Texila International Journal of Public Health
ISSN: 2520-3134
DOI: 10.21522/TIJPH.2013.13.01.Art079

# Therapeutic Applications of Fluorides in Dental and Medical Diseases-A Systematic Review

Sirigala Lavanya[1,2*], K. Hemashree[2], Prathiba Ramani[2]
[1]*Department of Oral Pathology, Government Dental College and Hospital, Vijayawada, Andhra Pradesh, India*
[2]*Department of Oral Pathology, Saveetha Dental College and Hospital, Saveetha University of Medical Sciences, Chennai, Tamil Nadu, India*

***Abstract***

*A systematic review was conducted to evaluate the therapeutic applications of fluoride, focusing on dental and medical uses. Searches were performed across five major databases: PubMed, Embase, Cochrane Library, Scopus, and Web of Science. A combination of MeSH terms and keywords was used to cover four domains: Fluorides, Dental Therapeutics, Medical Therapeutics, and Outcomes. Inclusion criteria focused on human studies published in English between 2000 and 2024, while exclusion criteria eliminated non-human studies, irrelevant topics, and grey literature. This systematic review analyzed 34 studies on fluoride's therapeutic uses. Fluoride was consistently effective in preventing and managing dental caries, with combinations like 38% silver diamine fluoride (SDF) and 5% sodium fluoride (NaF) varnish showing higher efficacy. High-fluoride mouth rinses and toothpaste reduced demineralized lesions in orthodontic patients, while Arg-NaF varnishes are effective against enamel erosion. Sodium hyaluronate with fluoride improved gingival health. Some studies noted potential negative effects on dental materials, such as reducing sealant bond strength, highlighting the need for further research on fluoride's broader applications and material interactions. In medical contexts, fluoride demonstrated stabilizing effects in conditions like otosclerosis and osteoporosis, though findings were inconsistent across studies. Fluoride is observed to have a positive role in preventing and treating dental and bone diseases. Studies showed fluoride in specific doses could enhance tooth caries resistance and enamel erosion. Fluorides act in controlling osteosclerosis and osteoporosis by stabilizing disease progression and improving bone density. However, more research is needed to fully understand its long-term effects and optimize its use in both fields.*

***Keywords:*** *Dental Caries, Enamel Erosion, Fluorides, Gingival Health, Osteoporosis, Osteosclerosis.*

## Introduction

Fluorides have long been recognized as crucial agents in both dental and medical therapeutics, offering significant benefits in preventing and managing a wide range of conditions [1]. Water is the major dietary source of fluoride. Other important sources of fluoride are tea, seafood that contains edible bones or shells, medicinal supplements, and fluoridated toothpaste. Dietary fluoride is absorbed rapidly in the stomach and small intestine. One-quarter to one-third of the absorbed fluoride is taken up into calcified tissues, whereas the rest is lost in the urine. In bone and teeth, fluoride can displace hydroxyl ions from hydroxyapatite to produce fluorapatite or fluorohydroxyapatite [2].

Fluoride affects bone mineral, bone cells, and bone architecture. Fluoride at physiological levels promotes osteoblast proliferation, increases bone mass, as well as increases osteoblast activity via the upregulation of

***Received: 28.10.2024 Accepted: 10.01.2025 Published on: 28.03.2025***

****Corresponding Author: slavanyamds@yahoo.co.in***

markers such as alkaline phosphatase (ALP), bone morphogenetic protein (BMP), and bone gla protein (BGP). Fluoride at higher doses accumulates in mineralized tissues, notably in the lattice of bone and tooth crystals resulting in diseases known as dental fluorosis and skeletal fluorosis [2]. The dual role of fluoride in both preventing tooth and bone loss and potentially improving tooth and bone quality underscores its therapeutic potential, yet it also highlights the need for more comprehensive studies to understand the long-term effects of fluoride on these tissues fully [2, 3].

The beneficial effects of fluoride on teeth and bone at various doses were used for therapeutic applications of fluoride in preventing and treating some diseases related to teeth, skin infections and bones [1]. Public health strategies have also leveraged the advantages of fluoride through initiatives like water fluoridation [4, 5]. Water fluoridation, in which a controlled amount of fluoride is added to the public water supply, was considered one of the greatest successes in public health in the twentieth century. Over the past 60 years, research studies conducted in several countries were remarkably consistent in demonstrating substantial reductions in caries prevalence as a result of water fluoridation. Although water fluoridation is the most widely used public health measure for caries prevention, less than 10% of the world's population has access to this intervention, as it is not feasible in many areas because of the nature of water supplies [4, 5]. Concurrently, recent opposition has been growing worldwide against fluoridation, emphasizing the potential and serious risk of toxicity [6]. Since the fluoride benefit is mainly topical, perhaps it is better to deliver fluoride directly to the tooth instead of ingesting it. Several modes of fluoride use have evolved, each with its own recommended concentration, frequency of use, and dosage schedule. In dentistry-topical fluoride applications such as caries prevention strategies, including fluoride toothpaste, rinses, and varnish applications have proven their effectiveness in some countries, but they are still not universally affordable [7]. Despite these well-documented benefits, there is a growing need to explore the interactions between fluoride treatments and various dental materials, such as titanium and stainless-steel alloys, which are commonly used in restorative procedures [8]. Understanding these interactions is vital for optimizing the use of fluoride in complex dental treatments and ensuring the long-term success of restorative interventions [9].

However, the potential of fluoride extends beyond dental applications, finding relevance in several medical contexts where its therapeutic properties are being increasingly recognized. This expanded role of fluoride in medicine is a promising area of research, with implications for various health conditions and treatments [1, 3, 10, 11]. One of the most significant medical applications of fluoride is its role in bone health, particularly in the prevention and treatment of osteoporosis [11]. Fluoride has been shown to enhance bone mineralization, a process critical for maintaining bone density and strength [3]. This is especially important in the context of osteoporosis, a condition characterized by weakened bones and an increased risk of fractures [12]. Clinical studies have investigated the use of fluoride in managing osteoporosis, with mixed results [13]. The dual role of fluoride in both preventing bone loss and potentially improving bone quality underscores its therapeutic potential, yet it also highlights the need for more comprehensive studies to understand the long-term effects of fluoride on bone health fully [13, 14].

This study aimed to assess the available data regarding the therapeutic uses of fluorides, considering both their efficacy and prospective topics for further investigation. To understand the relationships between the advantages and drawbacks of different forms of fluoride therapy in dental and medical aspects, answers to the following research questions were searched

1. Which Dental/Medical diseases opt for fluoride therapy?
2. Is the effect the same if applied in different forms of fluoride?
3. What are the impacts of time and duration of fluoride exposure on disease control?

## Materials and Methods

### Search Strategy

#### Database Selection

To ensure a comprehensive evaluation of fluoride applications, a systematic search was carried out across vital biomedical databases: PubMed, Embase, Cochrane Library, Scopus, and Web of Science. These databases were selected to capture relevant studies and thoroughly examine dental and medical fluoride applications. The search encompassed a broad range of literature to ensure a robust and diverse dataset for the review.

### Search Terms

A comprehensive and targeted search strategy was employed using a combination of Medical Subject Headings (MeSH) terms and keywords, organized into four domains: Fluorides, Dental Therapeutics, Medical Therapeutics, and Outcomes. In the Fluorides domain, search terms such as "Fluoride," "Fluoridation," "Fluoride Therapy," "Sodium Fluoride," "Stannous Fluoride," and "Fluoride Compounds" were used, yielding 80 studies from PubMed, 55 from Scopus, and 34 from Web of Science. For the Dental Therapeutics domain, terms like "Dental Caries," "Tooth Decay," "Enamel," "Dentin," "Dental Plaque," and "Oral Hygiene" were employed, resulting in 42 studies from PubMed, 30 from Scopus, and 20 from Web of Science. In the Medical Therapeutics domain, terms such as "Osteoporosis," "Bone Health," "Skeletal Fluorosis," "Antimicrobial," "Anti-inflammatory," and "Cancer Prevention" were used, retrieving 34 studies from PubMed, 24 from Scopus, and 16 from Web of Science. For the Outcomes domain, terms including "Efficacy," "Safety," "Adverse Effects," and "Health Outcomes" were applied, yielding 13 studies from PubMed, 10 from Scopus, and 6 from Web of Science. Boolean operators were used to refine the search. A total of 169 studies were identified across databases, and after removing duplicates and screening, 34 studies were included in the final review.

#### Inclusion and Exclusion Criteria

Inclusion criteria were broad, encompassing studies involving human subjects across all age groups to capture a broad spectrum of fluoride applications across different demographics. To comprehensively assess fluoride's therapeutic potential, the review considered any form of fluoride application or intake, including topical treatments, supplements, and water fluoridation. Only studies that compared fluoride treatments with a placebo, no treatment, or alternative therapies were included to evaluate the relative effectiveness of these interventions. The review focused on studies on fluoride use's efficacy, safety, and health outcomes. To maintain the relevance and timeliness of the review, only studies published between 2000 and 2024 were included, and only those published in English were selected to ensure consistency in data interpretation.

In contrast, exclusion criteria were strictly applied to eliminate studies that did not align with the review’s objectives. Non-human studies, such as animal or in vitro research, were excluded to focus exclusively on human-related data. Studies not directly related to the therapeutic use of fluorides were also excluded to maintain the review's focus. Additionally, studies that did not provide sufficient primary data or relevant outcomes were excluded to ensure the inclusion of only comprehensive and informative studies. Grey literature, including conference abstracts, dissertations, and non-peer-reviewed articles, was also excluded, providing the review was based solely on peer-reviewed and published research. This rigorous application of criteria was essential in compiling a dataset that would allow for a reliable and thorough evaluation of fluoride's therapeutic roles.

## Study Selection

### Screening Process

The study selection process was thoughtfully structured to ensure the accurate and comprehensive identification of pertinent studies. This process was implemented in two distinct phases, each carefully designed to maximize the inclusion of relevant studies while upholding rigorous standards for eligibility.

## Title, Abstract and Full Text Screening

During the initial phase, two independent reviewers meticulously screened the titles and abstracts followed by full-text screening of all studies retrieved from the initial search. This step was crucial in narrowing down the extensive pool of potential studies to those most relevant to the research question. The reviewers evaluated whether each study met the predefined inclusion criteria, focusing on the population studied, the interventions applied, and the outcomes measured. Any variances or disagreements between the two reviewers were thoroughly discussed and not dismissed outright. In cases where consensus could not be reached through discussion, a third reviewer was consulted to provide an impartial opinion and resolve any disagreements. This multi-reviewer approach ensured that the selection process was equitable and robust, thereby minimizing the risk of bias in study selection.

Studies that, at first glance, were pertinent based on their abstracts and titles but, upon closer inspection, did not match the entire inclusion criteria, had to be excluded. The review process was conducted consistently in both phases by adhering to predetermined criteria and standard operating procedures. This ensured that only the best and most relevant research was included in the final evaluation.

## PRISMA Flow Diagram

The PRISMA flow diagram revealed that 169 records were identified from databases. Before the screening process, 10 duplicate records were removed, along with 28 records excluded based on title screening. This left 131 records to be screened. Of these, 80 records were excluded during screening. The remaining 51 reports were sought for retrieval, but 2 reports were not retrieved. This led to the assessment of 49 reports for eligibility.

During the eligibility assessment, 5 reports were excluded: 8 due to being animal studies and 7 because fluorides were used as a preventive measure. Ultimately, 34 studies were included in the final review.

The PRISMA diagram as shown in Figure 1 provided a detailed, step-by-step overview of the study selection process, showcasing the meticulous and systematic approach taken in this review. This level of documentation and visualization is vital for ensuring the credibility and reliability of the review findings and facilitating replication by other researchers.

## Data Extraction

### Data Extraction Form and Process

The data extraction form and process were meticulously developed by the research team, comprising experts in fluoride research and systematic review methodology, to capture essential data points critical for analysis and synthesis. It included key sections such as study identification, population characteristics, intervention details, outcomes measured, results, and study limitations. To enhance the rigour of this process, the STROBE and CONSORT checklist was incorporated, ensuring comprehensive reporting of included studies. Feedback from the pilot testing was used to refine the form, ensuring that it was both comprehensive and user-friendly. This structured approach ensured that all relevant data were consistently and accurately extracted, facilitating a more reliable analysis of the included studies. Once the data were extracted and discrepancies resolved, the information was entered into a pre-designed spreadsheet. This spreadsheet was specifically formatted to facilitate the subsequent analysis, ensuring that all relevant data points were organized and easily accessible for further evaluation.

## Quality Assessment

### Risk of Bias and Quality Assessment Process

Assessing the quality of the included studies was a critical component of this systematic review, to minimize bias risk as it directly impacted the validity and reliability of the review's findings and, reviewers followed the same principles as followed in the above steps. This detailed assessment provided a clear picture of the internal validity of the RCTs included in the review.

The process of quality assessment was conducted with the same level of rigour as the data extraction process and followed the same steps. The results of the quality assessments were then summarized and presented in a graph and summary in Figures 2 & 3 format, which provided a clear and concise overview of the quality of the included studies. This summary allowed for easy identification of studies with a high risk of bias, which could impact the overall conclusions of the review. By presenting the quality assessment results transparently, the review ensured that readers could critically appraise the reliability of the findings and the potential influence of bias on the review's conclusions.

Statistical analysis was not feasible due to of different designs of the studies.

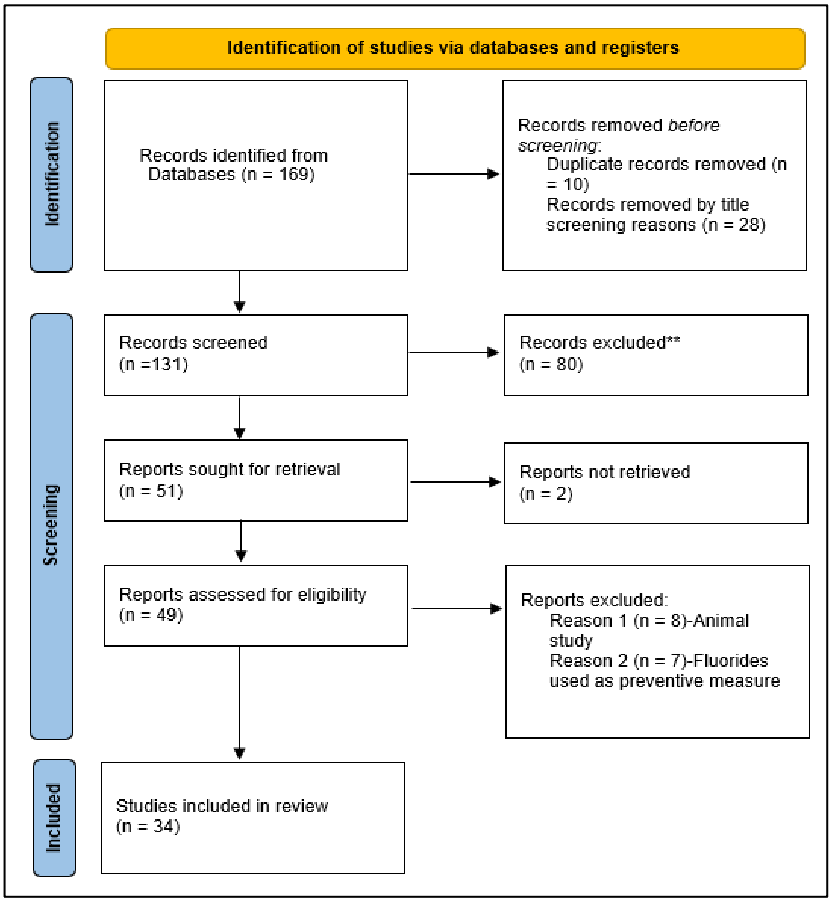


**Figure 1.** PRISMA Flow Chart

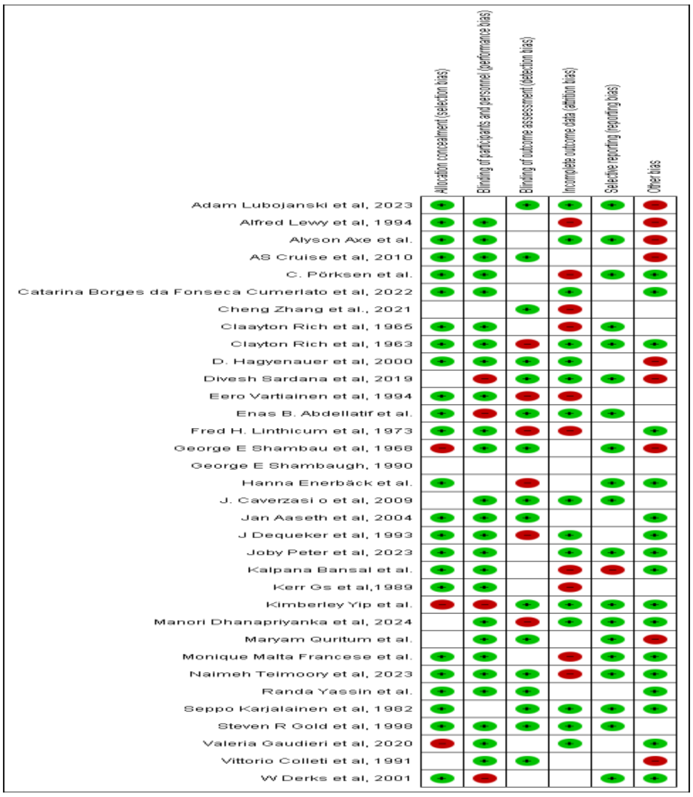

**Figure 2.** Risk of Bias Graph

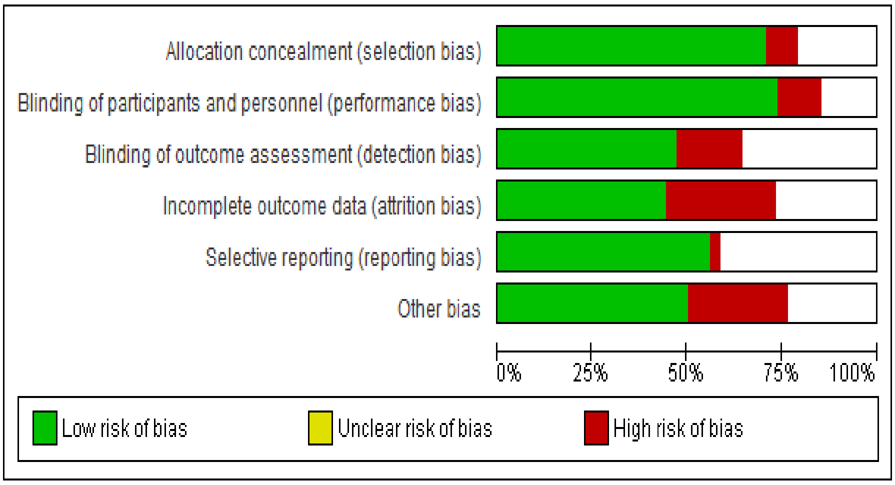


**Figure 3.** Risk of Bias Summary

**Table1.** Summary of Dental Fluoride Application Methodologies and Their Effects

| S. No | Authors | Population Sample | Methods Used | Results | Conclusions | Limitations | Future Research |
|---|---|---|---|---|---|---|---|
| 1 | Enas B. Abdellatif et al., 2023 [23] | 220 children, 110 per group | A randomized, controlled, parallel-group trial comparing 38% SDF | A higher percentage of arrested lesions in the SDF + NaF group than in the | Combining SDF and NaF increases caries arrest rates, | Follow-up limited to 6 months; lack of radiographic assessment. | Longer follow-ups and studies, including radiographic assessments, are needed. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | with 5% NaF varnish vs. SDF alone. Lesion status was assessed after six months. | SDF alone (77.7% vs. 73.2%, p = 0.04). Significant difference in moderate lesions, not in advanced. | especially for moderate lesions. | | |
| 2 | C. Pörksen et al., 2023 [24] | 288 children, 141 interventions, 147 placebos | Clinical examination: The intervention group received a lozenge with 2% arginine and probiotics. Caries activity was analyzed over 10-12 months. | No statistically significant differences, though the interventio n group showed reduced caries progression and fewer active lesions. | Daily lozenge use with arginine and probiotics may reduce caries progressio n, though results were not statisticall y significant . | None explicitly mentioned. | Further research on pre- and probiotics for caries prevention. |
| 3 | Maryam Quritum et al., 2024 [25] | 360 children <4 years, active lesions (ICDAS ≥ 3) | A randomized trial comparing single NSF application vs. SDF with 6-month follow-up. Impact on oral health-related quality of life (OHRQoL) assessed. | Both NSF and SDF improved OHRQoL, with NSF showing better results. | NSF may be a better option for ECC managem ent due to a more significant impact on quality of life. | None explicitly mentioned. | Further research is needed to confirm findings and explore other areas of ECC management. |
| 4 | Hanna Enerbäck et al., 2023 [26] | 270 adolescent orthodontic | Three-armed RCT comparing fluoride | Compared to the control, there is a | High-fluoride mouth rinses and | Non-double-blind design; unregistered protocol. | Future studies should explore double-blind designs and more |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | patients (12-20 years) | mouth rinse, high-fluoride toothpaste, and control group. Demineralization was assessed before and after treatment. | lower incidence of demineralized lesions in high-fluoride toothpaste and mouth rinse groups. | toothpaste are recommended to prevent demineralized lesions during orthodontic treatment. | | extended follow-up periods. |
| 5 | Kimberley Yip et al., 2022 [27] | 72 enamel specimens | In vitro study assessing surface roughness and Ca/P ratio after treatment with Arg-NaF varnish using SEM and AFM. | 4%/8% Arg-NaF and CPP-ACFP varnishes showed better preventive effects against enamel erosion than NaF alone. | Arg-NaF varnish can effectively prevent enamel erosion, especially with chlorpheniramine. | In vitro study with limited generalizability. | Future research should focus on in vivo effects and explore the impact of different acidic challenges. |
| 6 | Alyson Axe et al., 2019 [28] | 110 participants | Double-blind RCT is assessing the impact of toothpaste containing sodium hyaluronate on gingival health over six weeks. | Significant improvements in gingival health with sodium bicarbonate toothpaste compared to regular fluoride toothpaste. | There is no additional benefit of sodium hyaluronate over sodium bicarbonate. | None explicitly mentioned. | Further studies could explore the long-term impact and different formulations. |
| 7 | Randa Yassin et al., 2023 [29] | Children ≤ 4 years, 165 with active lesions | RCT compares 38% SDF vs. 5% NaF varnish plus MI sessions for mothers. Caries' arrest | No significant difference in overall caries arrest between groups, | Both SDF and NaF/MI can arrest ECC, with SDF being better for | Short follow-up period; potential confounding factors. | Longer-term studies are needed to assess the sustained effects of these interventions. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | was assessed over six months. | though SDF was better for advanced lesions. | advanced lesions. | | |
| 8 | Monique Malta Francese et al., 2022 [30] | 15 subjects in a crossover, double-blind study | In situ study using palatal appliances with bovine enamel and dentin. Comparison of TiF4/Chitosan toothpaste vs. commercial toothpaste on ETW. | Both kinds of toothpaste reduced ETW significantly, with no difference between experimental and commercial toothpaste. | TiF4/Chitosan toothpaste is effective against ETW, similar to commercial products. | Small sample size; in situ study limits generalizability. | Clinical trials are needed to confirm the efficacy of TiF4/Chitosan toothpaste in broader populations. |
| 9 | Kalpana Bansal et al., 2023 [31] | 226 children, 4-8 years old | RCT comparing success rates of GIC restorations using SMART vs. conventional techniques over 24 months. | No significant difference in restoration success rates, but children better accepted SMART. | SMART is a viable alternative for treating asymptomatic carious lesions in primary molars, especially in uncooperative children. | None explicitly mentioned. | Future research could focus on longer-term outcomes and applicability in various clinical settings. |
| 10 | Manori Dhanapriyanka et al, 2024 [32] | 16,375 children aged 1.5-14 years (33 studies) | RCTs in LMICs | SDF and NSF effectively arrest primary teeth caries; fluoride varnish and gel effectively | Valuable insights on professionally applied fluorides in LMICs | Low certainty of evidence | More rigorous evidence is needed to strengthen the findings |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | reduce new caries. | | | |
| 11 | Joby Peter et al, 2023 [33] | - | Water fluoridation, fluoride toothpaste | Water fluoridation and fluoride toothpaste reduce dental caries significantly. | Fluoride must be in saliva and plaque for decay prevention. | - | Consider supplementary fluoride in high-carbon communities. |
| 12 | Adam Lubojanski et al, 2023 [34] | - | Endogenous and exogenous fluoride prophylaxis methods | The paper characterizes the properties of fluoride and its effects on the human body. | Optimal fluoride amounts have positive effects on living organisms. | Overdose risk if fluoride intake is uncontrolled. | Long-term effects of fluoride prophylaxis methods on human health |
| 13 | Catarina Borges da Fonseca Cumerlato et al, 2022 [35] | 9 RCTs | Systematic review of RCTs comparing topical fluoride with placebo or toothbrushing | Topical fluoride may reverse incipient carious lesions in permanent teeth. | Home care with fluoride toothpaste may usually suffice for treatment. | The heterogeneity of data prevented meta-analysis. | Further studies with greater methodological rigor are needed. |
| 14 | Naimeh Teimoory et al, 2023 [36] | 250 teeth (148 in the fluoride group, 102 in the control group) | In vitro studies on topical fluoride and sealant bond strength | Fluoride application without washing decreased sealant bond strength significantly. | There was no change in bond strength when tooth surfaces were washed after fluoride. | - | Impact of various fluoride application techniques on sealant adhesion |
| 15 | Divesh Sardana et | Only three studies included | Randomized/ quasi-randomized | The fluoride rinse group | Limited evidence on | A limited number of trials | Well-designed randomized controlled |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | al, 2019 [37] | | controlled clinical trials | had fewer EWSLs than the placebo. | effectiveness in EWSL reversal post-treatment. | included for review | trials on self-applied fluoride effectiveness |
| 16 | Cheng Zhang et al., 2021 [38] | - | 19F MRI, 18F PET, and ultrasound for disease imaging | Fluorinated compounds used in imaging, therapeutics, and environmental remediation. | Importance of controlling fluorine-fluorine interactions in biological behavior. | PFAS poses potential health risks. | Develop new strategies for efficient environmental removal and remediation of PFAS. |

*Statistical Analysis was not Feasible due to of Different Designs of Studies

**Table 2.** Summary of Fluoride Application Methodologies and Their Effects in Medicine

| **S. No** | **Authors** | **Population Sample** | **Methods Used** | **Results** | **Conclusions** | **Limitations** |
|---|---|---|---|---|---|---|
| 1 | A S Cruise et al, 2010 [39] | Population sample size not specified in the text. | Literature review conducted using Medline and PubMed databases | Sodium fluoride may preserve hearing and reduce vestibular symptoms in otosclerosis. | Sodium fluoride can reduce deterioration in hearing for otosclerosis patients. | Limited evidence from one placebo-controlled trial. |
| | | Sampling methods not discussed in the text. | Double-blind, placebo-controlled trial and case-control series analyzed | Evidence suggests reduced hearing deterioration in treated otosclerosis patients. | Lower doses of sodium fluoride effective in halting disease progression. | Variation in treatment doses and duration without clear guidelines. |
| 2 | W Derks et al, 2001 [40] | 19 patients treated with fluoride, 22 untreated controls | Fluoride therapy for cochlear otosclerosis | Fluoride therapy halted progression of sensorineural hearing loss in patients. | Fluoride therapy halted SNHL progression in cochlear otosclerosis patients. | CT evaluation not reliable for fluoride therapy efficacy assessment |
| | | No information | Audiometric and | No clear relationship | No clear correlation | No clear relationship |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | provided on sampling methods | computerized tomography evaluation | found between otospongiotic lesions on CT and SNHL. | between CT findings and SNHL severity observed. | between otospongiotic lesions and SNHL severity |
| 3 | J Dequeker et al, 1993 [41] | | Fluoride therapy for osteoporosis | Fluoride increases axial bone density but not cortical bone. | Fluoride therapy increases axial bone volume in osteoporotic patients. | Controversial treatment despite 30 years of research |
| | | | Effects of fluoride on bone density and fractures | Approximately one third of patients are non-responders to fluoride therapy. | Fluoride's therapeutic window is narrow; best for axial osteoporosis. | Approximately one third of patients are non-responders |
| 4 | George E. Shambaugh, 1990[42] | Population sample size not provided. | Answer: | Fluoride therapy for otosclerosis is considered experimental and unproven. | Fluoride therapy for otosclerosis is experimental and unproven. | No double-blind placebo-controlled study in the US |
| | | Sampling methods not mentioned in the text. | | Lack of double-blind placebo-controlled study due to non-patentability of fluoride. | Lack of double-blind placebo-controlled study due to non-patentability. | Lack of funding due to inability to patent fluoride |
| 5 | Kerr Gs et al 1989 [43] | | Extensive morphological studies | Fluoride therapy for otosclerosis is regarded as experimental. | Fluoride therapy for otosclerosis is regarded as experimental. | Fluoride therapy for otosclerosis is regarded as experimental. |
| | | | Fluoride therapy efficacy reported | Efficacy of fluoride for otosclerosis is reported but experimental. | Efficacy of fluoride for otosclerosis is reported but experimental. | Efficacy of fluoride for otosclerosis is not fully established. |
| 6 | J. Caverzasio et al, 2009[44] | Population sample size not mentioned in the text. | In vitro: Al + F enhanced osteoblast proliferation | Aluminum potentiates fluoride effects on osteoblast proliferation | Aluminum potentiates fluoride effects on bone formation. | Inconsistent mitogenic effect of fluoride in cultured bone-forming cells. |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | and TyrP pathway. | and bone mass. | | |
| | | Sampling methods not discussed in the text. | In vivo: F + Al increased bone mineral density significantly. | Combination of fluoride and aluminum enhances tyrosine phosphorylation pathway. | Combination enhances tyrosine phosphorylation, osteoblast proliferation, and bone mass. | Factors affecting fluoride's mitogenic effect in vitro are unpredictable. |
| 7 | Vittorio Colletti et al, 1991 [45] | Population sample size: 128 relatives of otosclerosis patients. | NaF treatment in doses ranging from 6 to 16 mg. | NaF stabilizes early otosclerosis in over 60% of ears. | NaF stabilizes early otosclerosis, halting disease progression in over 60%. | |
| | | Sampling method: Relatives diagnosed with subclinical otosclerosis based on on-off effect. | Monitoring stapedius reflex morphology at 1, 2, and 5 years. | NaF arrests disease process in more than 50% at 5 years. | NaF shows effectiveness in preventing otosclerosis, suggesting a secondary prevention program. | |
| 8 | Fred H. Linthicum et al, 1973 [46] | 200 volunteers with surgically confirmed stapedial otospongiosis | Strontium85 used to determine calcium deposition in otosclerosis patients. | NaFl changed active otosclerotic foci to quiescence. | NaFl converts active otosclerosis to inactive phase. | No permanent harm in 1600 patients over 6 years. |
| | | Double-blind study with half receiving sodium fluoride and half placebo | Patients took 25 mg of NaFl daily for six months. | Patients showed gap closure and reduced sensorineural hearing loss. | NaFl therapy recommended for progressive sensorineural hearing loss. | Do not give to patients with severe chronic nephritis. |
| 9 | Clayton Rich et al, 1963 [47] | Population sample size: 68 cryolite miners | Balance studies conducted on six patients | Fluoride causes calcium retention in subjects with metabolic bone diseases. | Fluoride causes calcium retention in subjects with metabolic bone diseases. | Aching joint pain in some patients upon weight bearing. |
| | | Sampling method: Not | Patients placed on controlled | Fluoride may accelerate bone | Further clinical trials of fluoride are | Increased prednisone dose |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | specified in the text. | diet for consistency | formation or reduce resorption rate. | warranted for osteoporosis and Paget's disease. | may influence treatment results. |
| 10 | George E. Shambaugh et al, 1968 [48] | 546 adults in Framingham, Mass | Tetracycline labeling for calcium deposition evaluation | Sodium fluoride promotes calcium deposits, reduces bone resorption in rats. | Sodium fluoride shows potential for bone recalcification in otosclerosis. | Otosclerosis lesions may not always cause clinical symptoms. |
| | | Randomly selected for osteoporosis study | Sodium fluoride effects on bone calcium content | Fluoride inhibits experimentally induced osteoporosis in rats. | Fluoride promotes calcium deposits and reduces bone resorption in rats. | Fluoride treatment did not significantly change otosclerotic lesions in some cases. |
| 11 | Clayton Rich et al, 1965[49] | Population sample size: One man with severe primary osteoporosis | Radiographic densitometric methods | Increased calcium retention during sodium fluoride treatment | Fluoride therapy led to increased bone density. | Clinical response cannot argue for therapeutic efficacy. |
| | | Sampling method: Not applicable | Metabolic studies with balance measurement s | Radiographic bone density increase in metaphyses to low normal values | Progressive clinical remission observed in severe primary osteoporosis. | Difficulty in determining benefit due to limited pathophysiology understanding. |
| 12 | Valeria Gaudieri et al, 2020 [50] | Population sample size: 1,375 patients | 18F-sodium fluoride PET/CT imaging | 18F-NaF uptake associated with vascular calcification in CKD patients. | 18F-NaF uptake associated with vascular calcification. | Limited sample size |
| | | Sampling method: Retrospective analysis of patients undergoing PET/CT scans | Assessment of vascular calcification using imaging techniques | 18F-NaF PET/CT may predict cardiovascular events in high-risk patients. | 18F-NaF PET/CT may predict cardiovascular events. | Lack of long-term follow-up data |
| 13 | D. Haguenauer | Population sample size: | Followed Cochrane | Fluoride increases | Fluoride increases | High-dose fluoride linked to |

| | | | | | | |
|---|---|---|---|---|---|---|
| | et al, 2000 [51] | 1429 postmenopausal women | Handbook methodology for meta-analyses | lumbar spine bone mineral density. | lumbar spine bone mineral density. | nonvertebral fractures and side effects |
| | | Sampling method: Randomized controlled trials were conducted. | Structured approach to identify, extract, and synthesize results to minimize bias | Fluoride does not reduce vertebral fractures. | Fluoride does not reduce vertebral fractures. | Unclear factors responsible for differential effects with lower dosages |
| 14 | Jan Aaseth et al, 2004 [52] | Population sample size not provided. | Animal experiments | Fluoride stimulates osteoblasts, aiding bone formation. | Fluorides of 15-25 mg daily stimulate osteoblasts. | Insufficient documentation to define fluoride as essential in humans. |
| | | Sampling methods not discussed in the text. | Clinical studies | Fluoride in combination with antiresorptive medication shows promising results. | Further research needed on fluoride combination with antiresorptive agents. | Inadequate knowledge of biomedical effects of daily fluoride doses. |
| 15 | Seppo Karjalainen et al, 1982 [53] | 181,833 people in low-fluoride area, 71,180 in Kuopio town. | Drinking water fluoridation in low-fluoride area over 20 years. | No significant effect of fluoride on otosclerosis occurrence or age. | Fluoridation did not affect otosclerosis occurrence or age of onset. | No statistically significant differences in hearing results between groups. |
| | | Similar socioeconomic status; no specific sampling method mentioned. | Comparison of fluoride content in bone of residents. | Slightly beneficial influence on severity of otosclerosis. | Fluoridation slightly improved severity of otosclerosis in patients. | Fluoride intake time did not show significant differences in outcomes. |
| 16 | Steven R. Gold et al, 1998[54] | Population sample size: 2 patients | Fluoride treatment | Fluoride treatment resolved facial nerve stimulation in cochlear | Otosclerosis may increase risk of facial nerve stimulation in cochlear implants. | Fluoride treatment may cause gastrointestinal side effects |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | implant patients. | | |
| | | Sampling method: Empirical treatment with fluoride for facial stimulation. | Botulinum toxin injection | Fluoride led to continued successful use of cochlear implants. | Fluoride treatment showed dramatic improvement in refractory cases. | Fluoride is contraindicated in certain medical conditions |
| 17 | Eero Vartiainen e t al, 1994 [55] | Population sample size: 280 patients with otosclerosis. | Fluorine content determined in otosclerotic stapes footplate and skeletal bone. | Fluoridation benefits non-operated otosclerotic ears. | Fluoridation benefits non-operated otosclerotic ears. | No significant effect on hearing levels of operated ears. |
| | | Sampling method: Follow-up study on patients living in low-fluoride area. | Hearing levels assessed in otosclerosis patients living in low-fluoride area. | No significant effect on hearing levels of operated ears. | No significant effect on hearing levels of operated ears. | Limited impact of fluoridation on operated otosclerotic ears. |
| 18 | Alfred Lewy et al, 1994 [56] | 20,488 children in four counties with fluorine in water | Long-term experiment with nontoxic sodium fluoride in public drinking water | Fluorine may prevent some forms of deafness. | Fluorine may prevent deafness and other diseases. | Potential limitations include need for wider investigation and detailed correlation. |
| | | 21,200 children in Chicago with fluorine-free water | Survey of incidence of diseases in communities with fluorine in water | Fluorine's value in preventing dental caries is highlighted. | Fluorine's effect on bone and tissue is significant. | The effect of fluorine on various diseases requires further study. |

*Statistical Analysis was not Feasible due to of Different Designs of Studies

## Results

This systematic review evaluated the effectiveness of various fluoride application methods in different diseases in dentistry across different populations as summarized in Table 1. The review included 16 studies focusing on fluoride's impact on caries arrest, enamel mineralization, bond strength in dental materials, and overall preventive effects. The fluoride application methods examined included topical fluorides like sodium fluoride (NaF), silver diamine fluoride (SDF), sodium monofluorophosphate, and fluoride varnishes, as well as high-fluoride toothpaste, fluoride mouth rinses, and fluoride-containing toothpaste with additives such as arginine and chitosan.

The findings indicated that SDF and sodium monofluorophosphate effectively arrested caries, with sodium monofluorophosphate significantly improving oral health-related quality of life. Notably, combining 38% SDF with 5% NaF varnish resulted in higher caries arrest rates than using SDF alone. High-fluoride toothpaste and mouth rinses were effective in reducing demineralized lesions, particularly in pediatric and orthodontic patients. Additionally, Arg-NaF varnishes offered superior protection against enamel erosion compared to NaF alone. Sodium hyaluronate combined with fluoride improved gingival health, though without additional benefits over sodium bicarbonate.

However, the review also identified concerns about fluoride's potential negative effects on dental materials, such as reduced sealant bond strength. *In vitro* studies suggested that fluoride application without subsequent washing could reduce sealant bond strength, though this effect could be mitigated by washing after fluoride application. While fluoride gels and varnishes promoted enamel mineralization, they occasionally compromised the bond strength of dental materials.

The therapeutic effects of fluoride in medical studies including 18 studies were also explored as summarized in Table 2, focusing on its impact on conditions like otosclerosis and osteoporosis.

The findings generally indicated that sodium fluoride (NaF) has a stabilizing effect on otosclerosis, often halting disease progression, reducing hearing loss, and increasing bone mineral density, particularly in the lumbar spine for osteoporosis patients. However, results across different studies were inconsistent, and the use of fluoride remains controversial due to limited evidence from double-blind, placebo-controlled trials.

## Discussion

This study presents the findings of a comprehensive review of research aimed at understanding the therapeutic applications of fluoride in treating various dental and medical (bone) conditions. The systematic review is based on 34 studies identified in selected scientific databases using keywords and Boolean operators.

Fluoride is essential for dental care and plays a crucial role in preventing and treating dental caries and enamel erosion, especially during special conditions like orthodontic treatment [15, 16, 17]. Fluoride therapy helps repair damaged tooth enamel by incorporating the mineral fluorapatite into the enamel. While fluorapatite is not a natural component of human teeth, it is found in the teeth of sharks. The main mineral in natural tooth enamel is hydroxyapatite, not fluorapatite. Fluoride reduces tooth enamel decay by forming fluorapatite and incorporating it into the enamel. Fluoride ions slow down the demineralization of tooth enamel and speed up the remineralization process in the early stages of cavity formation. These effects occur through the demineralization and remineralization cycle. Remineralization, which is crucial for preventing decay, happens when fluoride is present in the mouth. Fluoride ions are involved in three principal reactions of remineralization [9, 50, 51].

1. Iso-ionic exchange of $F^-$ for $OH^-$ in apatite: $Ca_{10}(PO_4)_6(OH)_2 + 2F^- \rightarrow Ca_{10}(PO_4)_6F_2 + 2OH^-$
2. Crystal growth of fluorapatite from a supersaturated solution: $10 Ca^{2+} + 6PO_4^{3-} + 2F^- \rightarrow Ca_{10}(PO_4)_6F_2$
3. Apatite dissolution with $CaF_2$ formation: $Ca_{10}(PO_4)_6(OH)_2 + 20F^- \rightarrow 10 CaF_2 + 6PO_4^{3-} + 2OH^-$

Iso-ionic exchange by the replacement of $F^-$ for $OH^-$ in apatite and crystal growth of fluorapatite from supersaturated solutions can occur during exposure to low levels of fluoride (0.01–10 ppm F) over long periods. The reaction of apatite dissolution with $CaF_2$ formation occurs in higher levels of fluoride (100–10,000 ppm F) and the addition of $CaF_2$ or a $CaF_2$-containing compound [24]. All forms of topical fluoride exposure such as toothpaste, gels, varnishes, and mouth rinses appeared to play similar roles in the prevention and remineralization of dental caries and tooth erosion. though there was no available comparative study [15, 16, 17, 19]. The difference existed in ease of application and patient acceptability.

Recent research has brought to light the substantial advantages of various fluoride applications, including sodium fluoride (NaF), silver diamine fluoride (SDF), and sodium monofluorophosphate (NSF) [15, 16]. Sodium fluoride, an established agent, has been proven to effectively reduce the incidence of caries, contributing to a considerable decline in caries prevalence over many years [21]. Silver diamine fluoride (SDF) has attracted attention for its dual function in halting carious lesions and preventing further decay, particularly in pediatric populations where traditional treatment compliance can be challenging [22]. However, it should be noted that the application of SDF may result in tooth discoloration, which is an important consideration, especially in cosmetics [22]. Sodium monofluorophosphate has also demonstrated noteworthy efficacy, particularly in promoting enamel remineralization and enhancing oral health-related quality of life (OHRQoL) in children [23]. Its role in managing early childhood caries emphasizes its importance in pediatric dental care [23].

Using high-fluoride toothpaste and mouth rinses is another area supported by clinical research [22]. High-fluoride toothpaste, typically containing 1.1% sodium fluoride or 5000 ppm fluoride, has been shown to provide additional protection against caries and erosion compared to standard fluoride toothpaste [23, 24]. Mouth rinses with elevated fluoride concentrations contribute significantly to caries prevention and enamel demineralization, particularly during orthodontic treatment [28]. These products benefit high-risk populations and complement other preventive measures, emphasizing the importance of incorporating them into daily oral hygiene routines [30].

Fluoride's role in enhancing enamel mineralization is well-documented [20]. Fluoride gels and varnishes effectively promote the remineralization of demineralized enamel, thus restoring its structural integrity and resistance to future carious attacks [21]. Recent innovations include fluoride formulations with added agents such as arginine and chitosan, further enhancing fluoride's protective effects against enamel erosion [22]. These formulations are particularly beneficial for patients at high risk of erosion due to dietary or environmental factors, providing a promising strategy for preventing enamel wear [22].

However, there are notable concerns regarding fluoride application, particularly its impact on the bond strength of dental materials [28]. Fluoride's interaction with restorative materials can potentially affect their adhesion and longevity, which is crucial in clinical settings [29]. While fluoride's protective benefits for enamel are well-established, its impact on therapeutic procedures requires careful consideration to ensure both effective caries prevention and the durability of dental restorations [29]. Additionally, the efficacy of fluoride treatments can vary based on population characteristics, clinical circumstances, and study methodologies. This variability underscores the need for personalized treatment plans considering individual patient needs and risk factors [23].

The action of fluoride in preventing dental cavities occurs primarily after the teeth have erupted. Both primary and permanent teeth respond similarly to fluoride exposure in preventing cavities and remineralizing enamel erosion. This method is especially advantageous for children under 14 years old [23].

The therapeutic effects of fluoride, particularly sodium fluoride (NaF), on conditions like otosclerosis and osteoporosis have shown promising but inconsistent results across various studies [31, 32]. For otosclerosis, NaF appears to stabilize the condition, potentially halting disease progression and reducing associated hearing loss. Similarly, in osteoporosis, NaF has been observed to increase bone mineral density, especially in the lumbar spine [41]. Different forms of fluoride exposure by oral and parent in different doses in combination with other drugs were tried to treat osteosclerosis and post-menopausal osteoporosis [40, 41, 42]. Fluorides were shown to improve bone density but were not able to prevent fractures [44]. Fluoride therapy is mainly administered in adults and post-menopausal women. The duration of fluoride therapy depends on the intensity of the disease [33].

Side effects of dose and duration related of fluoride exposure also evident [6]. Future research needs to tackle current methodological limitations to improve the understanding of fluoride's role in dental and medical care. More well-designed randomized controlled trials (RCTs) with longer follow-ups and diverse populations are essential for generating robust evidence on fluoride's efficacy. More research with promising results available in dentistry compared to medical application probably due to difficulty in clinical trials.

This review highlights the comprehensive role of fluoride in both dental and medical care, focusing on its applications in caries prevention, enamel remineralization, and treatment advancements. Sodium fluoride (NaF), silver diamine fluoride (SDF), and sodium monofluorophosphate (NSF) have demonstrated significant efficacy in maintaining oral health, with clinical studies supporting their use in high-risk populations. Innovations in fluoride formulations, such as the inclusion of arginine and chitosan, present promising preventive strategies, particularly for patients vulnerable to enamel erosion and caries. However, despite the well-established benefits of fluoride, its potential adverse effects, such as its impact on dental material bond strength and the risk of fluorosis, require further investigation to optimize treatment protocols. Additionally, while fluoride's role in conditions like otosclerosis and osteoporosis is promising, more in-depth studies are necessary to clarify its therapeutic potential. The variability in study methodologies and patient populations further underscores the need for more robust, well-designed randomized controlled trials with diverse samples and standardized outcome measures to ensure the reliability of findings.

## Conclusion

Fluoride plays a vital role in both dental and medical care. In dental applications, strong evidence supports its effectiveness in preventing and treating caries and enamel erosion. Fluoride has demonstrated potential therapeutic benefits in medical contexts, particularly in stabilizing conditions like otosclerosis and osteoporosis. Sodium fluoride (NaF) has shown promise in halting disease progression in otosclerosis and improving bone mineral density in osteoporosis patients. However, the medical application of fluoride remains an area of ongoing research, with inconsistent findings and limited evidence from rigorous clinical trials. Further research is needed to clarify fluoride's long-term effects, optimize its therapeutic use in both dental and medical settings, and ensure its safe and effective application across diverse patient populations.

## Conflict of Interest

None.


## Acknowledgement

I sincerely thank my guide Dr.Prathiba Ramani for support in preparing this review.


## References


[1]. Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes,1997, Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Washington (DC): National Academies Press (US); Available from:https://www.ncbi.nlm.nih.gov/books/NBK109825/doi:10.17226/5776.PMID: 23115811.

[2]. Aoun, A., Darwiche, F., Al Hayek, S., & Doumit, J., 2018, The Fluoride Debate: The Pros and Cons of Fluoridation. Preventive nutrition and food science, 23(3), 171–180. https://doi.org/10.3746/pnf.2018.23.3.171

[3]. Everett, E. T., 2011, Fluoride's effects on the formation of teeth and bones, and the influence of genetics. *Journal of dental research*, 90(5), 552–560. https://doi.org/10.1177/0022034510384626

[4]. U.S. Department of Health and Human Services Federal Panel on Community Water Fluoridation 2015, U.S. Public Health Service Recommendation for Fluoride Concentration in Drinking Water for the Prevention of Dental Caries. *Public health reports (Washington, D.C.: 1974)*, *130*(4), 318–331. https://doi.org/10.1177/003335491513000408.

[5]. Iheozor-Ejiofor, Z., Worthington, H. V., Walsh, T., O'Malley, L., Clarkson, J. E., Macey, R., Alam, R., Tugwell, P., Welch, V., & Glenny, A. M., 2015, Water fluoridation for the prevention of dental caries. *The Cochrane database of systematic reviews*, 2015(6), CD010856. https://doi.org/10.1002/14651858.CD010856.pub2.

[6]. U.S. Environmental Protection Agency. Review of the Fluoride Drinking Water Regulation. 2019.

[7]. Petersen, P. E., & Lennon, M. A., 2004, Effective use of fluorides for the prevention of dental caries in the 21st century: the WHO approach. *Community dentistry and oral epidemiology*,32(5),319–321. https://doi.org/10.1111/j.1600-0528.2004.00175.x.PMID:15341615

[8]. Mankar, N., Kumbhare, S., Nikhade, P., Mahapatra, J., Agrawal, P., 2023, Role of Fluoride in Dentistry: A Narrative Review. *Cureus.* 2023 Dec 21;15(12):e50884. doi: 10.7759/cureus.50884. PMID: 38249196; PMCID: PMC10799546.

[9]. Hoque, M. E., Showva, N. N., Ahmed, M., Rashid, A. B., Sadique, S. E., El-Bialy, T., & Xu, H., 2022, Titanium and titanium alloys in dentistry: current trends, recent developments, and future prospects. *Heliyon*, 8(11), e11300. https://doi.org/10.1016/j.heliyon.2022.e11300 (Retraction published Heliyon. 2024 May 27;10(11):e31978. doi: 10.1016/j.heliyon.2024.e31978).PMID: 36387463; PMCID: PMC9640965.

[10]. Medjedovic, E., Medjedovic, S., Deljo, D., & Sukalo, A., 2015, Impact Of Fluoride On Dental Health Quality. *Materia Socio-Medica*, 27(6), 395–398. Https://Doi.Org/10.5455/Msm. 2015. 27.395-398. Pmid: 26889098; Pmcid: Pmc4733546.

[11]. Kleerekoper, M., 1998, The role of fluoride in the prevention of osteoporosis. *Endocrinology and metabolism clinics of North America*, 27(2), 441–452. https://doi.org/10.1016/s0889-8529(05)70015-3. PMID: 9669148.

[12]. Ginaldi, L., Mengoli, L. P., & De Martinis, M., 2009, Osteoporosis, inflammation and ageing. In Handbook on Immunosenescence: Basic Understanding and Clinical Applications (Vol. 9781402090639, pp. 1329–1352). *Springer*

*Netherlands*. https://doi.org/10.1007/978-1-4020-9063-9_64.

[13]. Haguenauer, D., Welch, V., Shea, B., Tugwell, P., & Wells, G., 2000, Fluoride for treating postmenopausal osteoporosis. *The Cochrane database of systematic reviews*, 2000(4), CD002825. https://doi.org/10.1002/14651858.CD002825.

[14]. Pak, C. Y., Adams-Huet, B., Sakhaee, K., Bell, N. H., Licata, A., Johnston, C. et.al, 1996, Comparison of nonrandomized trials with slow-release sodium fluoride with a randomized placebo-controlled trial in postmenopausal osteoporosis. *Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research*, 11(2), 160–168. https://doi.org/10.1002/jbmr.5650110204.

[15]. Abdellatif, E. B., El Kashlan, M. K., & El Tantawi, M., 2023, Silver diamine fluoride with sodium fluoride varnish versus silver diamine fluoride in arresting early childhood caries: a 6-months follow up of a randomized field trial. *BMC oral health*, *23*(1), 875. https://doi.org/10.1186/s12903-023-03597-5.

[16]. Pørksen, C. J., Ekstrand, K. R., Markvart, M., Larsen, T., Garrido, L. E., & Bakhshandeh, A., 2023, The efficacy of combined arginine and probiotics as an add-on to 1450 ppm fluoride toothpaste to prevent and control dental caries in children - A randomized controlled trial. *Journal of dentistry*, 137, 104670. https://doi.org/10.1016/j.jdent.2023.104670.

[17]. Quritum, M., Abdella, A., Amer, H., & El Tantawi, M., 2024, Effect of silver diamine fluoride and nano silver fluoride on oral health-related quality of life of children with early childhood caries: A randomized clinical trial. *Journal of dentistry*, 142, 104878. https://doi.org/10.1016/j.jdent.2024.104878.

[18]. Enerbäck, H., Lövgren, M. L., Strömberg, N., & Westerlund, A., 2023, Effect of high-fluoride toothpaste and mouth rinse on the prevention of demineralized lesions during orthodontic treatment: a randomized controlled trial. *European journal of orthodontics*, 45(5), 477–484. https://doi.org/10.1093/ejo/cjad044.

[19]. Yip, K., Lam, P. P. Y., & Yiu, C. K. Y., 2022, Prevalence and Associated Factors of Erosive Tooth Wear among Preschool Children-A Systematic Review and Meta-Analysis. Healthcare (Basel, Switzerland), 10(3), 491. https://doi.org/10.3390/healthcare10030491.

[20]. Axe, A., Burnett, G. R., Milleman, K. R., Patil, A., & Milleman, J. L., 2019, Randomized Controlled Clinical Study to Determine the Oral and Dermal Tolerability of an Experimental Denture Wipe. *Journal of prosthodontics : official journal of the American College of Prosthodontists*, 28(2), 138–145. https://doi.org/10.1111/jopr.12992.

[21]. Yassin, R., Amer, H., & Tantawi, M. E., 2023, Effectiveness of silver diamine fluoride versus sodium fluoride varnish combined with mother's motivational interviewing for arresting early childhood caries: a randomized clinical trial. *BMC oral health*, 23(1), 710. https://doi.org/10.1186/s12903-023-03456-3.

[22]. Francese, M. M., Gonçalves, I. V. B., Vertuan, M., de Souza, B. M., & Magalhães, A. C., 2022, The protective effect of the experimental $TiF_4$ and chitosan toothpaste on erosive tooth wear in vitro. Scientific reports, 12(1), 7088. https://doi.org/10.1038/s41598-022-11261-1.

[23]. Bansal, K., Shamoo, A., Mani, K., K, P. D., Verma, A., Mathur, V. P., & Tewari, N., 2023, Silver diamine fluoride modified atraumatic restorative treatment compared to conventional restorative technique on carious primary molars-A randomized controlled trial. *Journal of dentistry*, 138, 104698. https://doi.org/10.1016/j.jdent.2023.104698

[24]. Dhanapriyanka, M., Kosgallana, S., Kanthi, R. D. F. C., Jayasekara, P., Dao, T. M. A., Ha, D. H., & Do, L., 2024, Professionally applied fluorides for preventing and arresting dental caries in low- and middle-income countries: Systematic review. *Journal of public health dentistry*, 84(2), 213–227. https://doi.org/10.1111/jphd.12617.

[25]. Peter, Joby & Chandra, H., & Sakhare, Dhanashree, 2023, Systemic Fluorides and Dental Health. 10.2174/9789815080803123030018.

[26]. Lubojanski, A., Piesiak-Panczyszyn, D., Zakrzewski, W., Dobrzynski, W., Szymonowicz,

M., Rybak, Z., et.al; 2023, The Safety of Fluoride Compounds and Their Effect on the Human Body-A Narrative Review. Materials (Basel, Switzerland), 16(3), 1242. https://doi.org/10.3390/ma16031242.

[27]. Cumerlato, C. B. D. F., Santos, C. S. D., Rotta, R. N., Cademartori, M. G., & Corrêa, M. B., 2022, Is professionally applied topical fluoride effective in treating incipient caries? A systematic review. Brazilian oral research, 36, e083. https://doi.org/10.1590/1807-3107bor-2022.vol36.0083

[28]. Teimoory, N., Katebi, K., Ghahramanzadeh, A., & Vafaei, A., 2023, Effects of topical fluoride treatment on the bond strength of pit and fissure sealants: A systematic review. *Journal of dental research, dental clinics, dental prospects*, 17(2), 81–86. https://doi.org/10.34172/joddd.2023.39160

[29]. Sardana, D., Manchanda, S., Ekambaram, M., Yang, Y., McGrath, C. P., & Yiu, C. K. Y., 2019, Effectiveness of self-applied topical fluorides against enamel white spot lesions from multi-bracketed fixed orthodontic treatment: a systematic review. *European journal of orthodontics*, 41(6), 661–668. https://doi.org/10.1093/ejo/cjz015

[30]. Zhang, C., Yan, K., Fu, C., Peng, H., Hawker, C. J., & Whittaker, A. K., 2022, Biological Utility of Fluorinated Compounds: from Materials Design to Molecular Imaging, Therapeutics and Environmental Remediation. *Chemical reviews*, 122(1), 167–208. https://doi.org/10.1021/acs.chemrev.1c00632.

[31]. Cruise, A. S., Singh, A., & Quiney, R. E., 2010, Sodium fluoride in otosclerosis treatment: review. *The Journal of laryngology and otology*, 124(6), 583–586. https://doi.org/10.1017/S0022215110000241.

[32]. Derks, W., De Groot, J. A., Raymakers, J. A., & Veldman, J. E., 2001, Fluoride therapy for cochlear otosclerosis? an audiometric and computerized tomography evaluation. *Acta oto-laryngologica*, 121(2), 174–177. https://doi.org/10.1080/000164801300043361.

[33]. Dequeker, J., & Declerck, K., 1993, Fluor in the treatment of osteoporosis. An overview of thirty years clinical research. *Schweizerische medizinische Wochenschrift*, 123(47), 2228–2234.

[34]. Shambaugh G. E., Fluoride Therapy for Otosclerosis. Arch Otolaryngol Head Neck Surg. 1990;116(10):1217. doi:10.1001/archotol.1990.01870100111026.

[35]. Kerr, G. S., & Hoffman, G. S., 1989, Fluoride therapy for otosclerosis. *Ear, nose, & throat journal*, 68(6), 426–429.

[36]. Caverzasio, J., Imai, T., Ammann, P., Burgener, D., & Bonjour, J. P., 1996, Aluminum potentiates the effect of fluoride on tyrosine phosphorylation and osteoblast replication in vitro and bone mass in vivo. *Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research*, 11(1), 46–55. https://doi.org/10.1002/jbmr.5650110108.

[37]. Colletti, V., & Fiorino, F. G., 1991, Effect of sodium fluoride on early stages of otosclerosis. *The American journal of otology*, 12(3), 195–198.PMID: 1882968.

[38]. Linthicum, F. H., Jr, House, H. P., & Althaus, S. R., 1973, The effect of sodium fluoride on otosclerotic activity as determined by strontium. *The Annals of otology, rhinology, and laryngology*, 82(4), 609–615. https://doi.org/10.1177/000348947308200417.

[39]. Rich, C., Ensinck, J., & Ivanovich, P., 1964, The Effects Of Sodium Floride On Calcium Metabolism Of Subjects With Metabolic Bone Diseases. *The Journal of clinical investigation*, 43(4), 545–555. https://doi.org/10.1172/JCI104940.

[40]. Shambaugh, G. E., Jr, & Petrovic, A., 1968, Effects of sodium fluoride on bone. Application to otosclerosis and other decalcifying bone diseases. *JAMA*, 204(11), 969–973.

[41]. Rich, C., & Ivanovich, P., 1965, Response to sodium fluoride in severe primary osteoporosis. *Annals of internal medicine*, 63(6), 1069–1074. https://doi.org/10.7326/0003-4819-63-6-1069.

[42]. Valeria, Gaudieri., Emilia, Zampella., Adriana, D'Antonio., Alberto, Cuocolo. 18F-sodium fluoride and vascular calcification: Some like it hot.

*Journal of Nuclear Cardiology*, (2020).1-3. doi: 10.1007/S12350-020-02125-0

[43]. Haguenauer, D., Welch, V., Shea, B., Tugwell, P., Adachi, J. D., & Wells, G., 2000, Fluoride for the treatment of postmenopausal osteoporotic fractures: a meta-analysis. *Osteoporosis International: a Journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*, 11(9), 727–738. https://doi.org/10.1007/s001980070051.

[44]. Aaseth, Jan & Shimshi, Mona & Gabrilove, J., & Birketvedt, Grethe, 2004, Fluoride: A Toxic or Therapeutic Agent in the Treatment of Osteoporosis. *The Journal of Trace Elements in Experimental Medicine.* 17. 83 - 92. 10.1002/jtra.10051.

[45]. Karjalainen, S., Kärjä, J., Härmä, R., & Juola, E., 1982, Effect of drinking water fluoridation on stapedial otosclerosis in a low fluoride area. *Acta oto-laryngologica*, 94(1-2), 111–119. https://doi.org/10.3109/00016488209128895.

[46]. Gold, S. R., Miller, V., Kamerer, D. B., & Koconis, C. A., 1998, Fluoride treatment for facial nerve stimulation caused by cochlear implants in otosclerosis. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery*, 119(5), 521–523. https://doi.org/10.1016/S0194-5998(98)70116-0.

[47]. Vartiainen, E., Karjalainen, S., Nuutinen, J., Suntioinen, S., & Pellinen, P., 1994, Effect of drinking water fluoridation on hearing of patients with otosclerosis in a low fluoride area: a follow-up study. *The American journal of otology*, 15(4), 545–548.

[48]. Lewy A., 1944, Possible Value Of Nontoxic Concentrations Of Fluorine In The Prevention of Deafness From Otosclerosis And Fibrosis: Its Possible Value In Prevention Of Other Diseases. *Arch Otolaryngol.* 39(2):152–154. doi:10.1001/archotol.1944.00680010163005.

[49]. Ismail, A. I., & Hasson, H., 2008, Fluoride supplements, dental caries and fluorosis: a systematic review. *Journal of the American Dental Association* (1939), 139(11), 1457–1468. https://doi.org/10.14219/jada.archive.2008.0071.

[50]. Rošin-Grget, K., Peroš, K., Sutej, I., & Bašić, K., 2013, The cariostatic mechanisms of fluoride. *Acta medica academica*, 42(2), 179–188. https://doi.org/10.5644/ama2006-124.85.

[51]. Featherstone, J. D., 1999, Prevention and reversal of dental caries: role of low level fluoride. *Community dentistry and oral epidemiology*, 27(1), 31–40. https://doi.org/10.1111/j.1600-0528.1999.tb01989.x