



## Review article

## Recent advances in the use of inorganic nanomaterials as anti caries agents



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## ARTICLE INFO

## Keywords:

Anti-caries

Biofilm

Inorganic

Metal

Remineralization

## ABSTRACT

Caries is the most prevalent and widespread chronic oral disease. Traditional caries filling materials, due to their lack of anti-caries capabilities, can readily develop secondary caries. Nanomaterials proposed as an effective approach for caries treatment can inhibit biofilm formation. It also can not only reduce demineralization but also promote remineralization. In recent years, nanotechnology in anti-caries materials, particularly nano-adhesive and nano-composite resin, has advanced rapidly. Because inorganic nanoparticles (NPs) interfere with bacterial metabolism and inhibit biofilm development, inorganic NPs have emerged as a new trend in dental applications. Metal and metal oxide NPs by releasing metal ions, oxidative stress induction, and non-oxidative mechanisms showed significant antimicrobial activity. For applying metal and metal oxide NPs as anti caries agents, silver, zinc, titanium, copper, and calcium ions have been shown significant attention. Moreover, fluoride functionalized inorganic NPs were also employed to improve their efficacy of them. The fluoride-functionalized NPs can promote remineralization, and inhibit demineralization by enhancing apatite formation. In this review, we have provided an overview and recent advances in the use of inorganic NPs as anti caries agents. Furthermore, their antimicrobial, remineralizing, and mechanical impacts on dental materials were discussed.

## 1. Introduction

Dental caries, often known as tooth decay, is a common chronic disease. Dental caries is the most frequent among oral disorders, and it is one of the substantial problems in the oral cavity [1]. Caries affects people at all stages of their lives. According to the World Health Organization (WHO), dental caries is the fourth most expensive illness to treat, with a substantial worldwide disease burden [2]. Furthermore, based on WHO reports, caries affects between 60 and 90% of children and almost 100% of adults globally [3]. Factors associated with caries are cariogenic microorganisms, substrate, host/teeth, and time. This multifactorial condition is caused by an imbalance between mineral loss (demineralization) and mineral gain (remineralization). Dental caries is caused by the dissolving or demineralization of minerals, which destroys tooth structure. The last stage of continuous minerals loss often known as dental caries is associated with the destruction of tooth structure [4].

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<https://doi.org/10.1016/j.heliyon.2023.e15326>

Received 10 November 2022; Received in revised form 10 March 2023; Accepted 3 April 2023

Available online 8 April 2023

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Enamel can be dissolved in acids, even though it is the hardest tissue in humans. In fact, dental caries is induced by an acid-forming biofilm [5]. *Streptococcus mutans* and *Lactobacillus* are the main pathogens that are responsible for caries [6–8]. Consecutive net mineral loss is caused by the acidic attack of cariogenic bacteria present in dental plaque biofilm formation over the tooth [9].

The shift toward a pathogenic biofilm community is facilitated by an abundance of fermentable carbohydrates [10]. Microorganisms become physically shielded from quick buffering by saliva and embed themselves in an extracellular polymeric substances (EPS)-rich biofilm matrix as a result of repeated exposure to fermentable carbohydrates [11]. Localized regions of low pH within biofilms formed on tooth surfaces continue to select for aciduric microorganisms [12]. The homeostatic mineral balance is disrupted, leading to enamel demineralization, the biofilm is not cleared and frequent sugar consumption continues [11].

Hydroxyapatite ( $\text{Ca}_5(\text{PO}_4)_3(\text{OH})$ ), which is the key mineral component of the hard dental tissues (enamel and dentin) is the main target for the bacterial acids [13]. Consequently, the acidic medium causes loss or gain of calcium ( $\text{Ca}^{2+}$ ) and phosphate ( $\text{PO}_4^{3-}$ ) from the hard dental tissues [14]. Oral fluids such as saliva and biofilm fluid have supersaturated amounts of the mineral composition of enamel,  $\text{Ca}^{2+}$  and  $\text{PO}_4^{3-}$  [15]. As a result, under physiological conditions, these ions are constantly deposited on the enamel surface [16]. The pH decreases in the presence of bacterial acids, as a result, biofilm fluid becomes undersaturated concerning the mineral composition of enamel [17,18]. When the pH is below 6.5 and 5.5 for dentin and enamel, respectively, demineralization occurs due to the chemical dissolution of Ca and  $\text{PO}_4$  [19].

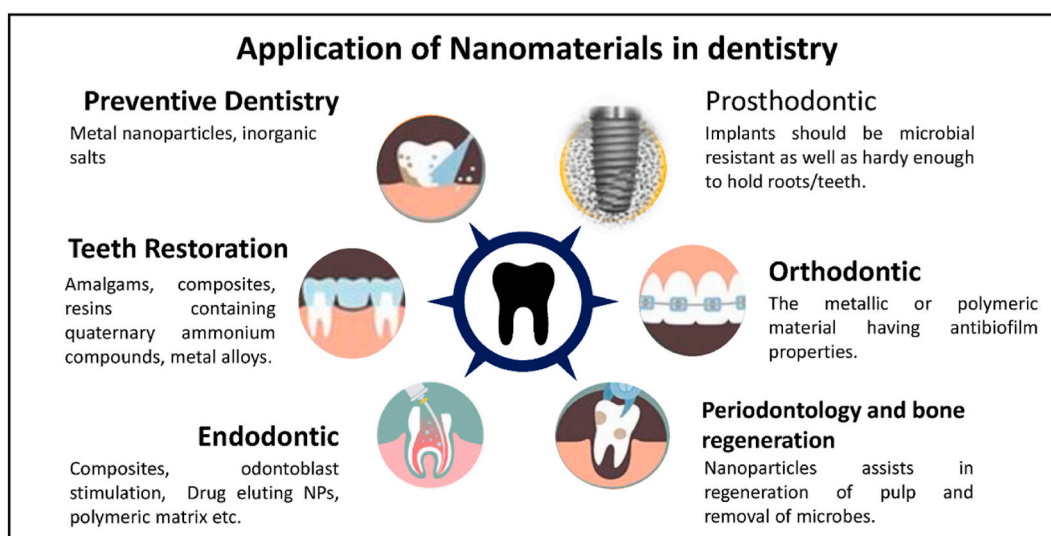
Because of superior aesthetic qualities and more conservative preparation processes, attractive tooth-colored restorative materials are preferred in the context of advanced demineralization associated with cavity development. Direct resin composite restoratives, enamel-dentin adhesives, and dental primers (adhesion promoters) are examples of clinical restorative polymer materials [20]. These clinical restorative polymer materials have similar primary chemical compositions. For more than 40 years, these materials have been employed as direct restorative materials to replace missing biological tissue. There are some reports that show that cariogenic biofilms growth has been facilitated by resin-based restorative materials [21,22]. By the way, dental caries without treatment can progress and result in pain and infection until tooth loss, because it is not self-limiting [23], while, it is preventable. Clinical investigations, however, have shown that the lack of anti-caries capabilities in dental filling and bonding materials may result in a high prevalence of secondary caries. As a result, in the realm of caries prevention and treatment, the development of novel anti-caries materials is a popular topic.

In the last few decades, preventive methods against dental caries have been significantly improved. In the development of anti-caries agents applying nanoparticles (NPs) has received great attention. Anti-caries nanomaterials have become a breakthrough in caries research, given the existing concerns and challenges in caries prevention and treatment as well as the unique advantages of nanomaterials.

Formal definitions of NPs are any particulate materials with at least one dimension in the 1–100 nm range [24]. There are various shapes of NPs such as spheres, rods, wires, sheets, cages, etc [25–28].

Compared to bulk materials their nano counterparts show unique properties. Nanomaterials in addition to having a high surface-to-volume ratio, and high surface energy, show unique mechanical, thermal, electrical, magnetic, and optical behaviors, etc. [29–31]. The unique features of NPs introduce them to a wide range of applications such as electronics, biology, energy, chemistry, and medicine [31,32]. In addition, further surface functionalization of NPs with desired functional groups make them suitable for a particular application [33,34].

With increased universal interest in nanotechnologies, inorganic materials have gained more and more interest. Antimicrobial, antiviral, and antifungal properties of NPs have been discovered comprehensively [35–37].



**Fig. 1.** Application of nanomaterials in dentistry. Reproduced with permission from Ref. [38], with the permission of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>). Copyright 2022, MDPI.

The literature reviews disclose that preventive dentistry, restorative dentistry, endodontics, implantology, prosthetic dentistry, oral cancers, and periodontology all benefit from NPs (Fig. 1) [38–47].

There are also some commercial dental nanomaterials available on the market (Fig. 2) [48].

Nanotechnology has shown considerable promise in the development of anti-caries materials in recent years [49–51]. According to current research, inorganic NPs can reduce biofilm production and remineralize carious lesions, therefore inhibiting tooth caries [39, 52]. Biomineralization stimulated by metallic NPs via facilitating remineralization of demineralized (cariou) tooth tissues. Furthermore, due to their ion balance in oral fluid, metallic NPs can overcome problems in a variety of oral disorders [51].

In order to prevent caries development and strengthen the mechanical properties of the materials, the metal and metal oxide NPs have been incorporated into dental materials. On top of that scalable production of inorganic NPs is easy. In addition, inorganic nanomaterials can be used as direct antibacterial agents, then inhibit dental caries, because it is one of the most common bacteria-related oral diseases [53]. The aim of this study is to provide an overview of the use of inorganic NPs in caries prevention. The development of inorganic NPs in the prevention of dental caries is discussed in this review.

## 2. Inorganic nanomaterials as anti caries agent

### 2.1. Silver nanoparticle (Ag NPs)

Silver shows a wide range of antibacterial capabilities, not only because of the ability to inactivate enzymes but also due to inhibiting replication of DNA and protein synthesis in bacteria [54]. Furthermore, silver ions can inhibit respiratory enzymes, resulting in cell lysis. Also, the cell wall and cytoplasmic membrane of bacteria can be attacked by Ag NPs, causing the denaturation of the cell wall and cytoplasmic membrane [55]. Although the specific mechanism of silver nanoparticles' antibacterial activity has not been fully elucidated, many antibacterial actions of silver nanostructures have been postulated.

Ag NPs are also gaining popularity due to their exceptional antibacterial action and low cost. Furthermore, Ag NPs have been used for caries prevention [56–58].

Several studies have been conducted to evaluate various formulations of Ag NPs for their ability to inhibit cariogenic bacteria. Cariogenic bacteria and their biofilms can be inhibited by Ag NPs [59]. However, it is concentration-dependent and treating time-dependent [60]. It also has been reported that green synthesized nanosilver particles show antimicrobial and antibiofilm activity against *S. mutans* and *L. acidophilus* microorganisms [61]. Furthermore, Ag NPs improve the microhardness of dental tissues while providing favorable antimicrobial qualities [62].

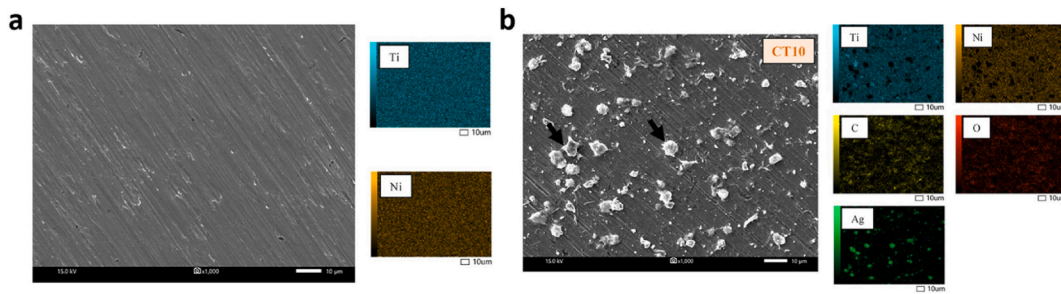
Pipattanachet et al. reported that nickel-titanium (NiTi) alloy coated with Graphene oxide/silver NPs (GO/AgNPs) have an antibacterial effect on the *S. mutans* biofilm (Fig. 3a and b) [63].

*Streptococcus mutans* as an oral pathogen that causes dental caries was attracted by AgNPs [64]. The NPs blocked the genes involved in *S. mutans* biofilm development over host teeth and gums (gtfB, gtfC, gtfD) as well as virulent protective factors (comDE, brpA, and smu 360) and survival promoter genes (gyrA and spaP, gbpB) as can be seen in Fig. 4a–h.

Jiménez-Ramírez et al. study shows the considerable antibacterial activity of Ag NPs in dental biofilms from subjects with and



Fig. 2. Dental nanomaterials available on the market. Reproduced with permission from Ref. [48], with the permission of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>). Copyright 2021, MDPI.



**Fig. 3.** a) SEM images and EDS mapping of the uncoated NiTi alloy sample. b) SEM images and EDS mapping of the 10 min GO/AgNPs coated NiTi alloy sample (CT10). Black arrows indicate the GO assembly with the Ag NPs. Reproduced with permission from Ref. [63], with the permission of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>). Copyright 2021, Springer Nature.

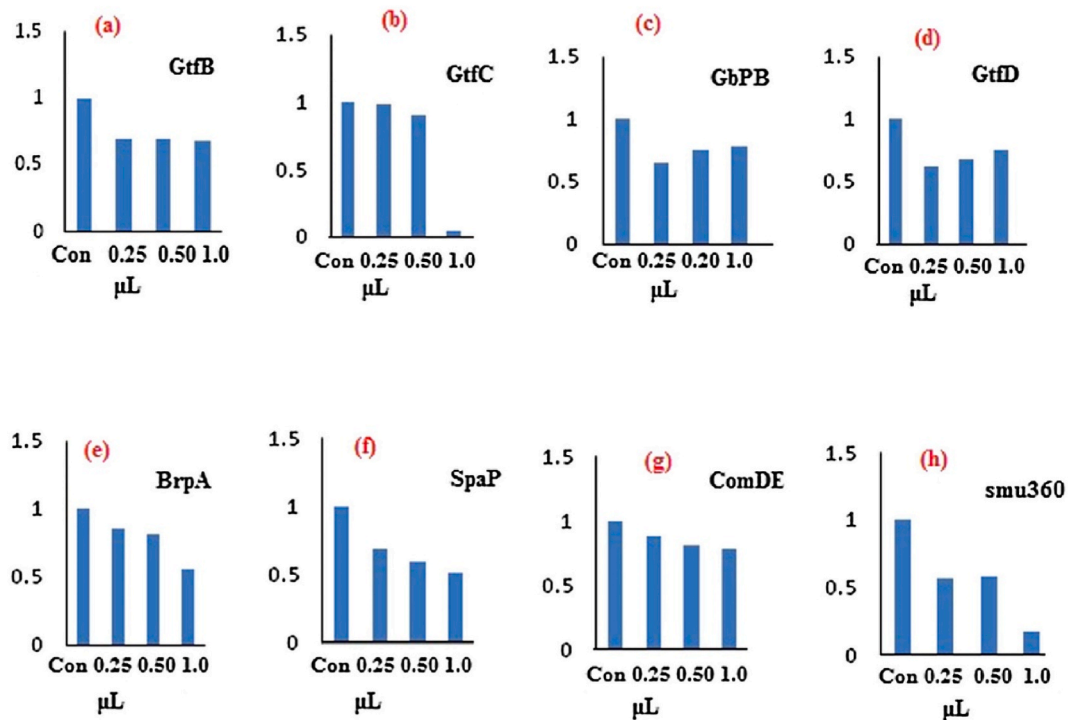
without dental caries [65].

The incorporation of Ag NPs into composite resins shows a considerable biofilm inhibition rate [66]. Compared to the control group a significant decrease in the colonies of *S. mutans* (99.76%), *S. sanguis* (99.93%), and *L. acidophilus* (99.61%) at 5% concentrations of Ag NPs, was seen.

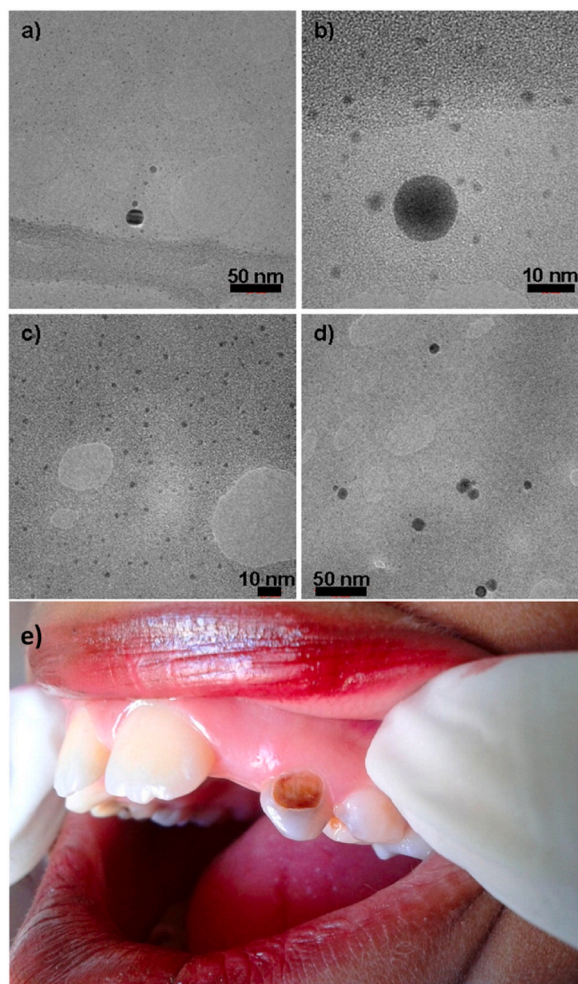
Sodium fluoride has been used as an anti-caries agent since 1940 [67]. Remineralizing artificial dentine caries using a fluoridated polyethylene glycol (PEG) coated Ag NPs is reported in 2020 [68]. The result shows that this NaF containing and PEG coated Ag NPs solution inhibit collagen degradation. Silver fluoride (AgF) NPs with long-term stability as an anti caries agent were synthesized by Favaro et al. [69]. AgF NPs in addition to have antimicrobial potential and remineralizing capacity, do not stain the enamel.

The antibacterial effect of Ag NPs against anaerobic bacteria shows size-dependent efficacy. The Ag NPs with a size of 5 nm show the highest antibacterial activity, compared to Ag NPs with a size of 15 nm and 55 nm [70]. In a clinical trial study, Nano Silver Fluoride (NSF) was used as an anti caries agent to arrest dental caries in children [71]. The NSF’s transmission electron microscopy (TEM) image is shown in Fig. 5a–d. Fig. 5e shows the teeth treated with NSF after 12 months. In the NSF group 81%, 72.7%, and 66.7% of the teeth exhibited arrested caries after seven days, five months, and 12 months, respectively. The NSF formulation shows efficient inhibition power against dentine caries without staining teeth.

There are also some studies that used Ag NPs along with others to improve the efficacy. Commercial composite resin was loaded



**Fig. 4.** a–h) Inhibition of virulence genes in *S. mutans* exposed to different concentrations of AgNPs. Reproduced with permission from Ref. [64], with the permission of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>). Copyright 2021, Elsevier.



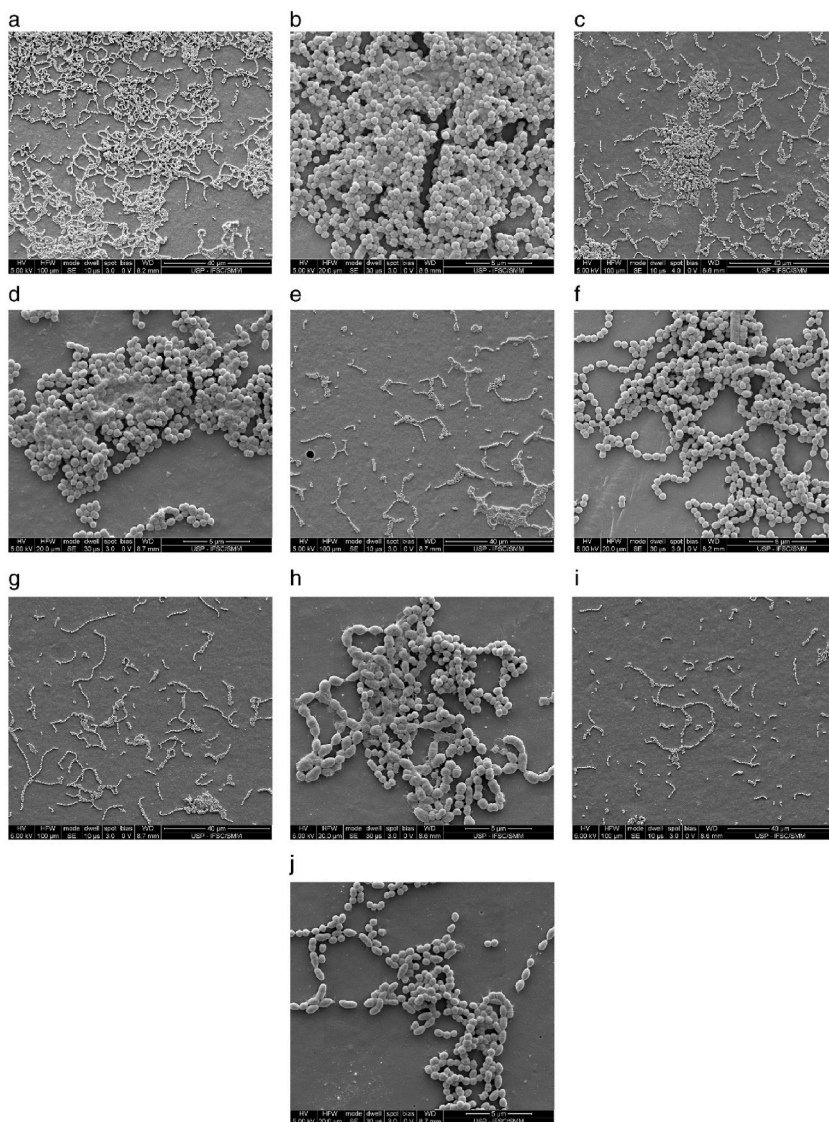
**Fig. 5.** a–d) TEM images of the NFS, and e) Photograph of tooth treated with NSF after 12 months. Reproduced with permission from Ref. [71], with the permission of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>). Copyright 2014, Elsevier.

with Ag decorated ZnO nanoparticles, and inhibition of *Streptococcus mutans* biofilm was evaluated [72]. Ag doped ZnO NPs were synthesized with two different methods: i) polymeric precursor's synthesis (ZPS) and ii) coprecipitation synthesis (ZCS). SEM images of *S. mutans* biofilms created on the surface of the original and modified composite resin containing 1 and 2% of ZCS and ZPS NPs are shown in Fig. 6a–j. In comparison to the unmodified composite specimens, there was a reduction in the number of adherent cells on the specimens containing NPs. Findings prove the potential of Ag and ZnO incorporated resin as an antibacterial dental restorative resin.

In another study, a conventional orthodontic adhesive incorporated with silver/hydroxyapatite NPs was formulated and their antibacterial properties were investigated after 3, 15, and 30 days [73]. Growth inhibition zones were observed for *Streptococcus mutans*, *Lactobacillus acidophilus*, and *Streptococcus sanguinis* bacteria in composite discs containing 5 and 10% silver/hydroxyapatite NPs. Furthermore, compared to the control group other groups reduced bacteria count as a result of the biofilm inhibition test. However, the antimicrobial activity varied greatly depending on the bacterial species and nanoparticle quantity.

Because calcium and phosphate ions are necessary for remineralization, the materials with calcium and phosphate ion-releasing capability are promising for remineralization [74]. Cheng et al. incorporated antibacterial agents, quaternary ammonium dimethacrylate (QADM), NPs of silver (NAg), and NPs of amorphous calcium phosphate (NACP), into calcium and phosphate ion-releasing resin composites [75]. Compared to the two commercial composites, the novel nanocomposites significantly reduced CFU counts, metabolic activity, and lactic acid generation in *S. mutans* biofilms. Combining QADM and NAg shows a greater antibacterial effect than either agent alone.

The coupling of Ag/ZnO nanocomposites with a light-emitting diode (LED) curing light, which is a clinically used instrument in dentistry, resulted in an effective synergistic antibacterial approach (Fig. 7a) [76]. Over a short irradiation duration (less than 5 min), the as designed integration showed a considerably improved anti-bacterial effect on *Streptococcus mutans* (*S. mutans*) in both planktonic and biofilm stages. Ag/ZnO nanocomposites under LED irradiation generate  $\cdot\text{OH}$  and  $\cdot\text{O}_2^-$ , resulting in improved antibacterial activity.



**Fig. 6.** SEM images of *S. mutans* mature biofilm adhered to a–b) unmodified, modified composite resin specimens with c–d) 1% of ZCS NPs, e–f) 2% of ZCS NPs, g–h) 1% of ZPS NPs and i–j) 2% of ZPS NPs. Reproduced with permission from Ref. [72]. Copyright 2019, with permission from Elsevier.

Furthermore, the biofilm-related gene expression was down-regulated and exopolysaccharide production was inhibited in this promising approach. Also, this combination has the potential to remove *S. mutans* biofilm by killing the bacteria trapped inside it (Fig. 7b).

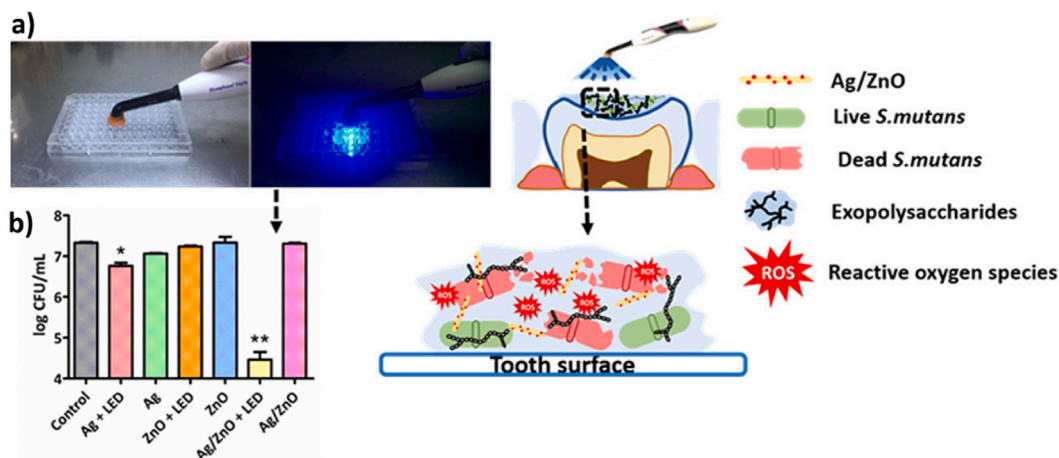
## 2.2. Zinc nanoparticles

*S. mutans* can be also inhibited by zinc NPs (Zn NPs) because they can reduce plaque formation [77].

The use of Zn NPs for effective dentin remineralization and tubular occlusion has been proposed. Zn NPs not only do not alter dentin bond strength but also inhibit matrix metalloproteinases (MMP) [78].

Compared to Zn NPs, Zinc oxide NPs (ZnO NPs) are more biocompatible [79]. In addition, ZnO NPs show better antimicrobial activity [80,81]. Garcia et al. evaluated the cytotoxicity and antibacterial potential of ZnO quantum dots (ZnOQDs) incorporated into adhesive resin against *S. mutans* and pulp fibroblasts, respectively [82]. Higher values of biofilm formation were seen in the control group, while in the ZnOQDs group, biofilm formation was reduced (more than 50%). However, the cytotoxicity study shows no difference in pulp fibroblasts viability between the adhesives [82].

Recently, nickel-titanium (NiTi) wires modified with ZnO NPs is prepared as an antimicrobial agent [83]. They investigated the effect of ZnO NPs with different morphology on antimicrobial activity. ZnO NPs with different morphology were achieved via five



**Fig. 7.** a) Schematic illustration of antibacterial activity of Ag/ZnO assisted with LED curing light. b) antibacterial activity of 1 mg/mL Ag/ZnO or ZnO and 40 µg/mL Ag NPs against planktonic *S. mutans* with or without 5 min LED illumination. Reproduced with permission from Ref. [76]. Copyright 2019, with permission from ACS.

coating methods, including chemical vapor deposition (CVD), chemical precipitation method, polymer composite coating, sol-gel synthesis, and electrospinning process. The result shows that the antibacterial activity of ZnO NPs was significantly increased with increasing the specific surface area of NPs prepared via the CVD coating method (Fig. 8).

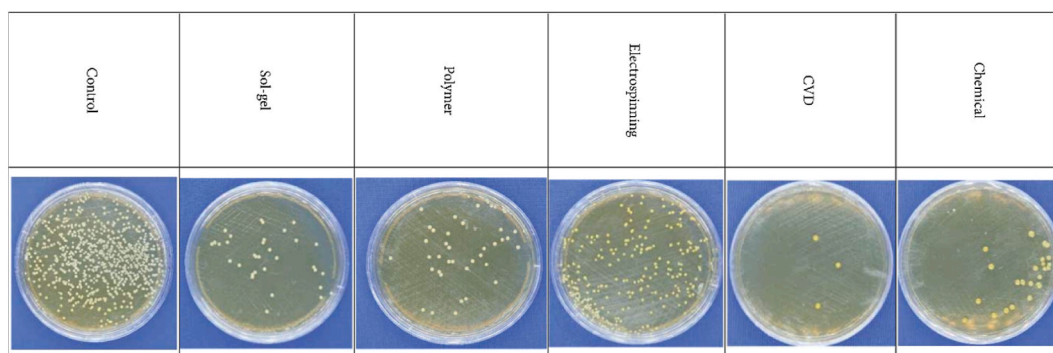
Malekhoseini et al. developed resin-modified glass ionomer (RMGI) containing ZnO NPs to improve its physical properties and antibacterial potential [84]. RMGI containing wt.% ZnO NPs showed the highest antimicrobial efficacy in the disc diffusion method. Another study shows that the chemical and mechanical properties were affected by adding ZnO NPs into composite resin [85].

Also, the effect of ZnO NPs on antibacterial and mechanical properties of adhesive of orthodontic brackets was evaluated [86]. However, compared to the control and XT<sup>TM</sup> groups the addition of ZnO NPs into the adhesive did not show any significant difference in terms of shear bond strength. But, when it came to antibacterial capabilities, compared to the control group ZnO NPs containing adhesives show better ability.

ZnO NPs also show effective anti-plaque agents, in addition to applying a potent antimicrobial against cariogenic bacteria. Barma et al. reported the anti-biofilm, acid-inhibiting, and anti-oxidant ability of ZnO NPs [87]. ZnO NPs with 0.1 mg/µL concentration showed a 24 mm zone of inhibition. At the same concentration, the ZnO NPs suppressed 90% of *S. mutans* biofilms. Moreover, ZnO NPs not only reduced 24 h acid production but also show the antioxidant ability. Also, their biocompatibility study reveals that the ZnO NPs at 0.1 mg/µL concentration do not show cytotoxicity on the HEK-293T cell line [87]. But, a biocompatibility study on the Hep G2 cell line shows that at the same concentration, the ZnO NPs caused very low cytotoxicity.

A study reported that the addition of 1% and 5% ZnO and chitosan NPs had no impact on the shear bond strength of the composite [88].

Pourhajibagher et al. developed zeolite-ZnO NPs (Zeo/ZnO NPs) for antimicrobial photodynamic therapy (PDT) [89]. The Zeo/ZnO NPs anti-biofilm and anti-metabolic activities were evaluated against pre-formed polymicrobial biofilms on the orthodontic brackets as PDT agent. After determining the hemolytic effect (Fig. 9a) and assessing cytotoxicity on human gum fibroblast cell line (HuGu) (Fig. 9b), the generation of intracellular reactive oxygen species (ROS) (Fig. 9c) was investigated. In Zeo/ZnO NPs-treated cells, no



**Fig. 8.** The effect of ZnO NPs with different morphology on antimicrobial activity (number of colonies). Reproduced with permission from Ref. [83], with the permission of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>). Copyright 2021, Hindawi.

substantial cytotoxicity or erythrocyte hemolysis was found. The Zeo/ZnONPs were photoactivated, under irradiation, resulting in ROS production, and reducing the cell viability and metabolic activity of polymicrobial biofilms dose-dependently.

Zn which is commonly used in dental materials and in mouth rinses at high concentrations acts as an inhibitor of MMPs [90,91]. Collagen is important for biomineralization, zinc improves hard-tissue mineralization by protecting collagen against MMPs [92,93]. Zn–CuO nanocomposites show lower embryotoxic than both ZnO and CuO, as a result, they may be considered safe antibacterial metal nanocomposites [94].

Adhesives containing ZnO and CuO NPs show antibacterial and anti-MMP ability without compromising bond strength [95]. In this line, Matsuda et al. introduced fluoride-containing ZnO and CuO nanocomposites as a strong antimicrobial agent [96]. More recently, Altankhishig et al. investigated the impact of fluoride-containing ZnO and CuO nanocomposites on the adhesive strength of bonding restorations [92]. In addition, antibacterial and MMP inhibitors of them were assessed. The self-etch adhesive system containing ZnO and CuO NPs granted an MMP inhibitory effect, while do not show negative influence on the mechanical properties. Also, it shows antibacterial and caries-prevention abilities.

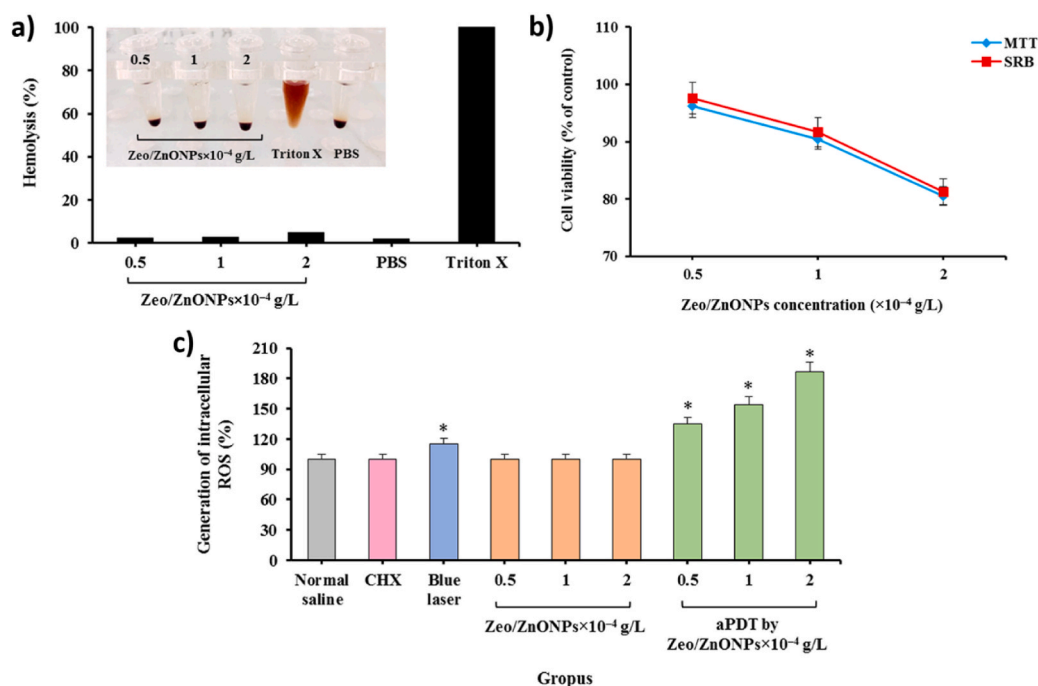
Zhang et al. harnessed biofilm microenvironment as a stimulus to chemodynamic treatment (CDT) as a suitable therapeutic approach [97]. They designed a nanocomposite containing Rose Bengal (RB) loaded copper-doped zinc peroxide NPs (ZnO<sub>2</sub>-Cu NPs), ZnO<sub>2</sub>-Cu@RB NPs, for CDT (Fig. 10). This in situ enhanced CDT can inhibit *S. mutans* efficiently within 10 min (greater than 8.0 log<sub>10</sub> CFU mL<sup>-1</sup>). Acid production of *S. mutans*, was weakened via ZnO<sub>2</sub>-Cu@RB NPs, as a result, it can inhibit extracellular polysaccharides formation.

### 2.3. Nano hydroxyapatite

The major inorganic component of teeth is hydroxyapatite, (Ca<sub>5</sub>(PO<sub>4</sub>)<sub>3</sub>(OH)). So, the synthetic nano particulate hydroxyapatite has physical and chemical properties that are similar to natural tooth hydroxyapatite. Because the hydroxyapatite was made up of Ca<sup>2+</sup> and PO<sub>4</sub><sup>3-</sup> can release Ca<sup>2+</sup> and PO<sub>4</sub><sup>3-</sup> to promote remineralization. To prevent cavities, a calcium and phosphate balance is essential [98,99].

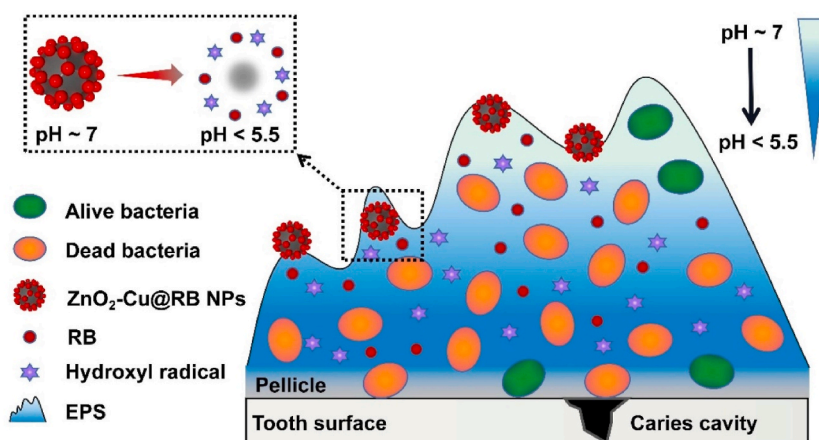
Due to the insolubility of calcium phosphates, the clinical application of calcium and phosphate ions has not been successful. However, on one hand, these ions can only be used at very low concentrations. On other hand, they not only are incompatible well with dental plaque but also do not adhere to the tooth surface. As a result, in the remineralization process, the bioavailability of calcium and phosphate ions is always limited. In this line, the preparation of new materials with high stress-bearing and caries-preventing properties via harnessing of advantages of nanotechnology has gained more and more attention [100].

Amorphous calcium phosphate incorporated into adhesive was used for remineralizing demineralized dentin in an *S. mutans* biofilm environment [101].



**Fig. 9.** a) Hemolytic effect of Zeo/ZnONPs. b) Cytotoxic effects of Zeo/ZnONPs on cell viability of HuGu cells. c) Intracellular ROS production in polymicrobial suspension following different treatments. Reproduced with permission from Ref. [89], with the permission of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>). Copyright 2021, BMC.





**Fig. 10.** Schematic illustration of the effects of  $\text{ZnO}_2\text{-Cu@RB}$  NPs on *S. mutans* and its oral biofilm. Reproduced with permission from Ref. [97]. Copyright 2022, with permission from Elsevier.

Nano-hydroxyapatite gel shows better remineralization ability than nano-hydroxyapatite toothpaste and fluoride varnish. However, compared to fluoride varnish both forms of nano-hydroxyapatite, toothpaste and gel form, show great remineralization power [102].

Adding Dimethylaminohexadecyl methacrylate (DMAHDM) and amorphous calcium phosphate NPs into a composite does not affect the mechanical properties [103]. As shown in Fig. 11a and b at cariogenic low pH the system released a high amount of Ca and P. In the composition of 3% DMAHDM + 30% amorphous calcium phosphate NPs, the composite not only shows high antibacterial effects but also reduced Biofilm lactic acid and polysaccharides [103].

After water-aging for 12 months, the composite containing microcapsules (made of poly (urea-formaldehyde) (PUF) shells containing triethylene glycol dimethacrylate (TEGDMA) and N,N-dihydroxyethyl-p-toluidine (DHEPT)) + DMAHDM + amorphous calcium phosphate NPs group exhibited no decrease in dentin bond strength, which was much greater than the other groups without DMAHDM [104].

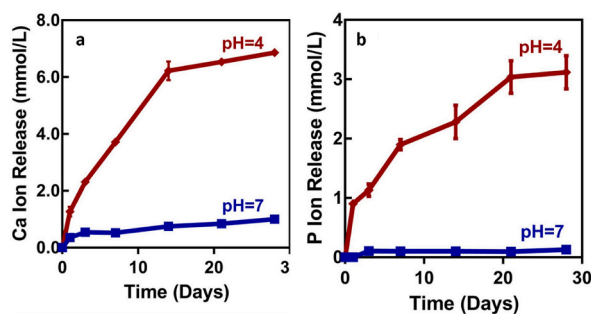
For caries prevention quaternary ammonium methacrylate (DMAHDM) and amorphous calcium phosphate NPs incorporated into resin sealants protected the demineralization of the enamel [105]. The designed system show pH-responsive calcium and phosphate-ion releasing (Fig. 12).

The surface integrity was restored by binding to the damaged enamel surface followed by filling the porous surface irregularities [106]. It has been reported that in repairing damaged enamel the use of nano hydroxyapatite with a size of 20 nm is effective [107]. Fluorides show just surface remineralization ability, while hydroxyapatite can penetrate into the deeper layers of the lesion [108,109].

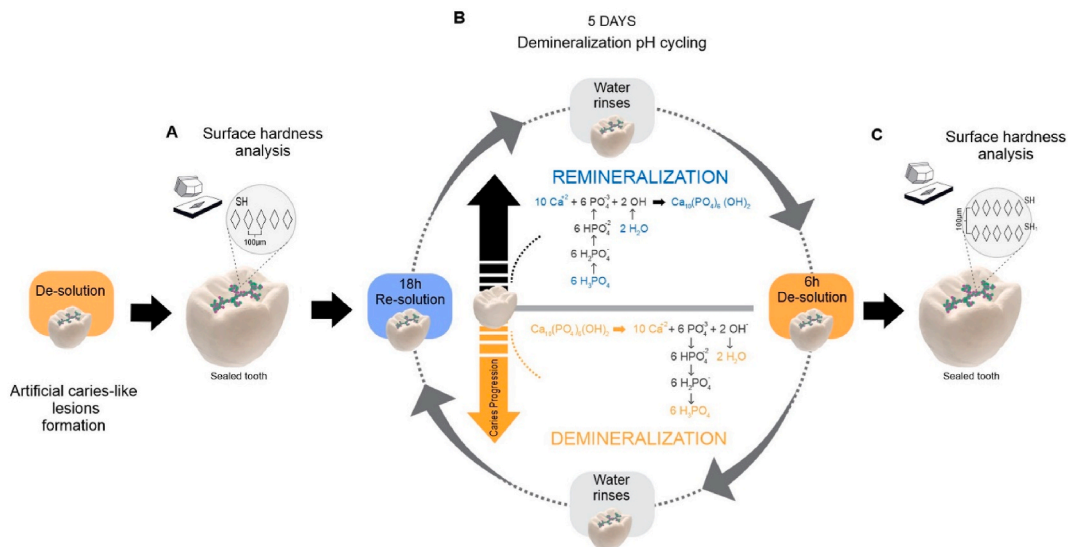
In another study, initial caries was remineralized effectively by toothpaste containing 5% nano-hydroxyapatite, at the same time healthy enamel demineralization was inhibited by it [110]. It also found that compared to a placebo lotion the use of dental lotion containing 5% nano-hydroxyapatite after tooth brushing caused better remineralization.

Mathew et al. developed remineralizing paste containing strontium doped nano hydroxyapatite (Sr-nHAp) with non-collagenous protein (NCP) analogue, chitosan [111]. In terms of antibacterial activity, the 20% Sr-nHAp formulation had better efficacy than the 10% Sr-nHAp paste. As a result, increasing the concentration of strontium boosted its effectiveness. As can be seen in Fig. 13a and b adding chitosan to the formulations showed greater antimicrobial efficacy.

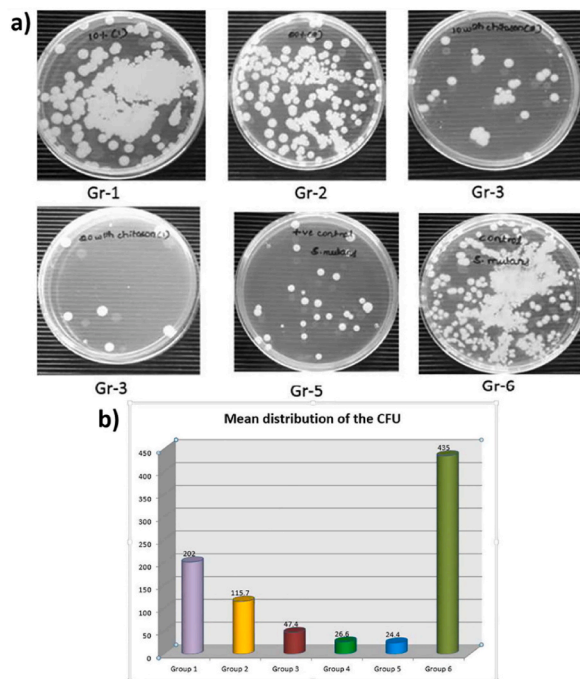
Yuan et al. developed salivary statherin protein-inspired poly(amidoamine) dendrimer (SN15-PAMAM) and amorphous calcium phosphate NPs incorporated into the adhesive for enamel remineralization (Fig. 14) [112]. It was found that under acid challenge the



**Fig. 11.** a) Calcium (Ca) and b) phosphate (P) ion releases from the 3% DMAHDM + 30% amorphous calcium phosphate NPs composite immersed in solutions of pH 4 and 7. Reproduced with permission from Ref. [103]. Copyright 2020, with permission from Elsevier.



**Fig. 12.** Schematic of the experimental design illustrating the reversal-reminalizing pH-cycling model. A. The artificial caries-like lesions are created in the pit and fissures of all teeth. The initial surface hardness is assessed. B. The caries-like lesions are sealed using the tested formulation and subjected to pH cycling for 5 days. C. The final surface hardness is assessed. Reproduced with permission from Ref. [105]. Copyright 2020, with permission from Elsevier.

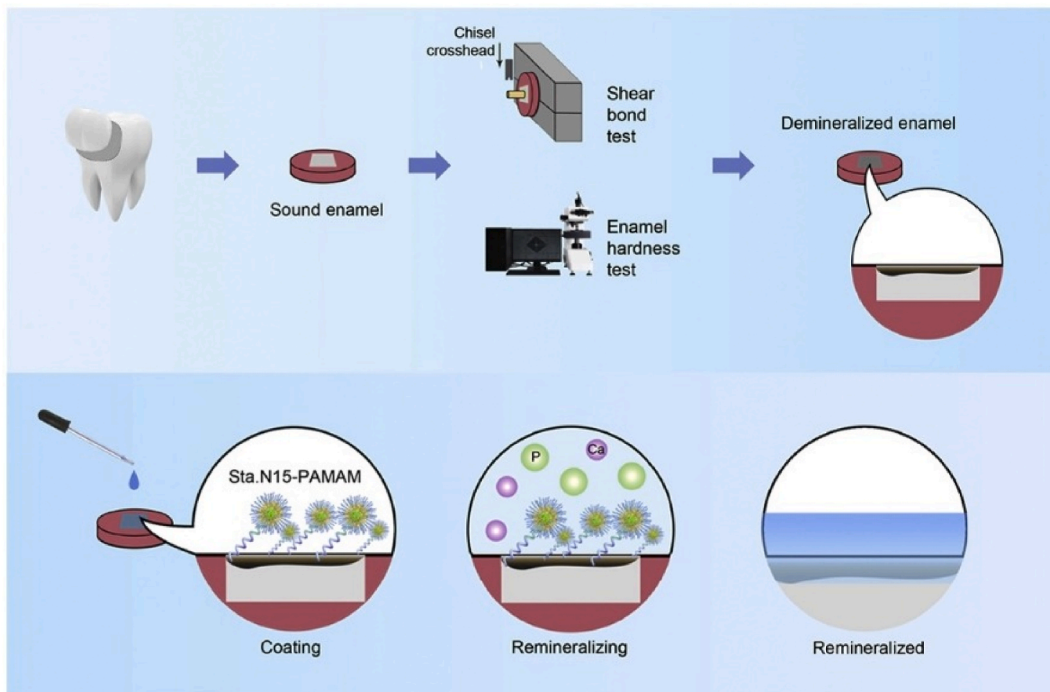


**Fig. 13.** a) Viable count of *S. mutans* in all the groups. b) Mean distribution of the microbial count ( $\times 10^6$ ) in all the groups. Reproduced with permission from Ref. [111]. Copyright 2020, with permission from Elsevier.

SN15-PAMAM + amorphous calcium phosphate NPs adhesive show higher enamel remineralization (90%) of artificial caries than the control.

#### 2.4. Nanosized calcium fluoride (N<sub>CaF</sub><sub>2</sub>)

A more acid-resistant variant of hydroxyapatite, fluorapatite (Ca<sub>5</sub>(PO<sub>4</sub>)<sub>3</sub>F), was formed by combination of calcium and phosphate



**Fig. 14.** Schematic illustration of demineralization of enamel and remineralization process by SN15-PAMAM + amorphous calcium phosphate NPs adhesive. Reproduced with permission from Ref. [112]. Copyright 2020, with permission from Elsevier.

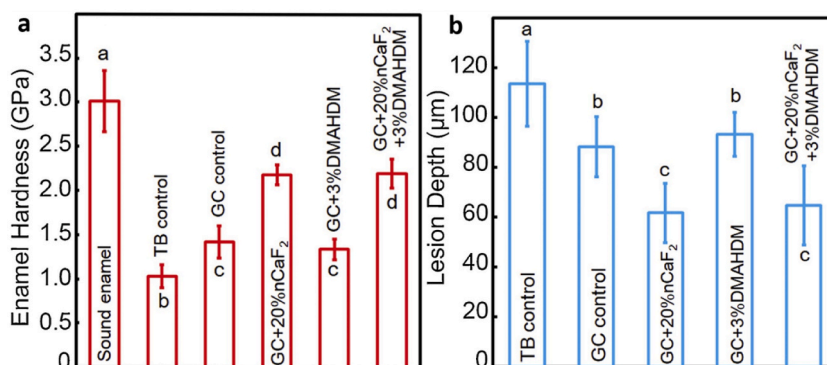
[113]. Calcium fluoride NPs can increase the fluoride concentration of oral fluid. As a result, it can be used as an anti-caries agent. It also enhances the effect of remineralization [114]. The shear bond strength of the composite does not affect by adding of 20 wt% nCaF<sub>2</sub> and 3 wt% DMAHDM into composite. The release of the F and Ca ions were increased at an acidic medium. The metabolic activity, polysaccharide, and lactic acid productions were reduced in the presence of produced cement. It increased the enamel hardness by 56% and decreased the lesion depth by 43%, in addition to lowering the biofilm CFU by 3 logs compared to the control (Fig. 15a and b).

Pit and fissure sealants due to having antibacterial and remineralization properties gain great attention in caries prevention. Pit and fissure sealants containing nano CaF<sub>2</sub> and DMAHDM not show only high fluoride release but also strong antibacterial activity [115].

Nano CaF<sub>2</sub> materials show sustained release behavior for a long time, in comparison to typical fluoride. Ghafar et al. prepared CaF<sub>2</sub> NPs and lignocaine incorporated into a thiolated chitosan-based bioadhesive [116]. Release study proves the sustained release pattern of lignocaine and fluoride following the Korsmeyer-Peppas model.

## 2.5. Titanium nanoparticles

Because of high biocompatibility, bioactivity, and antibacterial activity, the titanium NPs have potential in dental applications [117,118]. In a study, 1% w/w and 5% w/w TiO<sub>2</sub> NPs incorporated into orthodontic composite used for bonding metal brackets [119].



**Fig. 15.** Remineralization of enamel after 30 days of demineralization-remineralization cycles (mean ± sd; n = 6). a) Surface hardness of enamel. b) Lesion depth of enamel. Reproduced with permission from Ref. [114]. Copyright 2020, with permission from Elsevier.

The quantity of titanium released in the teeth that received 1% TiO<sub>2</sub> was the largest in the first two months, with no appreciable release at subsequent intervals. There was a large release of titanium in the second group got 5% at all intervals, with the maximum release in the second month. As a result, both 1% and 5% quantities are safe and within acceptable limits.

Moradpoor et al. synthesized TiO<sub>2</sub> NPs via a green approach by *Bacillus* sp. Bacteria [120]. According to the findings, TiO<sub>2</sub> NPs produced under green conditions inhibit fungus from growing by 73% (oral *Candida albicans* pathogen). It also reported that TiO<sub>2</sub> NPs incorporated in conventional glass ionomer cement and resin-modified glass ionomer cement, did not affect the bond strength of glass ionomers [121]. When compared to undoped TiO<sub>2</sub> NPs, nitrogen-doped titanium NPs had greater light absorption values. In dark conditions, nitrogen-doped TiO<sub>2</sub> NPs adhesives showed better antibacterial activity [122]. N-doped TiO<sub>2</sub> appears to be a viable antibacterial agent against cariogenic biofilms.

## 2.6. Copper nanoparticles

Copper NPs as one of the low-cost materials can prevent root caries by inhibiting the development and colonization of *S. mutans* on the surface of the tooth root [123]. At concentrations ranging from 64 to 128 µg mL<sup>-1</sup>, CuO NPs effectively suppressed the development of the tested standard strains of *Candida albicans* and *Streptococcus* spp. [124]. Soft denture liners containing CuO NPs at a concentration of 500 µg mL<sup>-1</sup> showed substantial inhibiting efficacy (75%) in biofilms production. The incorporation of CuO NPs dramatically reduced oral pathogen colonization and plaque formation. Moreover, compared to zirconia NPs (ZrO<sub>2</sub> NPs) copper doped zirconia NPs (Cu-ZrO<sub>2</sub> NPs) showed superior inhibitory action against *Lactobacillus* sp. [125].

Giti et al. presented that both CuO and TiO<sub>2</sub> NPs incorporated in polymethyl methacrylate (PMMA) denture base material at concentrations of 2.5% and 7.5% had significant antimicrobial activity against *S. salivarius*, *S. sanguis*, and *C. dubliniensis* [126]. It was found that the PMMA containing CuO NPs was effective against *S. mutans*. While TiO<sub>2</sub> was not statistically effective.

It has been found that Graphene oxide-Gu nanocomposites at a concentration of 10 µg/mL show antibacterial ability against *S. mutans* and 10 µg/mL [127]. Graphene oxide-Gu nanocomposites are able to decrease killing bacteria bioactivity. Mao et al. found that low-dose, graphene oxide-Gu nanocomposites with low cytotoxicity can disrupt exopolysaccharide matrix formation and further hinder optimum biofilm growth [127].

## 3. Conclusion and future perspective

Various inorganic based NPs (e. g. Ag, Zn, hydroxyapatite, NCaF<sub>2</sub>, titanium, and copper base NPs) have been shown to increase anti-caries capabilities in dentifrices and mouth-rinsing solutions. Furthermore, metallic NPs found in dental polishing agents and filling materials have been discovered to help prevent caries [128–131]. Metallic NPs, alone or in composites, have been shown to exhibit antibacterial and remineralizing capabilities. They can also be utilized to make dental materials with more mechanical and aesthetic properties.

Metal based NPs such as silver, zinc, titanium, and copper, have been developed for dental usage. Nanomaterials with better physiochemical, antimicrobial, or remineralizing capabilities have been generated as a result of breakthroughs in nanotechnology research and development.

In dentistry, nanotechnology offers a wide range of applications, particularly in the field of dental materials. Before maximizing the use of inorganic nanomaterials as anti caries agents, the potential toxicity of the nanomaterials needs to be addressed more and more. The stability of the synthesized NPs is also another critical factor that should be assessed further.

Basic mechanisms of dental caries pathogenesis and nanomaterial antibacterial mechanisms, are inadequate and should be further investigated, which is an essential aspect for clinical applications. In addition, the interaction of NPs with salivary proteins should be studied. Besides, the potential rapid release of nanomaterials and ions from the oral cavity, following saliva secretion and ingestion, is another problem.

Further research on the durability and long-term viability of these metal NPs and their conjugates is needed. Furthermore, investigations should look into bioavailability and biocompatibility, binding energy and binding potential to dental tissues, tooth tissue integrity and dynamics, and aesthetic outcomes. Biodistribution, clearance, and pharmacokinetics aspects of nanomaterials are other vital issues that should be studied.

Most studies show the efficacy of metallic NPs *in vitro*, while it should be assessed *in vivo*. Finally, clinical trials should be carried out to verify their efficacy in the prevention of dental caries.

### Ethical approval

NA.

### Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

### Funding statement

This work was supported by the Al-Mustaqbal University College, Babylon, Hilla [51001].

## Data availability statement

Data will be made available on request.

## Declaration of interest's statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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