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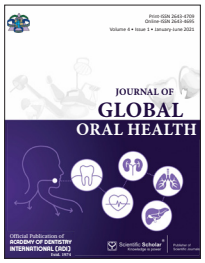

Review Article

Nanoparticles in caries prevention: A review

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ABSTRACT

Nanotechnology is the branch of engineering that uses molecular machines with precise structures that are less than or equal to 0.1 μm in size. The word nano denotes 10 to the power of minus nine or 1 billionth. Treatment options for dental caries have been extensively studied; among them, the role of nanoparticles is of recent interest. Nanoparticles have shown promising results in the field of caries prevention because of their unique physical, mechanical, and biological characteristics. Nanosized systems have distinctive properties due to their increased surface-to-volume ratio and increased bioavailability toward cells and tissues. Furthermore, improved surface area results in better mechanical interlocking of nanoparticles to the resin matrix. They prevent dental caries by antimicrobial, remineralizing, and anti-inflammatory mechanisms. Although many nanoparticles have been studied for their role in caries prevention, only a few materials which were extensively studied are included in this review.

Keywords: Caries prevention, Gold nanoparticles, Hydroxyapatite, Nanoparticles, Silver nanoparticles

INTRODUCTION

Dental caries is a multifactorial disease process caused by a microbial imbalance in the oral biofilm, provoked by frequent exposure to fermentable carbohydrates, resulting in the demineralization of dental hard tissues.[1,2] The primary etiological agents involved in the initiation of caries are *Streptococcus mutans*, *Actinomyces* spp., and non-*S. mutans streptococci*. Other species that play a crucial role in caries production are species of *Veillonella, Lactobacillus, Bifidobacterium*, *Propionibacterium,* low-pH non-*S. mutans streptococci*, *Actinomyces*, and *Atopobium*.[3]

Treatment for dental caries involves both conservative and preventive approaches which aim for specific person-to-person risk assessment by early detection of the disease and efforts are made to reverse or arrest dental caries, preserving tooth structure.[2,4] A large number of patients are still affected by caries despite the efforts and advancements in caries management. The ideal goal of any intervention/treatment would be the prevention of tooth decay. Changing the local conditions at the sites at risk proves a challenge in caries prevention.[5] Calcium and phosphate ions can reduce tooth demineralization, thus preventing dental caries. The salivary concentration of these ions will determine whether remineralization or demineralization will occur.[6]

Fluoride is the most commonly used remineralizing agent in the prevention of dental caries in the early stages.[6] Fluoride can react with hydroxyapatite forming fluorapatite or fluoridated hydroxyapatite.[6,7] These remineralizing agents are supplied either in liquid or semisolid forms, which can be easily administered and have good patient acceptability. The main disadvantage/hurdle is poor retention in the oral environment, resulting in suboptimal therapeutic

concentration and outcome.[8] The most common delivery systems for agents against dental caries are toothpaste, gels, tablets, and mouth rinses.[9]

Recent literature states that nanotechnology can aid in the prevention and management of dental caries by controlling plaque and helping in remineralization of initial caries.[10,11] This branch of engineering uses molecular machines with precise structures that are less than or equal to 0.1 μm in size. The word nano denotes 10^{-9} or 1 billionth. A nanoparticle is almost 1000 times smaller compared to micro and it measures 1/80,000 of the diameter of a human hair.[12,13] Nanoparticle-based aqueous suspensions are incorporated in a gel or paste form and used for oral applications.[14] Nanoparticles are preferred in biology and material science because of their unique properties such as uniformity, conductance, and specialized optical properties.[15]

Antimicrobial nanoparticles could inhibit bacterial growth and thus dental caries.[16,17] Nanoparticles that penetrate biofilms (plaque) and damage the extracellular polysaccharide matrix can enhance antibacterial efficacy and reduce the initiation of drug or antimicrobial resistance.[18]

Nanotechnology helps in treating dental caries by two important approaches. The first approach is the remineralization process, which uses nano-materials with fluoride and calcium releasing ability, namely, calcium phosphate, calcium fluoride, hydroxyapatite, and fluorohydroxyapatite. The second approach involves the administration of antibacterial nanoparticles such as silver, quaternary ammonium polyethylene amine, and zinc oxide.[19,20] Better outcomes are achieved by the combination of these two approaches. This review will give an insight into applications of nanotechnology in the prevention of early carious lesions and its role in remineralization.

PROPERTIES AND CLASSIFICATION OF NANOPARTICLES

General properties

Nanosized systems have distinctive properties due to their increased surface-to-volume ratio and increased bioavailability toward cells and tissues.[21,22] Improved surface area results in the better mechanical interlocking of nanoparticles to the resin matrix.[23] Superior mechanical properties are achieved by the addition of inorganic ceramic nanoparticles which are brittle and hard.[4] There is improved resistance to crack propagation and higher fatigue strength due to the reduction in areas of stress concentration.[24] Optical properties such as surface finish and translucency are improved when nanosized fillers are used in restorative materials.[25] Furthermore, there is better control of biodegradability and biodegradation rates in comparison to conventional composite materials.[26,27] The nanoparticles are classified as antimicrobial, remineralizing, and anti-inflammatory agents [Figure 1].

Anti-microbial and anti-inflammatory properties

The main etiological factor of dental caries is the presence of pathogenic bacteria that are organized within an extracellular matrix forming a biofilm.[28] The bacteria in biofilm are more resistant to antimicrobial treatment than planktonic organisms.[29,30] The nanoparticles have more effective antibacterial activity as the dimensions are reduced to the nanometer, resulting in an increased surface-to-volume ratio that allows them to interact and penetrate bacteria effectively.[31] Nanoparticles in caries prevention are classified based on their mechanism of action as mentioned in [Figure 1].[32]

SILVER NANOPARTICLES

Silver nanoparticles (Ag NPs) have been used for caries prevention in several studies.[33-44] These studies utilized silver nanoparticles in the form of silver nanocomposites, dentifrices, coated orthodontic brackets, nanosilver fluoride solutions, sealants, and glass ionomer cement with Ag NPs. *In vitro* research using Ag NPs and silver nanocomposites was done to treat and prevent secondary caries.[35,36] Ag NPs were also incorporated into the resin of orthodontic materials (adhesives, elastomeric ligatures, and removable retainers) for caries prevention.[37,38] Nanosilver fluoride solution was effective in remineralizing early enamel caries and arresting dentinal caries.[39-43] Clinical studies have proved that Ag NPs on orthodontic brackets can be used to prevent enamel caries[37] and that dental sealant with Ag NPs can be better than a traditional sealant in the prevention of enamel caries in first permanent molars.[44]

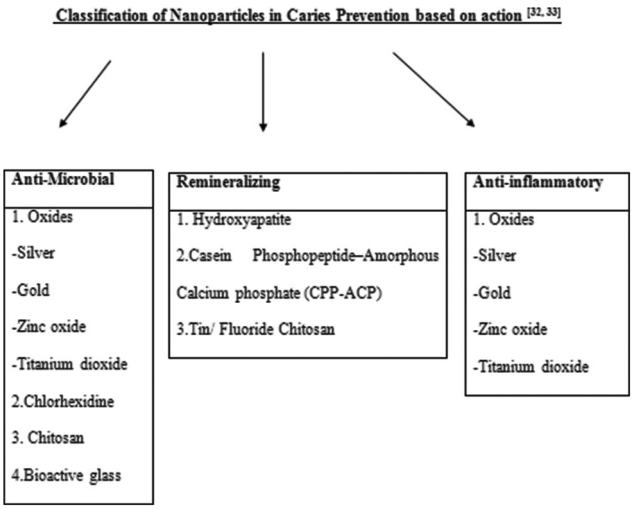

Figure 1: Classification of nanoparticles in caries prevention based on action.

Antimicrobial activity

In vitro experiments

In vitro studies have shown that Ag NPs have an antimicrobial effect against Gram-positive bacteria such as *Bacillus*, *Enterococcus*, *Listeria*, *Staphylococcus*, *Streptococcus*, and Gram-negative bacteria such as *Acinetobacter*, *Escherichia*, *Pseudomonas*, and *Salmonella*.[45-48] The size, morphology, and concentration of nanoparticles play an important role in determining the antibacterial activity of Ag NPs. With the decrease in size of Ag NPs, the stability and biocompatibility increases. The higher surface-area-to-volume ratio of the smaller nanoparticles allows them to penetrate biological surfaces more readily.[49-51] Ag NPs smaller than 30 nm showed strong antimicrobial activity against *Staphylococcus aureus* and *Klebsiella pneumoniae*. Ag NPs with sizes ranging from 5 to 20 nm have strong antimicrobial activity against *S. aureus*.[52] Thus, small Ag NPs are more toxic against bacteria than large particles, and this further increased when the nanoparticles were oxidized.[53]

Silver ions are also released from materials that penetrate through microbial membranes and disrupt deoxyribonucleic acid replication and protein synthesis.[54] These ions can also deactivate respiratory enzymes and ultimately cause cell lysis. Ag NPs can accumulate on the pits of the cell wall and cause membrane denaturation.[55]

Ahmed *et al*. evaluated the action of toothpaste with and without Ag NPs against *S. mutans*[34] and reported that Ag NPs had antimicrobial activity against *S. mutans*. The mean diameter of the zone of inhibition was 20.14 ± 0.96 mm for toothpaste with Ag NPs, whereas no zone of inhibition was observed with the toothpaste without Ag NPs.

Abadi *et al*. demonstrated the antibacterial efficacy of an alcohol-free mouthwash with a low concentration of colloidal Ag NPs (0.024–50 μg/ml).[56]

Effects on enamel and dentin

Most studies done on enamel and dentin with Ag NPs were *in vitro* experiments. Ag NPs can reduce the production of lactic acid in biofilm and may have the potential to reduce the demineralization of teeth.[35] Ag NPs can attach to hydroxyapatite crystals in the carious lesion.[41] Furthermore, silver ions released from Ag NPs can form insoluble silver chloride on dental hard tissue, which increases the mineral density of dental hard tissue.[15] Ag NPs can preserve exposed collagen in carious teeth by inhibiting and deactivating bacterial collagenases as well as proteinases in saliva and the dentin matrix, such as activated matrix metalloproteinases and cysteine cathepsins.[57] The preserved collagen thus acts as a scaffold for the deposition of a mineral crystal. Espíndola-Castro *et al*. suggested that nanosilver fluoride particles were capable of staining dentin; however, the same laboratory model concluded that brushing cycle removed the stain.[58]

Ag NPs in caries prevention

Ag NPs were combined with other nanoparticles, such as calcium glycerophosphate and zinc oxide, to produce multifunctional nanocomposites for caries prevention.[59] Ag NPs were also added into restorative materials, such as adhesives and filling resins, which can prevent secondary caries without compromising mechanical properties.[36]

Sound enamel treated with Ag NPs had a shallower lesion depth compared to enamel treated with water after biofilm challenge.[35] Besides, microhardness was increased when enamel with artificial caries was treated with Ag NPs.[57,60] The microhardness value of enamel caries treated with nanosilver fluoride was higher than that of enamel caries treated with sodium fluoride.[41]

A clinical trial reported that the mineral loss in first molars was reduced when treated with dental sealants containing Ag NPs.[44] Nanosilver fluoride also arrested dentin caries of children in two clinical trials.[39,42]

Laboratory studies claim that silver nanoparticles restrain the growth of cariogenic bacteria. Bacterial collagenase activity has been known to be impeded by Ag NPs and they also protect the collagen matrix. Therefore, Ag NPs can be useful in caries prevention. However, it is essential to prove the same with well-designed randomized clinical trials. Furthermore, staining caused by Ag Nps should be taken into consideration before clinical usage.

GOLD NANOPARTICLES

In vitro experiments

Gold (Au) is reported to have a weak antimicrobial effect against bacteria and fungi.[61-64] A combination of gold nanoparticles (Au NPs) with tetracycline or with ampicillin can improve the antibacterial activity.[65,66] Au NPs exhibit anti-inflammatory action by reducing reactive oxygen species (ROS) production by decreasing lipopolysaccharide-induced cytokine production such as interleukin (IL)-1β, IL-17, tumor necrosis factor, and modulating mitogen-activated protein kinase and phosphatidylinositol 3-kinase pathways.[67]

Hernández-Sierra *et al*. evaluated NPs of Ag, zinc oxide, and Au of 25 nm, 80 nm, and 125 nm average sizes. The results stated that a higher concentration of Au NPs than that of Ag NPs was required to observe bacteriostatic and bactericidal effects on *S. mutans*.[68] Junevičius *et al*.[69] compared the antimicrobial effect of toothpaste containing Ag NPs and

Au. Au NPs containing toothpaste had a lower antimicrobial effect against Gram-negative bacteria when compared to Ag NPs containing toothpaste. The concentration of Au NPs required to achieve the desired effect is more compared to other nanoparticles. Furthermore, they are reported to have a weak antimicrobial effect which makes them less preferable compared to other nanoparticles used for caries prevention.

ZINC OXIDE NANOPARTICLES

Antimicrobial activity

In vitro studies

Zinc ions have demonstrated good antibacterial action which is elevated when it exists as zinc oxide nanoparticles.[70] Yamamoto found that as the particle size decreased, there was an increase in the antibacterial activity. This increase was assumed to be owed to the added H_2O_2 generated from the surface of ZnO.[71]

Zinc oxide nanoparticles (ZnO NP) have antibacterial properties against both Gram-positive and Gram-negative bacteria.[72] The generation of hydrogen peroxide (H_2O_2) from the surface of ZnO hinders bacterial growth.[71] The liberation of oxygen species on the surface of ZnO can significantly damage microorganisms.[73] Zn is effective against *S. aureus,*[74] *Porphyromonas gingivalis* and *Actinomyces naeslundii,*[73] *Escherichia coli*,[71] *Streptococcus sobrinus*,[16,75] and *S. mutans*.[76] Zinc oxide nanoparticles have photocatalytic activity and high stability.[77]

ZnO NPs in caries prevention

In vitro experiments

The inclusion of 2–5 wt% of zinc oxide nanoparticles to resin composite can provide antibacterial property without altering their properties.[78,79] The addition of ZnO and Cu nanoparticles in universal adhesive systems may provide antimicrobial activity, improve the integrity of the hybrid layer,[80] and adhesive mechanical properties.

In vivo experiments

In vivo research with Zn-containing mouth rinse has demonstrated high substantivity in the oral cavity which is active against *S. mutans*. The only adverse effect related to the use of zinc ions in mouth rinses is their unpleasant astringent taste. Zinc has the least tendency to stain oral tissues when compared to other active ingredients such as Ag, Sn, or chlorhexidine.[81]

Ag/ZnO nanocomposite showed enhanced antibacterial activity against *S. mutans*. The antibacterial mechanism involves the direct destruction of cell structure and membrane function, as well as the generation of ROS to oxidize biomacromolecules.[76] ZnONPs are effective against Gram-positive and Gram-negative bacteria in *in vitro* studies. *In vivo* studies are necessary to confirm these results. Furthermore, when added to composite, it is effective against cariogenic bacteria, but their effect on mechanical properties of composite needs to be further investigated. If used in mouth rinses, their staining property and taste should be considered.

TITANIUM DIOXIDE

In vitro studies

Titanium dioxide (TiO2) is physically and chemically stable, non-toxic, and exhibits antibacterial activity.[82] TiO_2 is effective against *E. coli*, *S. epidermidis*, *S. pyogenes*, *S. mutans*, and *Enterococcus faecalis*.[83] TiO_2 has demonstrated photocatalytic activity, with the release of ROS that attacks the bacteria from outside the cell wall.[84] TiO_2 causes a lipid peroxidation reaction that subsequently collapses the cell membrane structure and therefore inhibits its functions leading to cell death.[84] TiO_2 particles are used in dental composites to match the opalescence of natural teeth.[85] The addition of TiO_2 to composites can improve mechanical properties.[86,87] They also demonstrated improved compressive strength when incorporated in glass ionomer cement (GIC).[88] In another study by Elsaka *et al.*,[89] it was reported that GI-containing 3% (w/w) TiO_2 nanoparticles demonstrated superior mechanical and antibacterial properties compared to conventional GI. TiO_2 is used in orthodontic composite as it is antibacterial and does not affect the shear bond strength.[90] As titanium dioxide incorporated resin composite is found to be biocompatible, it can be used as a restorative material.[91] TiO_2 in the composite resin can decrease *S. mutans* biofilm formation over the composite resin surface.[92] TiO_2 nanoparticles have proved to be effective against cariogenic bacteria. They have been demonstrated to improve the mechanical properties when added to composite and GIC. Thus, a material that can provide antibacterial property without reducing the mechanical property can be awaited in the future.

CHLORHEXIDINE

In vitro studies

Chlorhexidine (CHX) has broad-spectrum antimicrobial activities and is a widely prescribed antiplaque agent.[93,94] To overcome the rapid and uncontrolled release of free CHX from resin matrices, two methods, namely, encapsulation or nanoparticulation, are used. Nano-encapsulated particles exhibit rapid penetration and bioavailability with increased biological efficacy and decreased potential cytotoxicity.[95]

Seneviratne *et al*. coated CHX on mesoporous silica NPs with inner pore channels of approximately 2.5 nm. The results demonstrated that CHX NPs had antibacterial effects against both planktonic and biofilm bacteria such as *Aggregatibacter actinomycetemcomitans*, *E. faecalis*, *Fusobacterium nucleatum*, *S. mutans*, *P. gingivalis*, and *S. sobrinus*.[96] Barbour *et al*. developed antimicrobial chlorhexidine hexametaphosphate (CHX HMP) nanoparticles from CHX and sodium hexametaphosphate at ambient temperature and pressure.[97] There was a sustained release of CHX for more than 50 days.[97,98] Nanocarriers such as spherical poly-lactic-co-glycolic acid,[99] poly (ethylene glycol)-block-poly-(L-lactide),[100] nano-silica wires, and spheres[101-106] were studied for sustained delivery of CHX in the oral environment. A paste containing CHX HMP nanoparticles embedded into GIC has been shown to release chlorhexidine for at least 14 months.[107] A recent study demonstrated that the CHX carrier nanosystem based on iron oxide magnetic nanoparticles (IONPs) and chitosan was able to reduce biofilm formation of *C. albicans* and *S. mutans* in single or mixed cultures.[108] CHX-HMP nanoparticles aid in achieving CHX rich oral environment for a longer duration and at higher concentration compared to the conventional solution of CHX digluconate. Furthermore, the potential antibacterial effect of CHX nanoparticles aids in the treatment of biofilm-related oral diseases such as dental caries.

CHITOSAN

In vitro experiments

Chitosan nanoparticles (ChNPs) are manufactured by crosslinking methods such as ion gelation with polyanionic sodium triphosphate.[109] ChNPs are used in dental restorative materials to control oral biofilms.[110] ChNPs incorporated dental varnishes demonstrated more potent antimicrobial activity than propolis, miwask, or chlorhexidine incorporated varnishes against *S. mutans*.[111] Rutin (a flavonoid from plant source with antibacterial activity) loaded into ChNPs possessed higher antibacterial activity compared with pure rutin or chitosan nanoparticles alone.[112]

Covarrubias *et al*. demonstrated antimicrobial activity of hybrid nanoparticles comprising copper nanoparticles with a chitosan shell (CuChNP) against *S. mutans*. CuChNP prevented *S. mutans* growth on the human tooth surface as well as disrupted and killed the bacterial cells in an established dental biofilm. Chitosan also interacted with tooth hydroxyapatite and bacterial cell wall, which improved the adhesion of copper to the tooth surface and improved the anti-biofilm activity.[113] In another study, chloroaluminum phthalocyanine (ClAlPc) encapsulated in chitosan nanoparticles (ChNPs) were found to be effective against *S. mutans* biofilm, encouraging its use in clinical studies.[114] ChNPs exhibit good biocompatibility and antimicrobial activity against cariogenic bacteria *in vitro* and they can be used as potential anticariogenic agents, though further *in vivo* studies are necessary to establish their clinical efficacy.

HYDROXYAPATITE

In vitro experiments

Acids produced by bacterial metabolism result in mineral loss from the hard tissue in the early stages of caries attack, but the collagen network remains unaffected. HA nanoparticles (HA NPs) are used to remineralize this organic scaffold by acting either as a direct replacement of lost minerals or as a carrier for lost ions.[115] HA NPs have been integrated into products for oral care such as dentifrices and mouthwash to promote the remineralization of enamel by replacing calcium and phosphate ions in the areas from which minerals were dissolved, restoring integrity.[116] An *in situ* study with HA NPs incorporated toothpaste showed that HA NPs can penetrate tooth porosities and can produce a protective layer on the tooth's surface against a carious attack.[117] HA NPs in toothpaste promote enamel regeneration by the formation of biomimetic film similar in morphology and structure to the biologic hydroxyapatite of enamel. The new layer of apatite showed resistance to toothbrushing due to the chemical bonds between the synthetic and natural crystals of enamel.[118]

Nano-HA paste showed a protective layer with globular deposits on artificially produced incipient caries-like lesions when compared to fluoride varnish and casein phosphopeptide–amorphous calcium phosphate (CPP-ACP).[119] A similar study showed that both nano-HA and CPP-ACP had a remineralizing effect on the early stages of caries.[120] Several *in vitro* studies reported the better remineralizing potential of HA NPs when compared to toothpaste containing calcium and potassium ions and sodium nitrate.[121-127]

HA NPs incorporated pit and fissure sealants demonstrated a remineralized region at sealant enamel interface. They also showed a higher degree of conversion and increased ion release.[128] Incorporation of HA NPs into dental composites promoted enamel remineralization at a potentially cariogenic pH of 4.[129]

In vivo experiments

An *in vivo* study showed a decrease in caries incidence by 56% in children brushing with a 5% HA NP toothpaste for 3 years.[130] The combination of nano-hydroxyapatite gel and ozone therapy was shown to remineralize initial approximal enamel and dentine subsurface lesions of posterior teeth.

However, the treatment procedures should be continued for a long time to achieve nonrestorative treatment of caries.[131] Mouthwash containing HA and Zn NPs helped in controlling bacterial biofilm formation and there was an accumulation of HA aggregates.[132-134] Nano-HA showed positive results in remineralization, making it preferable for caries prevention. Nano-HA is a relatively new material with good physical, chemical, and mechanical properties. However, its application in preventive dentistry should be investigated further.

CASEIN PHOSPHOPEPTIDE –AMORPHOUS CALCIUM PHOSPHATE (CPP-ACP)

In vitro and *in vivo* studies

CPP–ACP nanocomplexes decreased demineralization and enhanced remineralization of enamel by localizing at the surface of the tooth, bringing about buffering of the phosphate and calcium-free ion activities and maintaining a state of super-saturation.[135,136] They form a calcium and phosphate reservoir that is bound to plaque and dental surfaces.[137] A clinical trial conducted for 24 months demonstrated the efficacy of toothpaste containing CPP in preventing carious lesions.[138] Several *in vitro* and *in situ* studies have shown that toothpaste with CPP–ACP nano complexes prevented enamel demineralization produced by soft drinks.[139-141] Toothpaste containing CPP–ACP NPs with *L. rhamnosus* (probiotic strain) had effective remineralizing and antimicrobial efficiency.[142] CPP–ACP and fluoride were suggested to remineralize initial dental caries and white spot lesions. However, CPP–ACP had a slightly lower potential in the remineralization of early enamel caries compared to fluoride.[120,143-145] Studies supporting the clinical efficacy of CPP-ACP are limited and inconsistent. CPP-ACP nanocomplexes cannot be used as a substitute for fluoride or when other caries preventive interventions such as sealants and resin infiltration are available.

BIOACTIVE GLASS

In vitro studies

Bioactive glass nanoparticles (BAG NP) exhibited better remineralization potential when compared to conventional BAG due to increased surface area and higher Ca/P ratios, thus slowing the progress of dental caries.[146-148] When BAG NPs comes in contact with an aqueous solution, they will take a mesoporous shape, which allows the formation of apatite on the dentine surface. The pH rise provokes the precipitation of HA. Phosphate and calcium ions in the bioactive glass and minerals from saliva activate the mineralizing process.[149]

In vitro studies have demonstrated that BAG NPs could make dentin more acid-resistant by inducing mineral formation on dentin surfaces.[150,151] The new HA layer formed is similar to those of enamel or dentine and presents better resistance to abrasion.[152] The fluoride-containing bioactive glass had a better capacity for remineralization compared to BAG toothpaste and sodium monofluorophosphate toothpaste.[153]

BAG NPs toothpaste also demonstrated antibacterial properties.[154] BAG NPs can inhibit *S. mutans* biofilm.[155] BAG NPs can create an unfavorable environment for bacterial growth by the release of alkaline ions that cause an elevation in the pH. The addition of fluoride to BAG provided higher resistance to acid dissolution, allowing the formation of fluorapatite on the tooth surface.[156] This deposit of fluorapatite on the dentine surface occluded dentinal tubules and decreased permeability.[157] The main mechanisms of action of BAG NPs for caries management include antibacterial effect against cariogenic bacteria, inhibition of demineralization, and promotion of remineralization. Further research should be done to find the exact mechanism of action of bioactive glass in preventing dental caries in an intraoral environment.

CONCLUSION

Nanotechnology is relatively new and has promising potential in the development of new nanoparticles that can be used in the prevention of dental caries. Right now, oral care products such as toothpaste and mouth rinses contain NPs with anti-microbial, anti-inflammatory, and remineralizing properties. Although many NPs are used in dental restorative materials to prevent caries that are more effective than traditional materials only few which are extensively researched are highlighted in this review. Nanodentistry will be cost-effective, time-saving, and prevent the patients from future complex dental procedures. Although there are various reports with positive results in favor of nanoparticles, the clinical application of these techniques for caries prevention is limited. Further studies on dosage, viability, steps to overcome toxicity, and the performance of nanoparticles in the oral environment are necessary.

Declaration of consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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