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The Complex World of Toothpaste Diversity, Meeting Patient Clinical Needs. An Umbrella Review

Jeanie Suvan^{1,2}  | Crystal Marruganti²

¹Oral Sciences, University of Glasgow Dental School, School of Medicine, Dentistry and Nursing, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK | ²Unit of Periodontology, Endodontology, and Restorative Dentistry, Department of Medical Biotechnologies, University of Siena, Siena, Italy

Correspondence: Jeanie Suvan (jeanie.suvan@glasgow.ac.uk)

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ABSTRACT

Background: Amidst numerous recent advancements in toothpaste formulations and active ingredients, some clinicians may believe all toothpastes are similar despite differences in their active ingredients and corresponding clinical application.

Aim: This umbrella review aims to provide clinicians with an overview of toothpaste ingredients and evidence of efficacy for a variety of oral conditions, including gum health issues, caries, dentine hypersensitivity, tooth surface loss, oral malodour and tooth whitening (staining).

Methods: The focused question for the review was ‘What is the efficacy of common toothpaste active ingredients in preventing or treating oral conditions including gum health issues, caries, dentine hypersensitivity, tooth surface loss, oral malodour and tooth whitening (stain removal)?’. Therefore, an umbrella review design was followed focused on review articles, that is, systematic and/or narrative reviews of randomised clinical trials, observational or in vitro studies whenever available. Seventy-two reviews were identified through electronic search of OVID. Quality assessment was performed based upon the PRISMA checklist. Data was extracted according to relevance to the listed oral conditions.

Results: Nineteen toothpaste ingredients were identified to treat six oral conditions, including six types of fluoride. Evidence of efficacy of active ingredients varied and with six reported to have significant benefits for the prevention or treatment of the targeted oral condition. Differences were particularly evident in the efficacy of types of fluoride.

Conclusions: Toothpaste active ingredient efficacies are diverse. As such, oral healthcare providers should consider recommendation of toothpastes containing appropriate active ingredients by effectively targeting oral conditions/diseases according to each patient's needs.

1 | Introduction

More than ever before, oral health is considered an integral part of overall health. Likewise, paradigms of achieving oral and general health increasingly re-emphasise the role of the patient in self-care. Toothpaste plays an indisputably important part in patient oral self-care. Although the concept

of toothpaste use during toothbrushing is longstanding, and fluoride has been accepted as an essential part of toothpaste, scientific advancement during recent decades have resulted in numerous choices of toothpastes with the possibility of addressing both a wider range of oral conditions and a further breadth of choice formulations [1]. However, the continual advancement and multiplicity of ingredients or toothpaste

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choices potentially leaves clinicians and patients with only general knowledge of toothpaste formulations, lacking a detailed understanding of important differences in toothpaste ingredients and their application to various oral conditions [2–4]. When asked by a patient ‘what toothpaste should I use?’, many clinicians might respond ‘they are all the same as long as it has fluoride’, despite advancements in toothpaste formulations that would suggest differences in clinical application [2]. This umbrella review purposes to provide clinicians with an overview of toothpaste ingredients and the evidence of efficacy for a variety of oral conditions including gum health, caries prevention, dentin hypersensitivity, tooth surface loss, oral malodour and tooth whitening.

1.1 | Toothpaste Purposes

Toothpastes are far from being an invention of modern times. The first evidence dates to ancient Egyptians in 3000–5000 BC. Early toothpastes were a combination of powders such as ground shells, pumice, charcoal or bark supplemented by herbs and a liquid, most commonly water. They were created to clean the teeth by removing food or stain and to improve mouth taste or odour [5]. Despite many advancements made throughout the centuries, it was not until the end of the 19th century that toothpaste was packaged and marketed in a collapsible tube. Later, it was designed to reduce tooth pain, strengthen the teeth and reduce inflammation in the mouth, with fluoride first tried in toothpaste formulations in 1914 [5]. Therefore, development focus shifted from making brushing a pleasant experience to incorporating therapeutic active ingredients and improving their substantivity in the oral cavity to maximise efficacy of preventive or therapeutic benefits [1]. As a result, toothpaste composition has become increasingly complex with many different ingredients, active and non-active, acting together to obtain the products currently available.

Depending on the active ingredients and geographical region, over the counter toothpastes may be classified as cosmetic products, medicinal product or medical device for regulatory purposes. Classification of a given paste relies on the composition, mode of action and available evidence of the effects in light of regulatory definitions of the three categories [6]. Regardless of classification, formulations may be beneficial in the prevention of disease or keeping teeth or oral tissues in good condition in some manner. Brushing remains the most universally performed oral hygiene self-care habit to remove plaque. Hence, the role of the toothpaste as well as research and development in this area is pivotal to maximise the therapeutic effects of the active ingredients for the management of the conditions affecting oral cavity. With prevention and patient self-care essential to achieving oral health for everyone, the role of toothpaste in both promoting toothbrushing habits and delivering therapeutic agents is undeniable.

1.2 | Roles of Patient and Dental Professionals in Self-Care and Oral Health

As stated by the World’s Health Organisation (WHO), disease prevention aims to reduce or minimise the burden of diseases

as well as their associated risk factors [7]. The Global Burden of Disease Study (GBD) reported on several oral conditions, in particular dental caries and periodontal diseases, as constituting major burdens on the global healthcare systems due to their high prevalence and their high cost of long-term management [8, 9]. As such, disease prevention is of the utmost importance to reduce patients’ morbidity as well as healthcare costs.

Prevention can be defined as primary, secondary or tertiary. Primary prevention refers to all the actions that aim to avoid the manifestation of a disease. Secondary prevention refers to all the actions that aim to achieve early detection of a disease and to intervene before the onset of the full symptoms of a disease. Tertiary prevention refers to all the actions aiming to reduce the effects and complications of the disease [10]. Patients’ self-care and adherence to healthy lifestyles constitute the core of disease prevention; as such, each patient plays a pivotal role in the prevention and management of oral conditions. All oral conditions share many risk factors, and poor oral hygiene is one of the most relevant ones. Hence, improving patients’ domiciliary oral hygiene habits should be one of clinicians’ priorities.

While it is true that plaque removal is mainly ‘mechanical’, toothpaste research has more recently demonstrated that active ingredients may exert significant clinical benefit in the management of specific oral conditions despite their low substantivity in toothpastes. Given the significant potential benefit and the array of toothpaste formulations currently available, dental professionals should consider choosing the appropriate toothpaste with an active ingredient that targets the oral conditions/diseases diagnosed in the patient. Furthermore, they have a role in downstream (primary) prevention through educating patients on active ingredients relevant to their oral care to facilitate patient choices of consumer products. In addition, dental professionals may play a role in increasing awareness of other healthcare professionals such as general practitioners of the potential therapeutic benefits of toothpastes and the differences in active ingredients. Therefore, all dental professionals must understand the products they are recommending to patients to ensure they are used correctly, safely and appropriately.

1.3 | Toothpaste Composition

Toothpaste formulation must meet both the requirements of consumers pertaining to taste or **mouth** feel, while also ensuring the stability and effect of so called non-active and active ingredients. They should be formulated in such a way that a toothpaste slurry will be formed with saliva and help in the dispersion of the active ingredients in the oral cavity. Numerous factors need to be considered to maintain sufficient stability to allow the active ingredients to yield their effect. For the purpose of this review, non-active ingredients include those that are not directed at an oral condition but rather play a role in the consistency, taste, foaming or abrasiveness of the toothpaste. The term active ingredients will refer to those that demonstrate activity that could be considered therapeutic in that it facilitates prevention or improvement of an oral condition.

1.4 | Non-Active Ingredients

Non-active toothpastes ingredients generally include surfactants, humectants, binders, colouring agents, abrasive systems and water or a base of some sort. Surfactants serve the purpose of contributing to toothpaste consistency and solubility, resulting in thickening or foaming and reducing surface tension of the toothpaste/saliva slurry so it coats the teeth more readily [11]. They also play a role in dissolving flavour, dispersing ingredients and preventing bacterial contamination. Examples of common surfactants are sodium lauryl sulphate (SLS), cocamidopropyl betaine, sodium methyl cocoyl taurate and PEG-60 hydrogenated castor oil. Humectants are water absorbing substances that prevent toothpastes from becoming dry, facilitating a smooth and glossy appearance while also providing delivery of some active ingredients by increasing their solubility. Rheology modifiers also contribute to maintaining an appropriate consistency of the paste. Further inactive ingredients include water, colouring and flavouring agents [5].

All toothpastes have an abrasive ingredient which serves to facilitate mechanical removal of plaque and whitening of teeth through the removal of extrinsic stain, associated particularly with the removal of pellicle (saliva-derived film which forms on enamel). Abrasiveness is determined by particle hardness, size, shape, concentration, viscosity of the paste and presence of soluble ingredients such as surfactants or polyphosphates. It can often be misinterpreted if relying on a single characteristic. For example, sodium bicarbonate is often assumed to be highly abrasive based upon its particle size; however, it is one of the least abrasive due to its high solubility by water. Toothpastes are given an abrasiveness score based upon relative enamel abrasiveness scale (REA) or relative dentine abrasiveness scale (RDA) as defined by the American Dental Association (ADA) [12, 13]. While a toothpaste abrasiveness is needed for plaque and stain removal, it should be balanced to ensure minimal hard tissue loss and soft tissue damage with maximum cleaning efficiency, a low RDA and REA while maintaining high pellicle cleaning ratio values are key. A maximum RDA of 250 / REA < 40 is recommended, and toothpastes with lower RDAs are considered preferential for protecting hard tissues [12].

1.5 | Active Ingredients

Active ingredients contained in toothpastes have a variety of possible therapeutic effects and work in very different ways, with some having more than one effect. Those can be broadly categorised as anti-plaque, anti-gingivitis, anti-caries, anti-hypersensitivity, anti-tooth surface loss, anti-malodour or whitening. The mechanism of action can vary such as with anti-plaque agents that might be bactericidal or bacteriostatic. Table 1 provides an overview of the main categories.

The most common active ingredients in current toothpastes include sodium fluoride (NaF), stannous fluoride (SnF₂), sodium monofluorophosphate (SMFP), amine fluoride (AmF), potassium nitrate (KNO₃), sodium bicarbonate, triclosan, arginine, amorphous calcium phosphate (ACP), casein

TABLE 1 | Categories of toothpaste active ingredient activity.

Action	Description
Anti-plaque	Capable of reducing plaque levels through facilitating plaque removal or interfering with plaque biofilm formation, adhesion or composition often through bactericidal or bacteriostatic activity
Anti-gingivitis	Capable of reducing bleeding/gingivitis largely through disruption of plaque but also through possible anti-inflammatory activity
Anti-caries	Capable of inhibiting formation of caries by preventing demineralisation or promoting resolution of initial caries by enhancing remineralisation
Anti-hypersensitivity	Capable of relieving symptoms of dentine hypersensitivity via nerve desensitisation or physical blockage/occlusion of dentinal tubules
Anti-tooth surface loss	Capable of preventing tooth surface loss via the formation of an extra layer on the tooth structure or via promotion of tooth remineralisation
Anti-malodour	Capable of antimicrobial or oxidising activity interfering with formation of volatile sulphur compounds (VSC) responsible for malodour
Whitening/Stain removal	Capable of achieving extrinsic stain removal and prevention. It is important to note that whitening agents can only aim to obtain extrinsic stain removal and not intrinsic, as the latter would entail changing the texture/structure of the tooth

phosphopeptide—ACP (CPP-ACP), cetylpyridinium chloride (CPC), hydroxyapatite, SLS, calcium sodium phosphosilicate (CSPS/Novamin), strontium chloride, blue covarine, charcoal, chlorhexidine (CHX), oxidising agents, phosphates, xylitol, zinc ions (Zn) and various natural ingredients. Further details of these ingredients and their mode of action will be covered as they pertain to each or condition.

This introduction shows that toothpaste formulations are not 'all the same as long as they have fluoride', and there are currently many more choices of toothpastes becoming available which do not contain fluoride. The aim of this umbrella review was to review and provide a summary for clinicians, based on the most current evidence available, about the efficacy of common toothpaste active ingredients for the various oral conditions mentioned earlier. Based on a search of published evidence pertaining to toothpaste efficacy in the context of various oral conditions, a narrative summary was created to highlight the efficacy of various toothpaste ingredients. The aim was not to compare products but rather to summarise the mode of action

and efficacy of key active ingredients to increase overall understanding of toothpaste ingredient choices to provide an easy reference summary to facilitate clinical decision making and individualised recommendations for each patient.

2 | Methodology

Given the number of published systematic reviews, an umbrella review approach was chosen. Umbrella reviews allow authors to summarise a broad scope of elements surrounding a theme or topic [14]. As such, an umbrella review is a summary of existing systematic reviews. This umbrella review is reported following the PRISMA and PRIOR guidelines [15, 16].

2.1 | Focused Question [PICO(S)] and Eligibility Criteria

The focused question for this umbrella review was ‘What is the efficacy of common toothpaste active ingredients in preventing or treating oral conditions including gum health issues, caries, dentine hypersensitivity, tooth surface loss, oral malodour and tooth whitening (stain removal)?’ Eligibility criteria following the PICO(S) strategy were: (i) Population: participants affected by any oral condition/disease including gingivitis/periodontitis, dental caries, halitosis, tooth stains/discolorations, dentine hypersensitivity or tooth surface loss (i.e., abfractions, abrasions and erosions); (ii) Intervention: administration of a toothpaste with a specific active ingredient to targeting any of the conditions mentioned above; (iii) Comparison: administration of a placebo toothpaste or a regular marketed fluoridated toothpaste; (iv) Outcomes: changes in the surrogate measures of severity and extent of each targeted condition; (v) Studies: systematic and narrative reviews of randomised clinical trials, observational or in vitro studies whenever available, otherwise original articles comparing, clinically or in vitro, the efficacy of specific active ingredients in managing the targeted oral condition. Only articles in English were deemed eligible.

2.2 | Search Strategy, Quality Assessment and Data Extraction

All procedures of search strategy, screening, data extraction and qualitative analyses were performed by two independent authors (C.M. and J.S.). To identify potential reviews, the electronic database Ovid was searched for the previous 20 years up to 22nd November 2023. Keywords and subject headings were merged appropriately using the specific syntax for the database. Additional relevant literature was included through the manual search of significant references in the lists of the included articles. The search terms are summarised in Table 2, and the full search strategy is reported in the Table S1.

Titles and abstracts were first screened to identify potentially eligible articles for full text analysis. After duplicates exclusion, articles were reviewed in full text. The final decision for inclusion of the articles was made at the full text level, and any discrepancy was solved through discussion. Information on authors' names, year of publication, sources searched and inclusion criteria, as well as interventions, outcomes and findings were extracted together with efficacy data relevant to the included oral conditions of the review. The methodological quality of the included reviews was assessed by both authors using the PRISMA guidance tool and considered in summarising strength of the available evidence [17]. Relevant data was extracted from the included reviews by two authors (C.M. and J.S.) by category of oral condition and active ingredient and described in the text format by an oral condition. Qualitative analyses consisted of summary of key points and were formulated based on a body of evidence pertaining to each condition. No quantitative analysis was conducted.

3 | Results

The electronic searching resulted in 499 hits for screening of titles and abstracts following removal of duplicates. Initial screening identified 153 records of possible relevance

TABLE 2 | Search terms.

Focus	Search terms
Toothpaste as mode of delivery	Toothbrushing; toothpaste; dental enamel; micro hardness; surface roughness; dentifrices; pH; plaque, abrasiveness
Toothpaste composition	Fluoride, sodium fluoride, stannous fluoride, amine fluoride, monofluorophosphate, strontium chloride, potassium nitrate, triclosan, chlorhexidine, sodium bicarbonate
Gum health issues	Gingivitis; gingival, diseases, anti-plaque, anti-calculus, inflammation
Caries	Fluoride; caries; fluorosis; caries prevention; carious; cervical; dentine; early childhood caries; enamel; hydroxyapatite; primary teeth; chlorhexidine; demineralisation; fluoride varnish
Dentine hypersensitivity	Dentine hypersensitivity; desensitising toothpaste; dentine sensitivity
Tooth surface loss (TSL)	TSL, tooth wear, abrasiveness, abrasion, erosion, attrition, abrasion, demineralise, remineralisation, enamel remineralisation
Oral malodour	Halitosis, oral malodour, bad breath
Tooth whitening (stain removal)	Whitening toothpaste; abrasion; activated charcoal; tooth whitening

for retrieval of the full text article. Following further assessment, 72 articles were eligible as relevant for data extraction. Nineteen different active ingredients targeting six different conditions were identified, including at least six different fluoride salts. Figure 1 shows the PRISMA diagram summarising the screening process. Quality assessment resulted in categorisation of most reviews as moderate or high quality; however, significant heterogeneity in comparisons of toothpaste formulations and criteria used for inclusion of studies in meta-analysis in the various reviews [18].

The following sections summarise the key active ingredients efficacy categorised by oral condition including a table of key points, a short summary of the results, the mode of action of the ingredient, data extracted pertaining to the efficacy and side effects.

3.1 | Gum Health Issues

Gum health key points

- Clinical meta-data demonstrated a significant anti-plaque and anti-gingivitis effect of toothpastes containing stannous fluoride. The most recent formulations of stannous-containing fluoride toothpastes have overcome staining as the most common side effect
- Sodium bicarbonate containing toothpastes were demonstrated to have significant anti-plaque and anti-gingivitis effects, with little to minimal side effects
- The potential side effects combined with an unclear efficacy do not support the use of chlorhexidine as active ingredient for toothpastes
- There is insufficient and uncertainty of evidence to currently make recommendations regarding the risk and benefits of natural active ingredients as well as CPC in toothpastes

Gingivitis is a highly site-specific inflammatory condition that is usually initiated by dental plaque biofilm accumulation [19]. It is an inflammation of the gingiva characterised by gingival swelling, redness and often bleeding following gentle stimulus such as toothbrushing or interdental cleaning. The role of dental plaque in gingivitis development is well established. Furthermore, it is well documented that thorough and frequent mechanical removal of dental plaque is an effective means of preventing or treating gingival inflammation [20]. The removal of dental plaque relies heavily on individual self-care. Despite diligent efforts, adequate plaque removal is challenging for patients, requiring both a consistent routine and appropriate technique in the use of oral hygiene aids [21]. As such, anti-plaque or antibacterial agents have been investigated for numerous years as adjunctive agents to attempt to improve the efficacy of self-performed mechanical plaque control. In the context of gum health, the therapeutic effects that active ingredients may exert mainly relate to the anti-plaque and anti-gingivitis effects, i.e., they can facilitate plaque removal, interfere with biofilm formation and/or reduce gingival bleeding.

3.1.1 | Active Ingredients

3.1.1.1 | Metal Salts (SnF₂, Including SnF₂ Plus Amine Fluoride)

3.1.1.1.1 | Metal Salts Summary. Evidence suggests that toothpastes with 0.45% SnF₂ have a significant anti-plaque/anti-gingivitis effect over the short and medium term when compared to standard pastes or toothpastes containing triclosan. SnF₂ formulations containing polyphosphates and advanced silicas do not cause staining that was associated with SnF₂ formulations of the previous century.

3.1.1.1.2 | Mode of Action. SnF₂ has been included in toothpastes since the 1940s. It has been shown to have an antimicrobial effect. As such, it was found to prevent new bacteria from growing and adhering to the tooth surface, as well as to reduce the ability of the biofilm to promote the onset of gum disease.

3.1.1.1.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.1.1.1.4 | Side Effects and Indications/Instructions for Use. None of the mentioned formulations are medicines; they are all cosmetic or medical devices [22]. The older formulations of SnF₂ toothpastes were previously associated with tooth staining as a major side effect, although this side effect was overcome with the new formulations now on the market using polyphosphates and advanced silicas. Historically, the main clinical side effects of SnF₂ toothpastes were tooth staining, poor viscosity and strong metallic taste. These limitations were overcome by increasing the toothpaste stability by adding zinc phosphate, zinc citrate or vegetable glycerine, along with other ingredients [23].

An often-reported adverse event of toothpastes containing SnF₂ is staining. A systematic review comparing SnF₂ and triclosan reported that both studies evaluating staining showed a significantly higher risk for the group brushing with a SnF₂ containing toothpaste as compared with triclosan [24]. Reportedly, this risk can be reduced by adding hexametaphosphate (HMP) to the toothpaste, although the evidence in this regard is still limited [25].

3.1.1.2 | Chlorhexidine (Bisbiguanides)

3.1.1.2.1 | Chlorhexidine Summary. Chlorhexidine (CHX) is more commonly present as an active ingredient in mouthwash formulations than in toothpastes. Overall, there is minimal evidence to support the benefits of CHX as an active ingredient in toothpastes while the potential side effects are significant.

3.1.1.2.2 | Mode of Action. CHX is classed as a cationic bisbiguanide, which can be active towards gram-positive or gram-negative bacteria, facultative anaerobes and aerobes and/or yeasts. Therefore, it is bactericidal, bacteriostatic and anti-fungal. It is considered a cationic antiseptic, which means it interacts with the wall and membrane of bacteria to primarily inhibit growth through disruption of the lipid layer. Its bactericidal action is immediate but due to substantivity, that is, its adsorption onto tissue or pellicle-coated surfaces, provides prolonged bacteriostatic activity. It is considered as a challenge for use in toothpastes as may be deactivated by detergents such as SLS [25, 26].

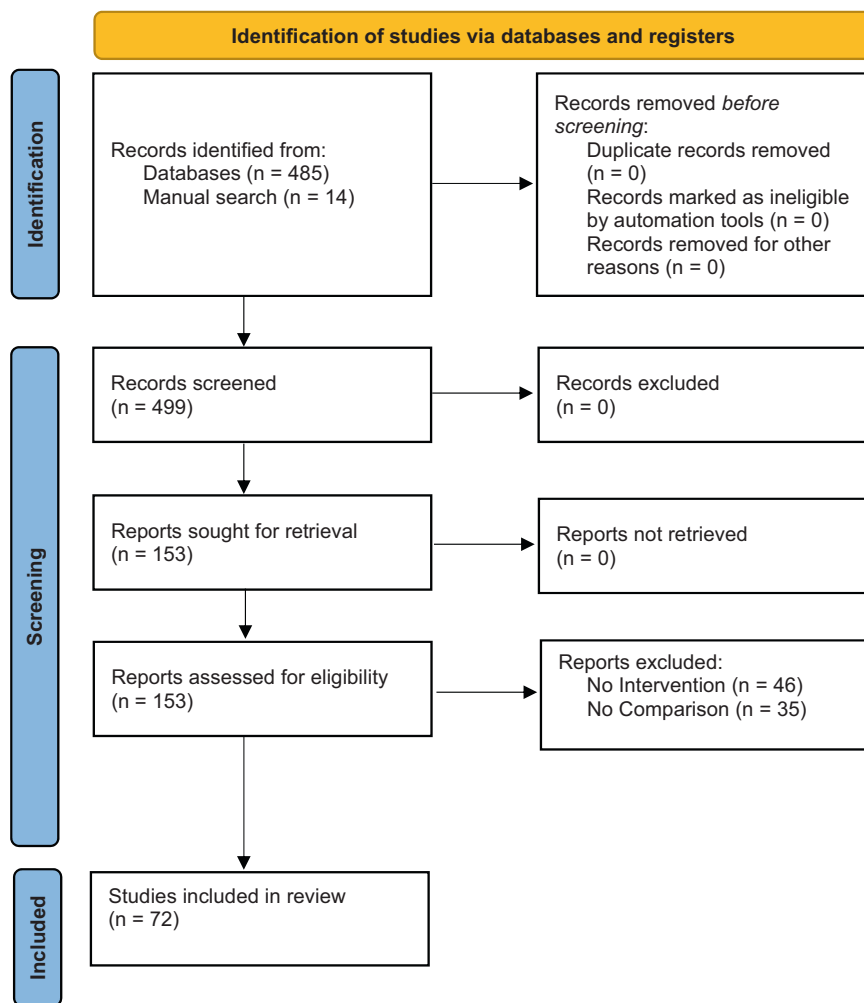


FIGURE 1 | PRISMA flow diagram.

3.1.1.2.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.1.1.2.4 | Side Effects and Indications/Instructions for Use. Significant difference in tooth surface discolouration or stain accumulations compared to placebo control was reported in more than half of the included studies [27]. It was noted that toothpaste formulations of CHX are challenging due to the risk of deactivation of the CHX by other toothpaste components [28].

3.1.1.3 | Sodium Bicarbonate (Baking Soda)

3.1.1.3.1 | Sodium Bicarbonate Summary. Evidence supports the benefit of sodium bicarbonate as an active ingredient in toothpastes with risk of minimal or no side effects.

3.1.1.3.2 | Mode of Action. Sodium bicarbonate, alkaline in composition, has a neutralising effect on acids produced by bacteria and reduces acidic components of various foods or drinks, hence potentially providing protection against tooth demineralisation and reducing risk of staining by acidic drinks such as red wine. For gingival health, it is reported to interfere with macrophage activity, facilitating an anti-inflammatory action. Furthermore, it interferes with the polysaccharide grid of the plaque biofilm, making the plaque less cohesive and easier to remove [29].

3.1.1.3.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.1.1.3.4 | Side Effects and Indications/Instructions for Use. Contrary to common belief, sodium bicarbonate has low abrasiveness attributed partially to its high solubility and its low intrinsic hardness. Its ability to minimise stain is associated with reduction of acid levels when consuming acidic staining foods such as red wine, therefore minimising the potential porosity of the enamel surface. It is virtually free of side effects [30].

3.1.1.4 | Cetylpyridinium Chloride (CPC)

3.1.1.4.1 | CPC Summary. CPC is not commonly found in toothpaste formulations; therefore, evidence is lacking to inform on risks or benefits in CPC in toothpaste formulations.

3.1.1.4.2 | Mode of Action. CPC was found to lead to the destruction of the bacterial cell membrane, inhibition of the bacterial cell metabolism and cell death [31, 32]. CPC can be rapidly absorbed by oral surfaces, with a substantivity reaching 3–5 h [33]. However, CPC was found to be neutralised.

Specific agents include benzylconium chloride and CPC. Their mechanisms of action rely on the hydrophilic part of the CPC

molecule that interacts with the bacterial cell membrane, leading to its disruption, alteration of the bacterial cell metabolism growth inhibition and finally cell death [31, 32]. CPC is a monocationic agent due the positive charge of the mentioned active hydrophilic part. This characteristic allows rapid adsorption of this molecule to oral surfaces [34] with a substantivity of approximately 3–5 h [33], although it also rapidly loses its activity or becomes neutralised [34]. Its formulation is also complex since it is easily inactivated by other ingredients, which makes the study of its bioavailability important. There are no 6-month clinical trials assessing the efficacy of CPC-containing toothpastes.

3.1.1.4.3 | Clinical Evidence of Efficacy. There is limited evidence available supporting the use of CPC in toothpaste, with no 6-month studies. Overall, the available evidence only refers to mouthwashes, not toothpastes.

3.1.1.5 | Triclosan

3.1.1.5.1 | Triclosan Summary. Evidence suggests that triclosan-based toothpastes have significant anti-plaque and anti-gingivitis effects as compared to placebo; such clinical benefits were found to be comparable to those of SnF₂ toothpastes. However, the number of health concerns related to its use limit its availability in the marketplace.

3.1.1.5.2 | Clinical Evidence of Efficacy. Evidence of clinical efficacy and details of restrictions on use are presented in detail in Supplementary Evidence S2.

3.1.1.6 | Natural Active Ingredients. Increasing concerns over the collateral effects of chemical adjunctive agents such as increased resistance to antibiotics or antibacterial agents and evidence in medicine of the possible anti-inflammatory or healing benefits of herbal or natural remedies have perpetuated increased interest in plant-based or natural additives to toothpastes. Furthermore, the high prevalence of periodontal diseases globally and the potential high costs limiting accessibility in developing countries have fuelled this interest in natural ingredients [35].

3.1.1.6.1 | Natural Ingredients Summary. Herbal or natural toothpastes may be similar or better than non-herbal placebo toothpastes depending on the composition of the control toothpaste. When compared to fluoride toothpaste formulations, there is evidence that fluoride toothpastes are more effective in control of dental plaque and gingivitis. There is no evidence of adverse effects, although the lack of evidence and variability among studies suggests that there is a general lack of evidence regarding natural products, their efficacy and their safety.

3.1.1.6.2 | Mode of Action

Herbal. Herbal toothpastes can vary in composition, as there is no single definition of what constitutes a herbal toothpaste other than that ingredients considered as active are plant or essential oil based, with some ingredients listed below potentially having antibacterial or anti-inflammatory properties.

Aloe vera. *Aloe vera* (*Aloe barbadensis* miller) is an easily grown tropical plant found in hot and dry climates globally. The mucilaginous tissue, present centrally in the *Aloe vera* leaf, known as

Aloe vera gel is the extract used in various cosmetic products. As an active ingredient, it is reported to have moisturising, anti-inflammatory, antibacterial, anti-fungal and antiviral properties with widespread use for reducing inflammation and pain relief of minor burns or skin conditions [36, 37]. As highlighted, it has also been incorporated as an active ingredient in toothpastes. **Green Tea.** Green tea has been shown to be a rich source of polyphenols, which are antioxidants; therefore, it can decrease gingival oxidative stress and the presence of pro-inflammatory cytokines both systemically and locally [38].

Apitherapy (Bee Products). Apitherapy refers to the use of bee products such as royal jelly, propolis, honey or bee venom as natural forms of therapy for various medical conditions. Bee products have been reported to have antimicrobial effects as well as activity at the cellular level, also impacting cytokine activity to alter immune responses or inflammatory processes of chronic inflammatory diseases [39]. In vitro studies have shown antibacterial activity against *Porphyromonas gingivalis* (periodontal infections), *Candida albicans* (fungal infections) and *Streptococcus mutans* (caries) and disruption in biofilm formation [40].

3.1.1.6.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.1.1.6.4 | Side Effects and Indications/Instructions for Use. None of the reviews cited pertaining to efficacy reported any side effects associated with the various natural products. Tooth discoloration was the main side effect evaluated, but no significant occurrence was reported.

3.1.1.6.5 | Overall Clinical Relevance. There is a lack of evidence to support recommendations on the risks or benefits of natural active ingredients in toothpastes. Published evidence contains high levels of variability in comparator toothpastes and outcome measurements resulting in a high level of uncertainty of the existing evidence.

3.2 | Caries

Caries prevention key points

- The use of > 1000 ppmF toothpastes is recommended to prevent caries in adults, leading to a 25% reduction in caries. In older adults, > 1500 ppmF concentrations are suggested, and up to 5000 ppmF in individuals with high susceptibility to root caries
- In children, in the absence of other relevant fluoride sources, especially fluoridated drinking water, the toothpaste should contain ≥ 1000 ppm fluoride
- Clinical meta-analytical evidence suggests that 1.5% arginine-fluoride toothpastes have a significant caries preventive effect
- No significant difference was found between marketed fluoridated and hydroxyapatite as well as between ACP/ CPP-ACP toothpastes, respectively
- Limited clinical data showed the addition of 10% xylitol to fluoridated toothpastes may be effective in reducing caries

Dental caries is a common chronic non-infectious disease that results in the demineralisation and eventually in the destruction of the surface of the teeth (enamel and the underlying dentine) due to the conversion of free sugars into acids carried out by cariogenic bacteria. Dental caries has many risk factors including the frequent consumption of free sugars, inadequate domiciliary oral hygiene habits as well as individual susceptibility [41]. Depending on the age and the co-occurrence of other oral diseases, such as gum disease, dental caries can affect either the crown or the root of the teeth [42]. While the prevalence of coronal caries tends to be higher in children and adults, the prevalence of root caries tends to be higher in older adults (> 60 years), probably also due to the higher prevalence of gum disease causing recession and thus exposing the root surface [19, 42].

3.2.1 | Active Ingredients

3.2.1.1 | Fluoride

3.2.1.1.1 | Fluoride Summary. Fluoride-containing toothpastes have been demonstrated to have a significant caries-preventive effect leading to a 25% reduction in caries. 1000/1500ppm fluoride toothpastes are recommended for children, while in adults, a concentration of 1500ppm is recommended. In adults with high susceptibility to root caries, a high-fluoride (5000ppm) concentration of toothpaste is recommended.

3.2.1.1.2 | Mode of Action. Fluoride acts on caries by reducing enamel demineralisation during the acid attack, enhancing mineral gain and providing a more resistant enamel structure. The calcium fluoride precipitates on the enamel surface and plaque and functions as a reservoir for fluoride when the pH falls. As such, fluoride is able to promote remineralisation of early lesions and prevent the formation of new areas of demineralisation by altering the demineralisation–remineralisation cycle [43].

3.2.1.1.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.2.1.1.4 | Side Effects and Indications/Instructions for Use. The use of high concentration fluoride toothpaste (> 1500ppmF) should be allowed only after carefully considering the following (to prevent fluorosis): age and risk of fluorosis, water fluoridation in the community, presence of fluoride in any other products (therapeutic and non-therapeutic) and risk of caries and its morbidities [44]. 2800 and 5000ppm fluoride toothpastes have been launched as prescription toothpastes, whose use is recommended only in some cases in adults. Their use is not recommended for children [44].

3.2.1.2 | Arginine

3.2.1.2.1 | Arginine Summary. Among the many formulations of arginine-containing toothpastes, 1.5% arginine-fluoride toothpastes appear to retain the highest caries-preventative effect.

3.2.1.2.2 | Mode of Action

Arginine Non-Fluoridated (Arginine Bicarbonate-Calcium Carbonate Complex). The arginine would counter the fall in pH due to the acid production happening during the caries process, while the bicarbonate and carbonate components would neutralise the acids and keep the pH low to form base with arginine, thus leading to an increased alkalogenic microflora, preventing the onset of the carious process [45].

Low Concentration Arginine-Fluoride. Arginine synergized with fluoride can suppress acidogenic *S. mutans* in both planktonic and biofilm cultures [46]. In addition, the NaF/arginine combination synergistically is capable of reducing *S. mutans* but enriched *S. sanguinis* within the multispecies biofilms. More importantly, the optimal combination of NaF/arginine maintained a 'streptococcal pressure' against the growth of *P. gingivalis* within the alkalized biofilm. The optimal concentration tested here is 31.25ppm NaF and 0.625% Arg (identified as low concentration) [46].

3.2.1.2.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.2.1.2.4 | Side Effects and Indications/Instructions for Use. No specific side effects related to arginine usage were identified [47]. However, Zheng et al. [46] warned against high concentrations of arginine-fluoride (e.g., greater than 1.5%), as they can promote the overgrowth of oral anaerobes like *P. gingivalis* in the alkalized plaque. On the other hand, low concentrations of arginine were shown to be able to maintain the Streptococcus abundance (hence suppressing the abundance of *P. gingivalis*) [47].

3.2.1.3 | ACP and Casein Phosphopeptide ACP (CPP-ACP)

3.2.1.3.1 | ACP and CPP-ACP Summary. ACP and CPP-ACP toothpastes were found to have a significant caries-preventive and remineralising effect, especially in root caries.

3.2.1.3.2 | Mode of Action. ACP (unstabilised ACP): as ACP mixes with saliva, salts dissolve and calcium and phosphate ions are released; in the presence of fluoride, ACP becomes amorphous calcium fluoride phosphate (ACFP). In this phase, calcium and phosphate should be able to promote enamel surface lesion remineralisation. CPP stands for casein phosphopeptide, and it is a protein deriving from milk that stabilises high concentrations of calcium and phosphate at both acidic and basic pH, forming nanoclusters CPP-ACP and CPP-ACFP [48]. Such complexes will release the calcium and phosphate ions in the subsurface lesion, which will then deposit into the crystal voids. In the case of ACFP, this will lead to the formation of fluorapatite [48, 49].

These complexes mainly work in two ways: (i) facilitate remineralisation as described above; (ii) prevent the onset of demineralisation by binding onto the tooth surface (and to supragingival plaque), increasing the levels of bioavailable calcium and phosphate as well as increasing the plaque pH to alter the balance between remineralisation and demineralisation in favour of the former [49].

3.2.1.3.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.2.1.3.4 | Side Effects and Indications/Instructions for Use. There is a potential promotion of calculus formation with long-term use, but there are no long-term clinical trials available as evidence [48]. Another review reported no side effects of CPP-ACP toothpaste were reported [50].

3.2.1.4 | Hydroxyapatite

3.2.1.4.1 | Hydroxyapatite Summary. Despite the lack of long-term clinical trials, HAP was shown to have significant remineralisation effects on early carious lesions in laboratory studies.

3.2.1.4.2 | Mode of Action. Nano-hydroxyapatite is a component that is bioactive and biocompatible. 10% of nHA was found to be the optimal concentration for remineralisation of early enamel lesions. nHA fills up the enamel micropores of the areas of demineralisation and thus favours remineralisation; moreover, nHA attracts further calcium and phosphate thus promoting the integrity and growth of enamel crystals [51].

3.2.1.4.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.2.1.4.4 | Side Effects and Indications/Instructions for Use. No side effects reported.

3.2.1.5 | Calcium Sodium Phosphosilicate Bioactive Glass (e.g., Novamin)

3.2.1.5.1 | CSPS Summary. Despite the lack of long-term clinical trials, Novamin was shown to have a significant action on early carious lesions.

3.2.1.5.2 | Mode of Action. When in the oral environment, it interacts with saliva to release phosphate, sodium and calcium. This results in the formation of a layer of crystalline hydroxycarbonate apatite layer that is structurally and chemically similar to natural tooth mineral. Hence, it can induce remineralisation of enamel and dentine lesions as well as prevent demineralisation in case of decreased salivary pH [52].

3.2.1.5.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.2.1.5.4 | Side Effects and Indications/Instructions for Use. No potential side effects were reported.

3.2.1.6 | Xylitol

3.2.1.6.1 | Xylitol Summary. Despite the high heterogeneity of the included studies, xylitol-fluoride-containing toothpastes were shown to have a significant caries-preventive effects.

3.2.1.6.2 | Mode of Action. Xylitol was found to have a caries-preventive action by reducing the *S. mutans* count and reduction in the acid lactic production by the bacteria [53].

3.2.1.6.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.2.1.6.4 | Side Effects and Indications/Instructions for Use. No potential side effects were reported, although clinical evidence on this topic is limited.

3.2.1.6.5 | Overall Clinical Relevance. Xylitol was found to have a significant adjunctive anti-carries effect when added to fluoride-containing toothpastes, although the clinical evidence with this regard is limited.

3.3 | Dentine Hypersensitivity

Dentine hypersensitivity key points

- SnF₂, arginine, potassium, strontium, hydroxyapatite and CSPS (e.g., Novamin) all demonstrated benefits over and above sodium fluoride
- SnF₂ showed the most beneficial effects over fluorides compared to other active ingredients, although one review also reported CSPS as having equally beneficial effects
- Evidence is lacking to suggest an optimal frequency or length of use required to observe benefits
- Dentin hypersensitivity assessment is challenging, resulting in heterogeneity of the evidence

Dentinal hypersensitivity is a highly prevalent condition with prevalence estimated to range of 33%–61% of adults with estimates varying according to research methodology and setting [54]. The definition adopted in 1983 and still used today states that dentine hypersensitivity is characterised by short, sharp pain arising from exposed dentine in response to stimuli, typically thermal, evaporative, tactile, osmotic or chemical, which cannot be ascribed to any other form of dental defect or pathology [55].

Treatment of dentine hypersensitivity includes the application of substances to occlude either the open dentinal tubules to prevent the hydrodynamic mechanisms that result in the stimuli triggering the pulpal nerve or those that obstruct the pulp nerve response without preventing movement of the dentinal fluid. Toothpastes are an obvious valuable delivery method for such active ingredients.

3.3.1 | Active Ingredients

3.3.1.1 | Calcium Sodium Phospho-Silicate

3.3.1.1.1 | Calcium Sodium Phospho-Silicate (CSPS) Summary. Evidence supports that CSPS (e.g., Novamin) may be beneficial in treating dentine hypersensitivity, particularly at higher concentrations.

3.3.1.1.2 | Mode of Action. When bioactive glass is in contact with body fluids, a series of chemical interactions take place between its ions and particles, resulting in the deposition of calcium and phosphorus, which in turn contribute to

formation of a hydroxycarbonate apatite layer similar to biological apatite. This apatite layer acts as a barrier to occlude the dentinal tubules.

3.3.1.1.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.3.1.1.4 | Side Effects and Indications/Instructions for Use. Some studies did not report adverse events while most studies did not observe adverse reactions. Two studies reported minor possible side effects such as gastro-intestinal upset; however, reports were too few and inconsistent to attribute them to the toothpaste use. It was noted that duration of use and relief of pain was variable, so it was not possible to define a particular protocol or regime of use due to individual patient variability of symptoms and reporting of pain.

3.3.1.2 | Arginine

3.3.1.2.1 | Arginine Summary. Evidence of the benefits of arginine is fairly consistent across a number of systematic reviews. There is strong evidence of benefit over placebo and evidence of moderate certainty of benefit similar or above other active ingredients.

3.3.1.2.2 | Mode of Action. Arginine is one of the active ingredients considered for treatment of dentinal hypersensitivity through occlusion of the exposed dentinal tubules.

3.3.1.2.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.3.1.2.4 | Side Effects and Indications/Instructions for Use. No adverse effects were reported by the reviews. Studies showed significant heterogeneity in frequency and duration of use.

3.3.1.3 | Stannous Fluoride (SnF₂)

3.3.1.3.1 | SnF₂ Summary. Published evidence supports the recommendation of SnF₂ for the treatment of dentine hypersensitivity. Its efficacy may be similar or better than other active ingredients but is consistently superior to placebo. Time of follow-up to observe benefits is variable and may be attributed to heterogeneity of the studies in the research area.

3.3.1.3.2 | Mode of Action. SnF₂ is another active ingredient considered for treatment of dentinal hypersensitivity through occlusion of the exposed dentinal tubules. The effect is attained because of stannous ions interaction with the dentine surface to form a layer on the tooth that withstands exposure to acid and ultimately occludes open tubules therefore preventing nerve stimulation and the resulting pain. This barrier is proposed to consist of stannous oxide or stannous fluorophosphate, both high in tin content and consequently found to be acid-resistant, therefore providing lasting effect [56]. It is important that the toothpaste formulation incorporate bioavailable gluconate chelated SnF₂ because the bioavailability is critical to the activity of the SnF₂.

3.3.1.3.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.3.1.3.4 | Side Effects and Indications/Instructions for Use. No adverse effects were reported by the reviews. Most of the studies demonstrating significant efficacy were based upon twice daily brushing for 1 min. Benefits were observed within as little as 3 days and maintained to 8 weeks [57].

3.3.1.4 | Strontium Chloride or Acetate

3.3.1.4.1 | Strontium Chloride Summary. Strontium salts demonstrated benefits over fluorides, however, most often of a smaller magnitude than other formulations.

3.3.1.4.2 | Mode of Action. Strontium is another of the active ingredients considered for treatment of dentinal hypersensitivity through occlusion of the exposed dentinal tubules. It can be used in combination formulations as well as alone.

3.3.1.4.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.3.1.4.4 | Side Effects and Indications/Instructions for Use. No adverse effects were reported by the reviews. Studies showed significant heterogeneity in frequency and duration of use.

3.3.1.5 | Potassium Nitrate, Chloride or Citrate

3.3.1.5.1 | Potassium Nitrate Summary. Evidence of efficacy is variable by systematic review. It suggests that potassium may reduce dentine hypersensitivity, but evidence of benefit is stronger for other active ingredients. Evidence of efficacy is more often of longer follow-up so it may be that a longer time is required to observe the benefits. There is no evidence of side effects or harm.

3.3.1.5.2 | Mode of Action. Different from most other dentine hypersensitivity active ingredients, potassium nitrate provided pain relief through depolarisation of the nerve, resulting in a reduction of the excitability of the nerve membrane. Given its different mode of action, it has been investigated in combination with various active ingredients that work to occlude dentinal tubules.

3.3.1.5.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.3.1.5.4 | Side Effects and Indications/Instructions for Use. No adverse effects were reported by the reviews. Studies showed significant heterogeneity in frequency and duration of use.

3.3.1.5.5 | Overall Clinical Relevance. Evidence from the systematic reviews strongly supports the desensitising efficacy of bioavailable SnF₂ toothpastes with stabilised SnF₂ formulations providing superior results than other forms of fluoride. Evidence does not suggest a concerning risk of side effects

from use of any of the active ingredients covered for prevention or treatment of dentine hypersensitivity. All formulations demonstrated some benefit in treating dentine hypersensitivity, although arginine, CSPA (e.g., Novamin) and SnF₂ resulted in higher magnitude of improvement.

3.4 | Tooth Surface Loss

Tooth surface loss key points

- Clinical meta-analytical data showed that NaF and SnF₂ containing toothpastes are effective in reducing enamel loss under erosive/abrasive challenges
-

The umbrella term ‘tooth surface loss’ includes all those conditions that lead to the loss of different parts of the tooth surface. As per the latest proposed definition, the cumulative surface loss of mineralised tooth substance due to physical or chemo-physical processes (dental erosion, attrition and abrasion). Tooth wear is not considered to be the result of dental caries, resorption or trauma [58]. Depending on the potential cause for tooth surface loss, tooth surface loss can be identified as abrasion, erosion or attrition.

Dental abrasion is defined when the tooth surface has been worn away by a mechanical process or friction (overzealous toothbrushing is one of the most common causes of abrasion). Erosion is defined when the tooth surface has been worn away by acids that reach the tooth surface either via eating or drinking or by coming up from the stomach. Attrition is defined when the tooth surface (usually the occlusal or incisal surfaces) is lost due to functional or parafunctional tooth-to-tooth contacts [59].

3.4.1 | Active Ingredients

3.4.1.1 | Fluoride

3.4.1.1.1 | Fluoride Summary. Fluoride products seem to be able to reduce enamel loss, but the paucity and heterogeneity of evidence warrants additional studies.

3.4.1.1.2 | Mode of Action. Fluoride promotes remineralisation of lesions and forms a stable and acid-resistant coating on the tooth surface [60].

3.4.1.1.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.4.1.1.4 | Side Effects and Indications/Instructions for Use. Same fluoride-related side effects mentioned in the caries prevention chapter.

3.4.1.2 | Stannous Fluoride (SnF₂)

3.4.1.2.1 | SnF₂ Summary. Evidence is conflicting with regards to the potential beneficial effect of stannous fluoride in preventing erosion/abrasion.

3.4.1.2.2 | Mode of Action. The stannous-containing salts form a resistant layer on the enamel surface, and it can interact with the salivary pellicle, or be incorporated into the demineralised enamel surface, hence reducing the tooth wear provoked by the synergic effect of erosion and abrasion [61]. Therefore, SnF₂ adheres to the surface of tooth enamel and forms a protective layer made of CaF₂, that is able to shield enamel from the effects of erosive acids [62].

3.4.1.2.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.4.1.2.4 | Side Effects and Indications/Instructions for Use. Same side effects as mentioned for SnF₂ in the gum health issues section.

3.4.1.2.5 | Overall Clinical Relevance. Clinical evidence of efficacy of toothpastes against tooth surface loss is scarce. Review of in vitro studies demonstrated a potential beneficial effect of stannous fluoride and CPP-ACP containing toothpastes.

3.5 | Oral Malodour

Oral malodour key points

- Although limited, a small body of evidence suggests that sodium bicarbonate as well as zinc-containing toothpastes are effective in reducing VSCs
 - Clinical meta-analytical data of RCTs suggest that SnF₂ toothpastes are more effective than fluoridated toothpastes in reducing immediate and ‘overnight breath’ or ‘morning breath’
 - Limited/inconclusive evidence supports the use of SLS for the management of oral malodour
-

In most cases, the occurrence of oral malodour is caused by tongue coating that is primarily caused by the degradation of anaerobic bacteria in the oral cavity. The mode of action to fight oral malodour usually aims to mark the odorous compounds either mechanically or chemically. The mechanical removal of tongue coating (i.e., through a tongue scraper) was proven to successfully reduce oral malodour; however, chemical agents may also be effective in managing bad breath [63]. Many ingredients have been proposed with this purpose; however, the clinical evidence of efficacy is extremely limited.

Antibacterial ingredients such as triclosan and metal ions like stannous and zinc appear to be effective in the control of oral malodour [64]. A systematic review investigating the efficacy of mechanical and chemical agents to reduce oral malodour reported ‘the majority of studies provided a significant reduction in oral malodour when evaluating products with an active ingredient (incorporated into a toothpaste or a mouthrinse) used adjunctively to toothbrushing’. No specific active ingredient was suggested due to the high variety of the included studies [63]. A review by Wylleman et al. [65] demonstrated that some promising results were found for fluoride-containing toothpastes and probiotics. The overall quality of the included studies was low.

3.5.1 | Active Ingredients

3.5.1.1 | Sodium Bicarbonate (Baking Soda)

3.5.1.1.1 | Sodium Bicarbonate Summary. Sodium bicarbonate was found to effectively reduce oral malodour.

3.5.1.1.2 | Mode of Action. Different modes of action were proposed including the conversion of odorous to non-odorous forms as well as its antibacterial activity [66].

3.5.1.1.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.5.1.1.4 | Side Effects and Indications/Instructions for Use. A recent statement by the European commission recently deemed the use of zinc ions in toothpaste as safe only up until 1% concentration [67].

3.5.1.2 | Zinc Ions

3.5.1.2.1 | Zinc Ions Summary. Laboratory evidence suggests that zinc ions have an antibacterial effect; however, there is limited clinical research investigating benefits in the mouth. There is limited clinical evidence to support zinc ions containing toothpastes to reduce oral malodour.

3.5.1.2.2 | Mode of Action. Zinc-containing toothpastes have been suggested to reduce oral malodour via two main modes of action: (i) direct binding to gaseous H_2S products causing the malodour and (ii) suppressing the growth of VSC-producing oral bacteria [68]. Burnett and co-workers used an in vitro model to assess the mode of action of zinc-containing toothpastes against oral malodour. In this in vitro model, zinc ions reacted chemically with hydrogen sulfide to remove the odorous component of halitotic breath; the zinc toothpaste was found to remove 90% of hydrogen sulfide from the perfusate gas (causing 'bad breath') [69]. In an in vitro model of bacterial growth, Kang and co-workers found zinc chloride toothpaste effectively inhibited bacterial growth by reducing the concentration of specific bacteria (e.g., *A. actinomycetemcomitans*, *F. nucleatum*, *P. gingivalis*, *T. denticola*, and *T. forsythia*) and their VSC production [70].

3.5.1.2.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.5.1.2.4 | Side Effects and Indications/Instructions for Use. A recent statement by the European commission recently deemed the use of zinc ions in toothpaste as safe only up until 1% concentration [67].

3.5.1.3 | SLS

3.5.1.3.1 | SLS Summary. Very limited clinical evidence supports SLS-containing toothpastes as ingredients to prevent/manage oral malodour.

3.5.1.3.2 | Mode of Action. Different modes of action were proposed, all of them pointing towards a strong antibacterial activity and the capacity to remove anaerobes and VSC-producing bacteria and debris [71].

3.5.1.3.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.5.1.3.4 | Side Effects and Indications/Instructions for Use. Side effects were reported, such as mucosal desquamation, irritation or inflammation of oral mucosa or the dorsal part of the tongue, ulcerations and toxic reactions in the oral cavity [72].

3.5.1.4 | Stannous Fluoride (SnF_2)

3.5.1.4.1 | Stannous Fluoride Summary. Though limited and with a short term follow-up, clinical meta-data supports the use of stannous fluoride-containing toothpastes to prevent oral malodour and specifically 'morning breath'.

3.5.1.4.2 | Mode of Action. Stannous ions were found to be able to capture VSC; moreover, they were found to have a strong anti-plaque and antibacterial activity, hence promoting VSC reduction [73].

3.5.1.4.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.5.1.4.4 | Side Effects and Indications/Instructions for Use. No side effects were reported.

3.5.1.4.5 | Overall Clinical Relevance. Sodium bicarbonate, stannous fluoride as well as SLS-containing toothpastes were found to be effective in reducing oral malodour, though the clinical evidence is still extremely limited. The use of toothpastes containing active ingredients such as sodium bicarbonate and stannous fluoride, targeting not only oral malodour but also other prevalent oral conditions like gum disease and dental caries, is therefore recommended.

3.6 | Whitening/Stain Removal

Whitening key points

- No clinical meta-data is present on charcoal and blue covarine containing toothpastes; however, the high abrasiveness of charcoal toothpastes was reported in many in vitro studies
- Peroxide was found to be clinically effective in achieving stain removal; however, increased surface hardness and decreased microhardness of the teeth was also reported in in vitro studies
- Although no meta-analytical data are present, some clinical studies have reported a significant stain removing effect of sodium bicarbonate containing toothpastes. Its efficacy was found to be significantly increased by adding 1% hydrogen peroxide
- Though limited, clinical evidence supports the use of phosphates to achieve extrinsic stain removal with no side effects reported

The final colour of the teeth is given by the intrinsic colour of the teeth and by the presence of any extrinsic stain that may form on the tooth surface. While the intrinsic tooth colour is linked by light scattering and absorption of both enamel and dentine, the extrinsic colour is affected by the absorption of different materials on the acquired pellicle of the enamel, which ultimately cause tooth staining [74]. Many active ingredients have been proposed on the market to remove extrinsic staining; these active ingredients can be classified as either abrasives, chemical or optical agents, depending on their mechanism of action for stains removal. Though other modes of action have been tested (i.e., chemical and optical agents), it has been widely demonstrated that a certain level of abrasiveness is required for the toothpaste to effectively remove stains. It is important to note that any 'whitening toothpaste' can be effective in removing extrinsic tooth discolouration, but it has no effect in changing the intrinsic colour of the teeth. A systematic review comparing whitening toothpastes to regular toothpastes concluded that all tooth whitening toothpaste formulations reduced extrinsic tooth staining irrespective of presence of a chemical discolouration agent or not. The review did not report results according to active ingredient [75].

3.6.1 | Active Ingredients

3.6.1.1 | Charcoal

3.6.1.1.1 | Charcoal Summary. Due to the limited clinical evidence and the potential side effects, charcoal-containing toothpastes are not recommended for whitening/stain removal activity.

3.6.1.1.2 | Mode of Action. The activated charcoal binds to the deposits on the tooth surface, retaining plaque, bacteria and stains so that the stains and plaque can go away with the brushing. Plaque and stains are removed through the abrasive action of the charcoal toothpaste, which, however, is not able to change the intrinsic colour of the tooth [76, 77].

3.6.1.1.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.6.1.1.4 | Side Effects and Indications/Instructions for Use. Depending on the formulation and concentration, high abrasiveness and potential harm to the tooth hard tissues are observed [77].

3.6.1.2 | Oxidising Agents (Peroxide)

3.6.1.2.1 | Oxidising Agents Summary. Though promising, limited clinical evidence supports the use of oxidising agents of extrinsic stain removal. However, significant side effects arise with higher concentrations.

3.6.1.2.2 | Mode of Action. The main mode of action to remove stains includes the abrasiveness effect. Oxidising agents include carbamide peroxide or hydrogen peroxide or a combination of both.

3.6.1.2.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.6.1.2.4 | Side Effects and Indications/Instructions for Use. Increased surface roughness and decreased micro-hardness of the hard tissues depending on the formulation and concentration are observed [78].

3.6.1.3 | Blue Covarine

3.6.1.3.1 | Blue Covarine Summary. Though promising and without apparent significant side effects, limited clinical evidence supports the use of blue covarine for extrinsic stain removal.

3.6.1.3.2 | Mode of Action. Blue covarine is a pigment that, like enamel, scatters wavelengths in the blue range resulting in a yellow-to-blue tooth colour shift of the surface it has been applied to. Following brushing extracted teeth in vitro, blue covarine was found to be deposited onto the tooth surface and to indeed give a yellow-to-blue colour shift with an overall improvement in tooth whitening [74].

3.6.1.3.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.6.1.3.4 | Side Effects and Indications/Instructions for Use. No side effects reported so far; however, there is limited evidence with regards to its use.

3.6.1.4 | Sodium Bicarbonate

3.6.1.4.1 | Sodium Bicarbonate Summary. Limited clinical evidence supports the use of sodium bicarbonate containing toothpastes for extrinsic stain removal. However, its efficacy against periodontitis and dental caries and other dental conditions, as well as its limited side effects, may encourage its daily use.

3.6.1.4.2 | Mode of Action. Some studies have tested the whitening efficacy of baking soda toothpastes. Despite its relatively low abrasiveness, some studies demonstrated that its stain removal capacity is higher than other non-baking soda-containing toothpaste with higher abrasiveness [79]. Baking soda is classified as an abrasive, as such its mechanism for stain removal involves the removal of the stains forming on top of the acquired pellicle.

3.6.1.4.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.6.1.4.4 | Side Effects and Indications/Instructions for Use. No safety concerns were raised for baking soda-containing toothpastes. Its low abrasiveness compared to other whitening toothpastes makes it a desirable option to achieve stain removal while avoiding any harm to dental tissues caused by highly abrasive toothpastes.

3.6.1.5 | Polyphosphates

3.6.1.5.1 | Polyphosphates Summary. Limited clinical reviews support the use of phosphates compounds for extrinsic stain removal. However, its limited reported side effects may encourage its daily use.

3.6.1.5.2 | Mode of Action. Phosphate compounds include pyrophosphate, tripolyphosphate (STP) and HMP. The stain removal activity of phosphate compounds is based on their ability to displace anions, i.e., negatively charged macromolecules as well as the acquired enamel pellicle from tooth surfaces [80].

3.6.1.5.3 | Clinical Evidence of Efficacy. Evidence of clinical efficacy is presented in detail in Supplementary Evidence S2.

3.6.1.5.4 | Side Effects and Indications/Instructions for Use. No side effects of phosphates were reported.

3.6.1.5.5 | Overall Clinical Relevance. A large variety of different ingredients was proposed and tested to achieve an optimal stain removal effect. A certain amount of abrasiveness is needed for the toothpaste to effectively remove stains; however, excessive abrasiveness can harm the dental tissues. Ideally, ingredients with a cosmetic function (i.e., stain removal/whitening) as well as those with a therapeutic function (i.e., anti-plaque, anti-gingivitis, anti-caries, etc.) should be combined to meet cosmetic as well as therapeutic goals through domiciliary oral healthcare. As such among the many ingredients tested, sodium bicarbonate (either alone or in combination with peroxide) appears to be the most frequently tested ingredient having both a cosmetic and therapeutic function.

4 | Discussion

4.1 | Summary of Findings

Based on evidence included in this umbrella review, different active ingredients were found to be effective in targeting specific oral conditions. As for gum health, clinical meta-data demonstrated a significant anti-plaque and anti-gingivitis effect of toothpastes containing SnF₂, while overcoming staining as the most common side effect with its most recent formulation. Similarly, sodium bicarbonate (baking soda) containing toothpastes were demonstrated to have significant anti-plaque and anti-gingivitis effects, with little to minimal side effects. Triclosan-containing toothpastes were found to have significant anti-plaque and anti-gingivitis effects; however, the numerous health concerns suspended its use in many countries. Along the same lines, the potential side effects do not support the use of chlorhexidine as active ingredient for toothpastes. Finally, there is insufficient and uncertainty of evidence to currently make recommendations regarding the risk and benefits of natural active ingredients in toothpastes.

With regards to dental caries prevention and management, clinical meta-analytical evidence suggests that 1.5% arginine-fluoride toothpastes have a significant caries preventive effect. Different fluoride concentrations were recommended according to different age groups. In particular, the use of at least 1000 ppmF toothpastes is recommended to prevent caries in adults. In older adults, >1500 ppmF concentrations are suggested, and up to 5000 ppmF is suggested in individuals with high susceptibility to root caries. Moreover, clinical meta-analytical data showed that the addition of 10% xylitol to fluoridated toothpastes was effective in reducing caries by 13%. No significant difference

was found between marketed fluoridated and hydroxyapatite toothpastes. There was a lack of evidence of the efficacy of non-fluoridated toothpaste formulations for caries prevention.

Ingredients such as SnF₂, potassium, strontium, hydroxyapatite and CSPS (e.g., Novamin) all demonstrated benefits over and above sodium fluoride in the management of dentine hypersensitivity. SnF₂ showed the most beneficial effects over fluorides compared to other active ingredients, although one review also reported CSPS as having equally beneficial effects. However, evidence is lacking to suggest an optimal frequency or length of use required to observe benefits.

The evidence with regards to the efficacy of toothpastes in the management of tooth surface loss is still limited. The available clinical meta-analytical data showed that NaF- and SnF₂-containing toothpastes are effective in reducing enamel loss under erosive/abrasive challenges. However, there is evidence suggesting that different chemical and physical properties of the toothpaste might influence their effectiveness against tooth surface loss, e.g., abrasive system composition [81].

With regards to halitosis management, although limited, a small body of evidence suggests that sodium bicarbonate as well as zinc-containing toothpastes are effective in reducing VSCs. Clinical meta-analytical data of RCTs suggest that SnF₂ toothpastes are more effective than fluoridated toothpastes in reducing immediate and 'overnight breath' or 'morning breath'; hence, zinc- and SnF₂-containing toothpastes might be advised for the management of oral halitosis.

Peroxide is among the most tested active ingredients in toothpastes against stain removal. In fact, it was found to be clinically effective in achieving stain removal; however, increased surface hardness and decreased microhardness of the teeth was also reported. Moreover, although no meta-analytical data are present, some clinical studies have reported a significant stain removing effect of sodium bicarbonate containing toothpastes. Its efficacy was found to be significantly increased by adding 1% hydrogen peroxide. Finally, no clinical meta-data is present on charcoal containing toothpastes; however, their high abrasiveness was reported in many in vitro studies as side effect.

On a general note, very little evidence was reported on side effects, probably because products showing a large number of side effects do (and should) not get to market. Future studies should focus more on patients' experience and perception of toothpaste use as a parameter.

4.2 | Application to Oral Conditions

The main goal of this umbrella review was to shed light on the wide variety of active ingredients available for toothpastes and their efficacy in preventing and managing oral conditions. On these premises, it is essential to spread knowledge and awareness about the diversity of toothpaste formulations and their indications for use. As such, oral healthcare providers should prescribe specific toothpastes containing those active ingredients effectively targeting the patient's oral conditions/diseases. Based on the literature appraisal performed in this umbrella review, a figure is

created with guidance for clinicians to follow when prescribing specific toothpastes on a case-by-case basis (Figure 2). For example, if a patient is affected by both periodontitis and dentine hypersensitivity, a toothpaste containing SnF₂ could be recommended to manage both conditions. Along the same lines, if a patient complains about both bad breath and tooth stains, then a toothpaste containing sodium bicarbonate could be recommended. Please see Figure 2 for guidance on all the combinations of oral conditions and active ingredients reviewed.

4.3 | Patient-Centred Care

Toothpaste is an integral part of everybody's domiciliary oral hygiene habits, together with toothbrushes and interdental cleaning devices. The importance of domiciliary plaque control has been widely recognised by decades of literature in order to prevent and manage oral as well as systemic diseases and conditions which requires active patient engagement [82]. Based

on health behaviour change principles, individually tailored oral health regimes and product recommendations should be collaboratively chosen, engaging the patient, to meet individual patient needs and preferences [21].

Oral diseases have been associated with many systemic conditions affecting general health and present with many common risk factors, most often lifestyle-related behaviours. As such, lifestyle behaviour change interventions should be implemented to tackle chronic conditions using a multidisciplinary approach. Given the systemic repercussions of oral conditions on systemic health, leaving oral conditions untreated may reduce/complicate the management of other comorbidities such as diabetes and hypertension, and, on the other hand, treating oral conditions through oral health promotion may enhance the efficacy of the systemic treatments for the conditions affecting general health [82, 83]. An epidemiological analysis of a Korean National Health Screening database demonstrated that brushing one additional time per day was associated with 9% less risk of cardiovascular events [84].

Ingredient/Condition	Gum Health	Caries	Dentin Hypersensitivity	Tooth Surface Loss	Oral Malodour	Whitening
ACP/CPP-ACP	---		---	---	---	---
Arginine	---			---	---	---
Blue Covarine	---	---	---	---	---	
Charcoal	---	---	---	---	---	
Chlorhexidine		---	---	---	---	---
CPC		---	---	---	---	---
Fluoride (e.g. NaF, AmF)	---		---		---	---
Hydroxyapatite	---			---	---	---
Natural active ingredients		---	---	---	---	---
CSPS (e.g. Novamin)	---	---		---	---	---
Oxidising agents (peroxide)	---	---	---	---	---	
Phosphates	---	---	---	---	---	
Potassium Nitrate	---	---		---	---	---
SLS	---	---	---	---		---
Sodium Bicarbonate		---	---	---		
Stannous Fluoride						---
Strontium Chloride	---	---		---	---	---
Xylitol	---		---	---	---	---
Zinc ions	---	---	---	---		---

Legend

---	Inconclusive or limited clinical evidence	Clinical evidence in support	In-vitro studies only	Significant side effects reported
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FIGURE 2 | Summary of ingredients and applicability to oral conditions.

Furthermore, medical doctors (and general practitioners in particular) should integrate oral health promotion, in terms of improvement of domiciliary oral hygiene habits, to the promotion of other healthy lifestyles, such as healthy nutrition, physical exercise, proper sleep duration, made as part of the treatment of other systemic diseases. Along the same lines, enhancements of domiciliary oral hygiene habits in addition to lifestyle modifications in the dental setting are supported by the most recent guidelines for the treatment of periodontitis and dental caries among others [85, 86]. This joint approach between oral health-care providers and medical practitioners can be pivotal to successfully achieve healthier lifestyles, which include an optimal domiciliary oral hygiene routine as one of its pillars.

5 | Conclusions

Based on data retrieved for this umbrella review, toothpaste formulations were confirmed to be diverse with some active ingredients found to be effective for the treatment and management of the targeted oral condition. In particular, fluoride formulations should not all be considered equally efficacious in treatment of conditions that affect both the hard and soft tissues. As such, oral healthcare providers should consider recommendation of toothpastes containing appropriate active ingredients to effectively target oral conditions/diseases according to specific patient needs.

6 | Clinical Relevance

6.1 | Scientific Rationale for the Study

Toothpastes have increased in complexity over the years creating diversity in efficacy specific to individual patient needs. The rationale for this study was to provide an updated overview of evidence pertaining to toothpaste ingredient efficacy and their application to oral conditions.

6.2 | Principal Findings

Scientific evidence supports that a variety of toothpaste ingredients are efficacious in treating specific oral conditions.

6.3 | Practical Implications

Clinicians should individualised toothpaste recommendations according to patient needs and appropriate active ingredient.

Author Contributions

J.S. and C.M. both contributed to planning the review, electronic search and screening, review of evidence, synthesis of information and writing of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.