non-RCTs as with serious ROB [27–29] (Figure 3).

After SYRCLE's ROB tool evaluation only the article of Alexandria et al. [32] had low ROB, while the others were rated as with high ROB (Table 5).

Among *in situ* studies, the majority [36,39,40,43,44,46–48,51,52] had average risk ($n=10$; 55.55%) followed by low [8,32,41,42,45,49,50] ($n=7$; 38.88%) and high [38] ($n=1$; 5.57%) ROB (Table 6).

Results of individual studies and synthesis

In vivo *(humans) studies with TiF_4*

Among the six studies, three were about caries prevention [27,28,31] two were about caries treatment [29,32] and only one was about erosion treatment [30]. In caries preventive effect, TiF_4 showed better results than other fluorides in all trials, but in caries treatment, this compound showed no difference when compared with NaF or fluoride dentifrice. The article that observed the erosion treatment effect of TiF_4 showed that its effectiveness was worse than HF or SnF_2 [30] (Table 2).

In vivo *(animals) studies with TiF_4*

Articles with animals showed that TiF_4 has achieved better results in caries prevention that other fluorides in three studies: two in enamel [33,36] and one in dentine [35]. Only one article described TiF4 caries-inhibitory effect is at least as good as that of NaF in rats [33] (Table 3).

In situ *studies with TiF_4*

Among the 18 *in situ* articles, five [8,36–39] were about TiF_4 effect in caries prevention and all of them showed that this fluoride compound was effective in this subject. Three articles [40–42] of caries treatment observed that TiF_4 has remineralized carious surfaces when compared with NaF (solution, gel or varnish) and with placebo or no intervention. Studies of dental erosion prevention were five and results showed that TiF_4 had a good effect in this purpose in four studies [43–45,47] and, in one article, it did not achieve the preventive effect [46]. Regarding erosion treatment, all

Table 4. Data extraction of *in situ* studies.

		Sample-related information		Experimental intervention		Comparison interventions		Outcomes			
Authors/ country	Study design	Subjects/ age	Sample size/ substrate	Type of TiF4	Application method details	Intervention type	Application method details	Outcomes assessed	Outcomes evaluation methods	Periods of evaluation	Conclusions
[40] Brazil	Crossover, randomized and double-blind *in situ*	11 Volunteers (no age informed)	*n* = 170 /Bovine enamel blocks	4% TiF4 solution	1 min Single application	2% NaF gel	1 min Single application	Mineral content/ chemical evaluation/ surface topography	CSMH/EDS/SEM	Three 15-d phases, with a 7-d and a wash-out period between each phase.	There were no differences at the various layers among the groups, but titanium was able to substantially penetrate some fragments. The level of calcium and phosphorous for the TiF4 sample at all layers was higher than other groups and also showed more heterogeneity on enamel
[33] Brazil	Crossover, randomized and double-blinded *in situ*	12 Volunteers (19–31 years)	*n* = 72 /Bovine enamel blocks	4% TiF4 solution	24 h Single application	2.26% NaF varnish (Duraphat®) ______ placebo varnish ______ deionized water	24 h Single application	Mineral content/ chemical evaluation/ surface topography	CSMH/EDS/SEM	Four phases of 14 d each and a wash-out period (10 d) between each phase.	4% TiF4 varnish was able to reduce surface and subsurface enamel demineralisation under cariogenic challenge
[33] Brazil	Crossover, randomized and double-blinded *in situ*	12 Volunteers (no age informed)	*n* = 48 /Bovine enamel blocks	2.26% TiF4 varnish	1 min single application	2.26% NaF varnish (Duraphat®) ______ no intervention	1 min Single application	CFU/mineral content/ surface topography	Count of S mutans/ micro CT (ΔZ)/ clinical examination (white spot lesion)	Four phases of 14 d each and a wash-out period between each phase.	TiF4 and NaF varnishes were able to reduce the progression of the lesions *in situ*.
[38] Norway	Crossover and randomized *in situ*	12 Volunteers (no age informed)	*n* = 48 /Human cement blocks	4% TiF4 solution	1 min Single application	No intervention	——	Mineral content/ surface topography	Microradiography (ΔZ)/ Confocal laser scanning microscopy (CLSM)	4 weeks	The present study has shown that root surface caries can be prevented *in situ* by the single topical application of a titanium tetrafluoride solution.
[39] Brazil	Crossover and randomized *in situ*	05 Volunteers (no age informed)	*n* = 90/ Human cement blocks	4% TiF4 solution	1 min Single application	No intervention	——	Surface topography/ mineral content	SEM/CSMH	Two phases of 14 d each and a wash-out period between each phase.	The application of 4% TiF4 on occlusal surface is caries-preventive and results in the formation of a protective coating. However, a therapeutic caries-reverse effect could not be detected
[41] Brazil	Crossover, randomized and double-blind *in situ*	13 Volunteers (19–29 years)	*n* = 78/ Bovine enamel blocks	4% TiF4 solution or varnish	1 min Single application	5.45% NaF gel or varnish	1 min Single application	Mineral content	TRM	Three phases of 14 d each and a wash-out period between each phase.	TiF4 was able to decrease enamel demineralisation to a similar degree as NaF varnish, but only TiF4 formulations remineralised the enamel surface
[42] Brazil	Crossover, randomized and double-blind *in situ*	20 Volunteers (19–42 years)	*n* = 480/ Bovine enamel blocks	4% TiF4 varnish	6 h Single application	5.45% NaF varnish and a 5% placebo varnish	6 h Single application	Mineral content	TRM	Three phases of 14 d each and a wash-out period between each phase.	TiF4 varnish was the only treatment able to improve enamel remineralization
[45] Brazil	Crossover, randomized and		*n* = 120/ Bovine	0.042% NaF and 0.049%	10 ml for 60 s	SnCl2/NaF/AmF (ELMEX) and	10 ml for 60 s		Profilometer/ Wong–Baker	Three phases of 5 d each,	The experimental NaF/TiF4 mouth rinse has a similar

(*continued*)

Table 4. Continued.

Authors/ country	Study design	Sample-related information: Subjects/ age	Sample-related information: Sample size/ substrate	Experimental intervention: Type of TiF4	Experimental intervention: Application method details	Comparison interventions: Intervention type	Comparison interventions: Application method details	Outcomes: Outcomes assessed	Outcomes: Outcomes evaluation methods	Outcomes: Periods of evaluation	Conclusions
	double-blind *in situ*	15 Volunteers (18–27 years old)	enamel/ dentine blocks	TiF4 solutions		distilled water		Surface topography/ patient's satisfaction	Visual Scale (WBPS)	with an interval of 10 d among them	protective effect to the commercial one
[51] Norway	Crossover, randomized and double-blind *in situ*	7 Volunteers (25–55 years old)	$n = 56$/ Human enamel blocks	3.9% SnF2; 1.5% TiF4 and 2.1% NaF solutions	2 min	No intervention	——	surface topography	white light interferometry (WLI)	9 d	Topical fluoride treatment of enamel, in the form of either highly concentrated SnF 2 or in particular TiF 4 solution, is a promising method for preventing loss of tooth substance associated with intra-oral acid exposure.
[52] Brazil	Crossover, randomized, *in situ*	10 Volunteers (mean age of 24 years)	$n = 40$/ Bovine enamel blocks	1.23% TiF4 gel ____ 1.23% TiF4 gel + CO2 Laser irradiation	0.1 g for 1 min ____ CO_2 ultrapulsed for 10 s	Placebo gel ____ Placebo gel + CO2 Laser irradiation	0.1 g for 1 min ____ CO_2 ultrapulsed for 10 s	Chemical evaluation	histochemical Colouring Method (HCM)	5 d with a 2 d washout	Even though both CO2 laser irradiation and fluoride have been efficient to reduce progression of enamel erosion, the benefit-cost between the treatments should be considered.
[50] Brazil	Prospective, single-centre, double-blind and six-cell study in crossover and split-mouth	12 Volunteers (23–35 years)	$n = 72$/ Human enamel blocks	2.45% TiF4 varnish and TiF4 solution	1 min Single application	2.45% NaF varnish and NaF solution ____ placebo varnish ____ untreated control	1 min Single application	surface topography	profilometer	Three phases of 5 d each, with a washout time of 5 d between the phases	TiF4 varnish has similar protective potential as the solution and NaF formulations to reduce human enamel erosion
[46] Brazil	Crossover, randomized, *in situ/ex vivo*	10 Volunteers (19–30 years)	$n = 40$/ Human enamel blocks	4% TiF4 solution	1 min Single application	No intervention	——	Surface topography/ mineral Content/ chemical evaluation	profilometer/SEM/ SMHC/EDS	Two phases: 1st phase (7 d) and 2nd phase (2 d) with a 7 d washout	TiF4 solution was not able to prevent dental erosion *in situ*
[47] Brazil	Crossover, randomized, *in situ/ex vivo*	10 Volunteers (19–30 years)	$n = 40$/ Human enamel blocks	4% TiF4 solution	1 min Single application	No intervention	——	Mineral content	SMHC	7 d	The TiF4 solution was able to reduce permanent enamel softening caused by the erosive challenge *in situ*, in contrast, softening of deciduous enamel was increased
[43] Brazil	Crossover, randomized and double-blind *in situ*	12 Volunteers (20–35 years)	$n = 70$/ Root dentine blocks	4% TiF4 gel	4 min Single application	No intervention	——	Surface topography	SEM/ESEM	7 d	Even if TiF4 gel treatment was not able to generate a complete occlusion of dentinal tubules, it decreased the lumens diameter.
[44] Brazil	Crossover, randomized and double-blind *in situ*	12 Volunteers (20–35 years)	$n = 72$/ Root dentine blocks	4% TiF4 gel	4 min Single application	No intervention	——	Surface topography	profilometer/ ESEM/AFM	2 d and a wash-out of 5 d	4% gel TiF4 was able to reduce the progression of erosive/abrasive lesions in dentine in the first application and multiple applications reduced the

(*continued*)

Table 4. Continued.

Authors/ country	Study design	Sample-related information: Subjects/ age	Sample size/ substrate	Experimental intervention: Type of TiF4	Application method details	Comparison interventions: Intervention type	Application method details	Outcomes: Outcomes assessed	Outcomes evaluation methods	Periods of evaluation	Conclusions
											evolution of the erosive process.
[37] Brazil	Crossover, randomized and double-blind *in situ*	5 Volunteers (no age informed)	$n = 80$/ Human enamel blocks	1% TiF4 solution	1 min Single application	No intervention	——	surface topography/ mineral content	SEM/TRM	Two phases pf 14 d with a 4 d washout	1% TiF4 solution application, over deciduous and permanent enamel, probably changes the caries formation
[48] Norway	Paired, randomized and blind *in situ*	8 Volunteers (22–30 years))	$n = 64$/ Human enamel blocks	0.15% TiF 4 solution	2 min Single application	0.2% NaF and 0.4% SnF 2 solutions	2 min Single application	Surface topography	WLI (computerised optical microscope)	9 d	0.4% SnF 2 , 0.15% TiF 4 or 0.2% NaF solutions (all with 0.05 M F) significantly reduced enamel loss from erosion/abrasion *in situ*.
[49] Switzerland	Crossover and double-blind	10 Volunteers (23–64 years)	$n = 240$/ Bovine enamel and dentine blocks	1.55% TiF4 solution	1 min Single application	2.09% ZrF4, 3.18% HfF4 and 13.43% AmF solutions	1 min Single application	Surface topography	profilometer	Eight phases of 3 d with a 3 d washout	Tetrafluorides and AmF are able to reduce erosion and erosion plus abrasion *in situ* and are almost equally effective.

studies ($n = 5$) [48–52] demonstrated that TiF_4 was as effective as sodium fluoride.

Comparing the studies regarding dental substrate, among all *in situ* articles, only four studies [43–45,49] applied TiF_4 over dentine and observed that this compound showed a good response in prevention and treatment of dental erosion. Mantilla et al. [43,44] observed that even if TiF4 gel treatment was not able to generate a complete occlusion of dentinal tubules, it decreased the lumens diameter and an application of 4% gel TiF4 was able to reduce the progression of erosive/abrasive lesions in dentine in the first application and multiple applications reduced the evolution of the erosive process. Although, the experimental NaF/TiF4 mouth rinse has a similar protective effect to the commercial one (Elmex®) [44]. Regarding erosion treatment, Wiegand et al. [49] concluded that tetrafluorides and AmF are able to reduce erosion and erosion plus abrasion *in situ* and are almost equally effective.

Certainty of evidence

The evidence related to the outcomes caries and erosion was grouped according to the type (*in vivo*, *in situ* and animal study) and objective of the studies (preventive or therapeutic approach), regardless of the characteristics of the intervention using TiF4 and comparator groups. The certainty of evidence was very low for most of the syntheses, with the exception of those carried out for caries treatment outcome from *in vivo* and *in situ* studies, which presented low and moderate certainty, respectively. The ROB affected the evidence for most of the outcomes synthesized because the vast majority of included studies had important methodological limitations that could have altered the results. Only the evidence on erosion prevention and treatment from *in situ* studies and that related to caries prevention from animal studies, was considered inconsistent due to variation in the reported effects. It is important to mention that, although for GRADE evaluation the evidence on the rest of the outcomes was considered consistent, the compiled studies presented high clinical/methodological heterogeneity. The studies are different in relation to the characteristics of TiF4 (concentration, presentation) and comparator groups (no treatment, placebo, another type of fluoride, etc.).

Despite this, it was decided to synthesize the information, to show the state of the evidence from a panoramic perspective. Regarding the item indirectness, the specific outcomes evaluated by the studies constituted mostly indirect measurements for caries and erosion; therefore, the certainty of the evidence was downgraded. Besides, in relation to the evidence from animal studies, it was considered that results lack translatability for consideration in humans, which also affected the judgement for this item. Finally, the evidence was qualified as imprecise for most of the data due to the reduced number of individuals/test blocks/animals included in the syntheses (less than the threshold of 400 recommended by GRADE). Publication bias was considered unsuspected, and since the evidence was affected for some of the previously mentioned criteria, no item was considered to

Table 5. SYRCLE's risk of bias tool.

Authors//year questions	[33]	[34]	[36]	[35]
Was the allocation sequence adequately generated and applied?	Unclear	No	No	No
Was the distribution of relevant baseline characteristics balanced for the intervention and control groups?	Yes	Yes	No	No
If relevant, did the investigators adequately adjust for unequal distribution of some relevant baseline characteristics in the analysis?	Yes	Yes	No	No
Was the timing of disease induction adequate?	Yes	Yes	Yes	No
Could the investigator allocating the animals to intervention or control group not foresee assignment due to one of the following or equivalent methods?	Unclear	No	No	No
Did the authors randomly place the cages or animals within the animal room/facility?	Yes	Unclear	No	No
Is it unlikely that the outcome or the outcome measurement was influenced by not randomly housing the animals?	Yes	No	No	No
Was blinding of caregivers and investigators ensured, and was it unlikely that their blinding could have been broken?	No	No	No	No
Did the investigators randomly pick an animal during outcome assessment, or did they use a random component in the sequence generation for outcome assessment?	No	No	No	No
Was blinding of the outcome assessor ensured, and was it unlikely that blinding could have been broken?	Yes	No	No	No
Was the outcome assessor not blinded, but do review authors judge that the outcome is not likely to be influenced by lack of blinding?	Yes	Unclear	No	No
Were all animals included in the analysis?	Yes	Yes	Yes	Yes
Were the reasons for missing outcome data unlikely to be related to true outcome?	Yes	Yes	Yes	Yes
Are missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups?	Yes	Yes	Yes	Yes
Are missing outcome data imputed using appropriate methods?	Yes	Yes	Yes	Yes
Was the study protocol available and were all of the study's pre-specified primary and secondary outcomes reported in the current manuscript?	Yes	Yes	Yes	Yes
Was the study protocol not available, but was it clear that the published report included all expected outcomes (i.e. comparing methods and results section)?	Yes	Yes	Yes	Yes
Was the study free of contamination (pooling drugs)?	Yes	Yes	Yes	Yes
Was the study free of inappropriate influence of funders?	Yes	Yes	Yes	Yes
Was the study free of unit of analysis errors?	Yes	Yes	Unclear	No
Were design-specific risks of bias absent?	Yes	No	No	No
Were new animals added to the control and experimental groups to replace dropouts from the original population?	No	No	No	No
Score: yes/ no / unclear	17 / 3 / 2	12 / 8 / 2	8 / 14 / 0	9 / 12 / 1
Risk of bias	Low	High	High	High

raise the certainty. All the judgments issued for the evaluation of the certainty of the evidence are presented in Table 7.

Discussion

Due to a lack of consensus about the real benefits of TiF4 application in Dentistry, we proposed this present systematic review. Thus, all *in situ* and *in vivo* (humans and animals) studies were selected according to an eligibility criterion previously described, amounting a total of 28 articles, that supporting researchers about what is necessary to advance in terms of new studies on this subject. The analysis in general, TiF_4 suggested better results than other fluorides in order to control the enamel demineralization and enamel loss, supporting the hypothesis that TiF_4 are able to prevent dental caries and enamel wear progression in view of cariogenic challenge and erosive challenges.

This review showed that solutions and varnish were fluoride delivery methods most used, however, the real efficacy of TiF_4 to control the enamel demineralization and tooth structure loss has been subject of debate over the years, no articles published before the year 1972 met the inclusion criteria to this systematic review, since the first study with TiF4 was published by Shrestha et al. in 1972. The consulted literature shows that the protective mechanism of fluoride concerning dental caries and erosive wear are limited to the surface or the near surface layer of enamel [7,8,12,28,39].

We observed that the comparison of vehicle type and concentration of fluoride on dental caries and erosive wear progression are a difficult task, because many factors can impact on its protective potential, such as frequency of application, study design and control groups considered. Therefore, extrapolation of the results based on comparison of different products must be done carefully. Additionally, the negative control group choice (fluoride-free toothpaste or water) may also affect the mean difference between groups, mainly in erosion/abrasion studies.

Higher CaF2-like deposits formation occurs with lower pH and higher concentrated products, as well as longer application times [64]. Nevertheless, only one RCT study [32] was included varnish once a week for 4 weeks of application

Table 6. Hollanders et al. modified tool for *in situ* studies.

Authors	Are volunteers free from dental knowledge?	Are patient variables described properly?	Are samples randomly allocated to a group?	Are samples balanced/ rotated in the devices?	Were participants blinded to the purpose of the study?	Was the researcher doing the substrate analysis oblivious to the group the sample belonged to?	Was a sample size calculation carried out to determine optimal sample size?	Was the intervention compared to a control group that is in all other aspects the same? Location of control samples comparable to location of intervention samples?	Were materials related to the study outcome prevented from contaminating samples outside their own group?	Were all data reported? Dropouts reported well? Was the study carried out for the length of time it was planned? Is there no evidence to suggest that the authors measured more outcomes than they reported?	Score	Risk of bias
[40]	No	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	4	Average
[8]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	1	Low
[33]	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	3	Low
[38]	No	No	No	Yes	No	No	No	Yes	No	Yes	7	High
[39]	No	No	Yes	No	No	Yes	No	Yes	No	Yes	6	Average
[41]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	1	Low
[42]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	1	Low
[45]	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	3	Low
[51]	No	Yes	Yes	No	No	Yes	No	Yes	No	Yes	5	Average
[52]	No	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	4	Average
[50]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	2	Low
[46]	No	Yes	No	Yes	No	No	No	Yes	Yes	Yes	5	Average
[47]	No	Yes	Yes	Yes	No	No	No	Yes	No	Yes	5	Average
[43]	No	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	4	Average
[44]	No	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	4	Average
[37]	No	No	No	No	Yes	Yes	No	Yes	Yes	Yes	5	Average
[48]	No	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	4	Average
[49]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	1	Low

with caries assessment as outcome, while another RCT study [31] showed that an annual single application of TiF_4 solution was more effective than APF for treating incipient carious lesions. These differences in the frequency of application can limit the evidence of their supposed superior performance as protective agents, justifying the absence of metanalysis between studies.

Although titanium fluoride present effective protective potential in clinical trials models, evidence was graded as some concerns of bias for RCT and with serious ROB for non-RCTs, due to serious limitations regarding quality, consistency and precision across studies. Regarding the type of articles published, the most found were *in situ* studies, probably due to the convenience to select a sample for survey and guarantee the researcher to have more control of study variables [65]. Besides, *in situ* studies require a relatively small group of participants and costs, making it easier than the former in this aspect [65]. However, since multiple combinations of natural and experimental variables are included in *in situ* models, the study designs are complicated under various limitations, such as the type of substrate (human or bovine), the characteristics of fluoride, such as pH, concentration and type; the dental and erosive protocol performed. Additional factors are related to the power of analysis, such as sample sizes and sample allocation methods [66,67]. Other limitation is the ROB of the studies included in the analysis, as several studies even reporting that subjects or samples were randomized, did not specify how the sequence was generated and allocation was concealed. Thus, it would be desirable that future *in situ* studies consider informing these items to improve quality of the reports. Also, attention must be given to blinding aspects in future studies, since some studies did not follow or not report this information.

Animals' studies were evaluated according to SYRCLE's RoB TOOL in order to qualify them about their ROB. Among the articles in this subject, all of them showed a great performance of TiF_4 on caries prevention goal and enamel protection against demineralization [32–35]. Although only Alexandria's study had a low ROB due to be executed under guidelines, allowing its reproducibility and veracity. It is important to consider that when these articles were executed, in the last century, there were no guidelines and qualifiers available like we have nowadays. However, these articles were used as models for all studies made nowadays and the results of all animals' studies were the same, showing a great performance of TiF_4 when compared to other fluorides.

Regarding TiF_4 clinical use, only two studies reported some information regarding possible side effects of its application over enamel. Pedro et al. [68] and Pomarico et al. [29] reported tooth stain, 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 change 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 patient's diet may also have been responsible for

Table 7. Assessment of the certainty of evidence (GRADE).

Certainty assessment							
No of datasets	Design of the studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty
In vivo studies							
Caries prevention							
3	Randomized trials*	Serious[a]	Not serious	Serious[b]	Serious[c]	None	⊕◯◯◯ Very low
Caries treatment							
2	Randomized trials*	Serious[a]	Not serious	Not serious	Serious[c]	None	⊕⊕◯◯ Low
Erosion treatment							
1	Randomized trial	Serious[a]	Not serious	Serious[b]	Serious[c]	None	⊕◯◯◯ Very low
In situ studies							
Caries prevention							
5	Randomized trials*	Serious[a]	Not serious	Serious[b]	Serious[c]	None	⊕◯◯◯ Very low
Caries treatment							
3	Randomized trials	Not serious	Not serious	Serious[b]	Not serious	None	⊕⊕⊕◯ Moderate
Erosion prevention							
5	Randomized trials*	Serious[a]	Serious[d]	Serious[b]	Serious[c]	None	⊕◯◯◯ Very low
Erosion treatment							
5	Randomized trials	Serious[a]	Serious[d]	Serious[b]	Not serious	None	⊕◯◯◯ Very Low
Animal studies							
Caries prevention							
4	Experimental studies[†]	Serious[a]	Serious[d]	Very serious[b,e]	Serious[c]	None	⊕◯◯◯ VERY LOW

*Non-randomized studies are included.
[†]The studies were not randomized (or the process was not clearly explained).
[a]The certainty of the evidence was downgraded in one level because the studies had important methodological limitations and it is likely that they may have altered the results.
[b]Outcomes and assessment methods provide indirect evidence to measure the presence/absence of caries and/or erosion.; therefore, the certainty was lowered by one level.
[c]The certainty of the evidence was downgraded by one level due to the reduced number of individuals/animals considered in the synthesis (less than the threshold of 400 recommended by GRADE).
[d]The certainty of the evidence was downgraded by one level because the studies reported different effects.
[e]The evidence lacks translatability for consideration in humans.

this glaze's pigmentation and raised another hypothesis relates to the titanium reaction with phosphate groups on the tooth's surface with the oxygen atoms, forming a stable titanium dioxide [69]. Supporting these authors, Mosquim et al. [70] observed that both TiF4 varnish and TiF_4/NaF solution have shown staining potential like the commercially available varnish (NaF) and solution (Elmex®) on sound and eroded enamel.

Comparing the TiF_4 solution low pH and probably its toxicity, studies of Huggins and Froehlich [71], Shrestha and Olsen [24] and Shrestha et al. [25] that inoculated rats with TiF_4 and observed no toxic effect in their works. These results were corroborated by Alexandria et al. [33] that 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 of 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, development of studies focussed on other fluoride compounds such as TiF_4, which may have greater efficacy than NaF against tooth demineralization, is important [32]. Vieira et al. [72] also reported that hydroxypropyl-β-cyclodextrin/γ-cyclodextrin with TiF_4 did not induce critical cytotoxic effects and did demonstrate bactericidal potential against *Streptpcoccus 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.

Other fact that could compromise the clinical use of TiF_4 is its instability. Dutra [73] observed problems with TiF4 solution storage and due this, Morais et al. [74] compared two TiF4 solutions (a new brand and the other with 8 months after manipulation) that were applied before acid etch to brackets' bond over enamel. The authors found better results with the fresh TiF_4 solution. Probably when there is a titanium loss 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 [75]. It would undermine the remineralisation of the structure the final formed product [70]. In attempt of develop a novel TiF_4 fluoridated nanocomplex, which shows greater stability, Vieira et al· [71] made a study with β-cyclodextrins (βCDs) that showed that, among all-natural CDs, β-CD is the most accessible, the 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 improve thermal stability. Furthermore, it shall be highlighted that the efficacy of this compound is dependent on its native acidic pH (usually 1.2) [51], and although the efficacy of TiF_4 products were observed in this review, no

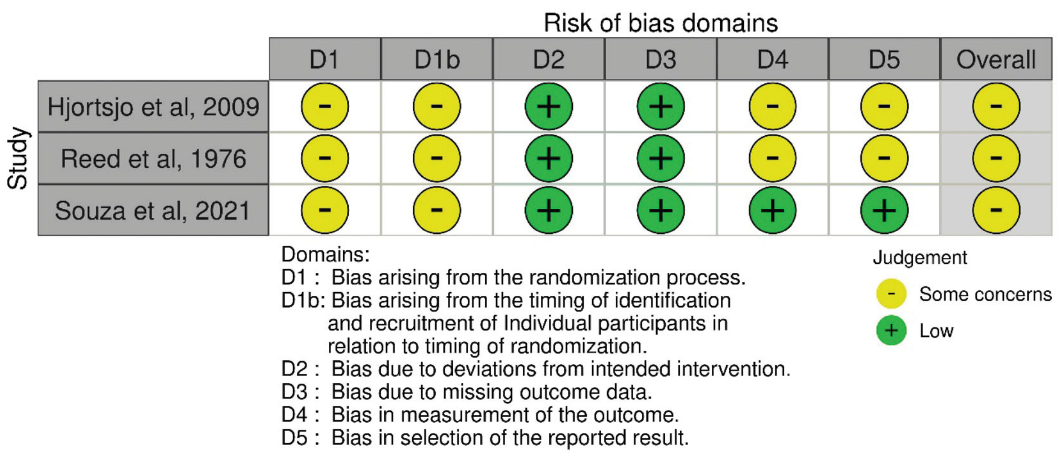

Figure 2. RCTs risk of bias assessment.

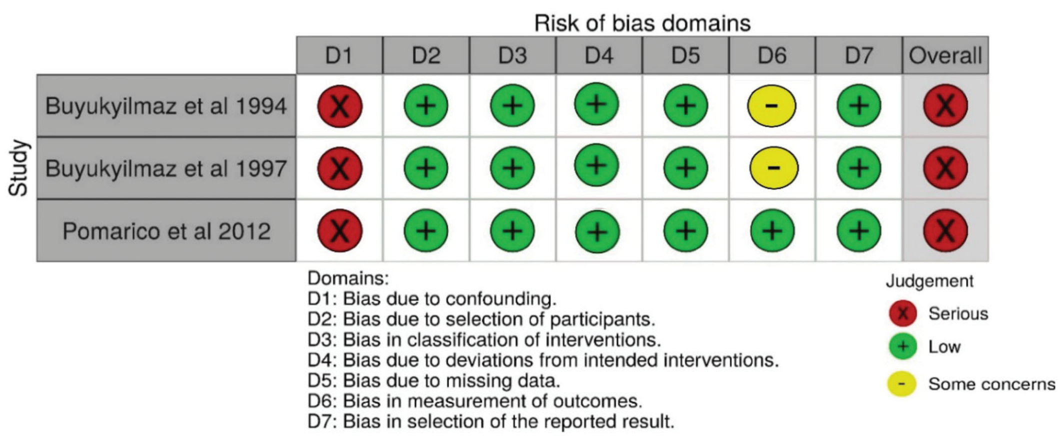

Figure 3. Non-RCT risk of bias assessment.

definite conclusions can be drawn to which vehicle promotes greater protection.

Facing this panorama, it is important to clarify that all evidence observed in this review was based on studies with heterogeneous methodologies, which did not allow us to calculate a meta-analysis nor to have a high certainty of the evidence. These facts do not enable us to widely recommend the clinical use of TiF_4. Furthermore, there is a lack of high quality RCTs in this subject, showing the importance and requirement that new randomized controlled trials conduction in this field should be done to improve the clinical applicability of this promising fluoride compound. Finally, it is strongly recommended further well-designed studies with better standardization of the methods and protocols used, in order to make comparison among them more reasonable and to increase the quality of evidence.

Conclusion

Although most of the results suggest a positive effect of TiF4 on the prevention and treatment of dental caries and dental erosion, it is not possible to have definitive conclusions due to the high methodological heterogeneity among the studies, and the very low quality of evidence for most outcomes.

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