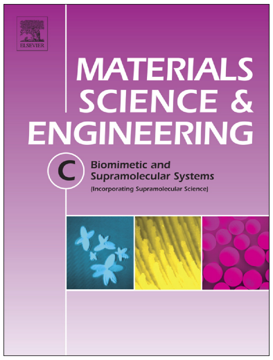

An overview of application of silver nanoparticles for biomaterials in dentistry

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An overview of application of silver nanoparticles for biomaterials in dentistry

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Abstract

Oral cavity is a gateway to the entire body and protection of this gateway is a major goal in dentistry. Plaque biofilm is a major cause of majority of dental diseases and although various biomaterials have been applied for their cure, limitations pertaining to the material properties prevent achievement of desired outcomes. Nanoparticle applications have become useful tools for various dental applications in endodontics, periodontics, restorative dentistry, orthodontics and oral cancers. Off these, silver nanoparticles (AgNPs) have been used in medicine and dentistry due to its antimicrobial properties. AgNPs have been incorporated into biomaterials in order to prevent or reduce biofilm formation. Due to greater surface to volume ratio and small particle size, they possess excellent antimicrobial action without affecting the mechanical properties of the material. This unique property of AgNPs makes these materials as fillers of choice in different biomaterials whereby they play a vital role in improving the properties. This review aims to discuss the influence of addition of AgNPs to various biomaterials used in different dental applications.

Keywords: Biofilm; silver nanoparticle; endodontics; periodontics; orthodontics; oral cancers.

1. Introduction

Nanotechnology is an essential technology of 21st century with groups of atom at nanoscale of 1-100nm[1–4]. Nanoparticles (NPs) can be obtained from natural sources or chemically synthesized or one of the by-products [5,6]. Due to its higher surface to volume ratio and antibacterial properties they have found applications in the field of medicine[7,8]. Among the various existing nanomaterials, AgNPs has gained attention owing to their distinctive physical and bio-chemical properties in contrast with their macro and micro complements. Silver is a safe antimicrobial agent which has a potential to kill 650 different types of diseases causing organisms [9]. AgNPs have been synthesized and have shown to possess potential antimicrobial actions [10]. Their smaller particle size with increased surface area provides antimicrobial action [11,12] at decreased filler level preventing negative effect on the mechanical properties of the biomaterial [13]. As biofilm organisms are resistant to antibacterial agents, small particle size of AgNPs makes it possible to penetrate cell membranes causing DNA damage and cell death [14,15]. In this review, we discuss influence of incorporation of AgNPs into different biomaterials used in restorative dentistry (composite resins and adhesives) [16,17], endodontics [18,19], periodontics, implant dentistry (titanium dental implants) [20–22], prosthetic dentistry (porcelain and acrylic resins), orthodontics (cements for brackets), oral cancers [23] **(Figure 1).**

2. Mechanism of actions of AgNPs

2.1. Antimicrobial action of AgNPs

The AgNPs have exhibited a broad spectrum antibacterial effect on both gram positive and gram-negative organisms and various drug resistant strains. Although various mechanisms have been proposed for antibacterial action, exact mode of action is not completely understood **(Figure 2)**. According to Jones and Hoek, 2010 [24], the most common modes of action can be free silver ions uptake causing interruption of ATP molecules and preventing DNA replication or formation of reactive oxygen species by AgNPs or direct damage of cell membrane by Silver ions (Ag^+). It is recognised that AgNPs forms pits in the cell wall of gram negative organisms causing increased permeability and cell death. So generally, AgNPs cause denaturation and oxidise the cell wall which leads to rupture of organelles resulting in cell lysis[25,26]. AgNPs also modify the phosphotyrosine profile of peptides which interrupts the organisms signal transduction and prevents multiplication [27].

The antibacterial action of AgNPs is mainly due to the release of Ag+ ions. Release of Ag+ is higher when fine AgNPs are used (less than 10nm particle size) for antibacterial action compared to larger AgNPs.[1] . Minimum inhibitory concentration (MIC) of AgNPs is in approximately 0.003 mg/mL for *Fusobacteriun nucleatum* [2], 0.04 mg/mL for *Streptococcus mutans* (Holla et al., 2012), and 0.5 mg/mL for *Actinomyces oris* [3] As per observation of experiment by Sondi et al., 2004, concentration of 50–60 μg cm^{-3} of AgNPs causes 100% inhibition of bacterial growth *Escherichia coli*.[26] Also bactericidal properties of AgNPs are size dependent. AgNPs in the range of 1-10 nm with direct interaction with cell membrane surface alters the permeability and causes cell damage.[28]

2.2. Antiviral action of AgNPs

It is suggested that AgNPs may bind with the outer proteins of viruses inhibiting their binding and replication. Though antiviral mechanism of AgNPs is yet to be completely known, it remains a scope for future research [29].

2.3. Antifungal action of AgNPs

AgNPs have exhibited antifungal action against 44 strains of various fungal species[30]. AgNPs action against *Candida albicans* could be destruction of cell membrane integrity inhibiting cell growth [31]. Thus, AgNPs can be one of the agents to prevent fungal infections related to oral structures. Concentration of 1 μg/ml of AgNPs incorporated in resins have shown potent antifungal activity without any cytotoxicity.[32]

3. Toxicity of AgNPs

The fact of toxic nature towards microbial agents of silver ions have been successfully implemented in research. Nanoparticle formulation of silver would enhance wide spectrum antimicrobial properties through enormous increase in surface area in nanoparticle formulation. Further, this antimicrobial properties are even evidenced against antibiotic resistance microbes and has also been proved synergistic effect with conventional antimicrobials [33–37]. Wide contribution of AgNPs in medical field has extended its role in dentistry, in prevention of bacterial adhesion, proliferation and finally formation of biofilm in several dental procedures [38]. Thus, application of AgNPs in oral preparations directly contacts with the teeth and surrounding cells and tissues within the oral cavity. Therefore, besides undeniable contribution towards oral health of AgNPs against infecting microbes and producing diseases, serious adverse events must be addressed to fulfil its safety requirements.

Adverse events of free Ag^+ in the industrial wastes are prominent due to the occurrence of argyria (skin discoloration) and argyosis (discoloration of eyes) of other associated side effects on renal, hepatic, gastrointestinal, respiratory adverse effects [39]. Additionally, several reports on toxic evidences of AgNPs, may be due to co-exposure with fluorides, or due to cytotoxicity to gingival fibroblast by capping agent, confirmed interest towards explorative study on it (Niska et al., 2016). Preclinical studies on rats has showed increased accumulation in females particularly in liver, kidney, colon, and jejunum as compared to the males. Further studies confirmed accumulation of silver in the glomerulus of the female rat kidneys, as supported by the pigmentations during histopathological studies. Additionally, affinity of silver towards sulphur, selenium and chlorine interfere in signal transduction [40]. Additional *in vivo* studies have indicated silver nanocarriers are deposited in the liver to produce its hepatic toxicities. Histopathological diagnosis revealed higher incidence of hyperplasia of bile duct with or without necrosis, pigmentation and fibrosis [41].

In vitro studies on rat liver cells have shown to have oxidative stress and impaired mitochondrial function[42]. Exposure to AgNPs has been associated with tissue damage especially in liver. No Observable Adverse Effect Level (NOAEL) of 30 mg ⁄ kg and Lowest Observable Adverse Effect Level (LOAEL) of 125 mg ⁄ kg has been observed for Ag NPs in rats.[43] Alternate studies also revealed oxidative damage of AgNPs through generation of reactive oxygen species *via* mitochondrial respiratory chain, could lead to interference in ATP generation. Such interference lead to apoptotic cell damage and DNA destruction and ultimately interfere the cell survival [44]. Contrarily, exposure of nasal AgNPs for 90 days does not produce any genetic toxicity irrespective of sex of the experimental animals [45]. Along with impaired mitochondrial function by AgNPs, these nanocarriers are known to cause leakage of the cell membranes and interfere with its ionic permeability, thus interfere with the action potential [7]. Recent studies have reported its potential to prompt oxidative damage, immune-toxicity, cytotoxicity, and apoptosis *via* interference in caspase activity. Apoptotic potential has further been explored by mitochondrial involvement through jun-kinase [46]. AgNPs are also known to produce toxicity on male reproductive system, where the nanostructured silver particles easily cross the barrier between blood and testes and reach to the male reproductive organ. Deposition of AgNPs in the testes adversely affect the sperm cell production [47]. Although, studies on AgNPs synthesized with ammonia and polyvinyl pyrrolidone showed to be non-inflammatory at low concentration (≤25 μg/mL) as these nanoparticles did not induce production of inflammatory mediators (interleukin-1β and interleukin-6), however, suggested to further clinical studies [48]. Several studies are supporting the underlying toxicities of AgNPs, although many more evidences are still necessary to support *in vitro* data through conduction of animal studies with the desired dosage level.

In endodontic treatment for as irrigants, AgNPs in concentration of 50 μg/ml (0.005%) has shown to be antibacterial in action and concentrations above 80 μg/ml could be considered cytotoxic levels.[19] Additionally, as reported in the observations by Frankova et al, AgNPs with spherical in structure and average size of 10 nm should be biocompatible for fibroblasts and keratinocytes.[49]

4. Influence of AgNPs incorporation in dental biomaterials [Table 1]

4.1. Acrylic resins for dentures

Poly (methyl methacrylate) (PMMA) acrylic resins are used for the fabrication of partial and complete dentures for replacement of missing teeth. The rough surface of these resins attract potential harmful organisms.[32] *C. albicans* is able to colonize these resins and is one of the key opportunistic pathogen [50]. Various mouthwashes and denture cleansing agents have been used for their eradication. However, these agents are not able to achieve complete elimination of these pathogens[51]. As AgNPs have been used with dental biomaterials, this review will highlight on influence of AgNPs on the mechanical and prevention of biofilm formations with acrylic resins**.**

Koruglu et al., 2016 investigated the effect of AgNPs (three concentrations 0.3 wt%, 0.8 wt% and 1.6 wt%) on the flexural strength, elastic modulus, impact strength and glass transition temperature of conventional heat polymerized acrylic resin and microwave polymerised acrylic resin. Highest flexural strength and elastic modulus was observed with microwave polymerized resin group with addition of 0.3 wt% AgNPs, while the lowest values were detected for the 1.6 wt. % AgNPs added conventional heat polymerized resin group. Incorporation of AgNPs had no effect on flexural strength and elastic modulus in conventional heat-polymerized resin group. However, these values decreased in microwave polymerized with addition of 0.8 and 1.6 wt. % AgNPs. Highest impact strength was obtained for conventional resin group without addition of AgNPs and the lowest for microwave-resin group with 0.8 wt. % AgNPs. There was no improvement in impact strength of both resin groups with the addition of AgNPs. Glass transition temperatures were highest for heat polymerized resin group but addition of AgNPs decreased the glass transition temperatures for both the groups [52].

Oei et al., 2011 investigated the effect of AgNPs incorporated in poly (methyl methacrylate) on mechanical and antimicrobial properties. It was demonstrated that there was improvement in the mechanical and anti-bacterial properties on addition of AgNPs. The release of silver ions reached a plateau at 7 days but the antibacterial activity extended till 28 days [53]. Acosta-Torres et al., 2012 investigated the effect of AgNPs incorporated in poly (methyl methacrylate) on biocompatibility and anti-fungal properties. Study demonstrated decreased adherence of *C. albicans* and exhibited no cytotoxicity, genotoxicity [32]. Matsuura et al., 1997 investigated the effect of silver zeolite containing silver ions incorporated in tissue conditioners on antibacterial and anti-fungal properties. The study revealed there was significant antifungal activity against *C.albicans* and antibacterial activity against *S. aurues, Pseudomonas aeruginosa* for 4 weeks[54]. Nam; 2011 investigated the effect of AgNPs incorporated in tissue conditioners on antimicrobial properties and fungicidal concentration of AgNPs. The study concluded that minimum bactericidal concentration against *S.aureus*, *S. mutans* at 0.1% Ag^+ incorporated and minimum fungicidal concentration against *C. albicans* at 0.5% Ag^+ incorporated after a 24 hours and 72 hours incubation period[23]. Fanet al., 2011 investigated whether modified method can produce AgNPs *in-situ* in PMMA and bisphenol, a glycidyl methacrylate resin, release silver ions and deliver effective antibacterial activity. The study demonstrated that the modified process generated AgNPs *in situ* using the resin's own curing process. Silver ions release was detected but it gradually diminished overtime. The AgNPs loaded resins also demonstrated antibacterial activity against *S. mutans* [55].

The data revealed that addition of AgNPs did not significantly affect mechanical properties of acrylic resin and also prolonged antimicrobial property to the acrylic resin. This is important in dealing with microbial colonization under denture base. Since AgNPs don't affect the mechanical property of acrylic resins, the novel acrylic resin incorporated with AgNPs could be developed as a denture base. They can also be added in tissue conditioners which are routinely used for ill-fitting dentures that are occasionally susceptible to microbial colonization. Having these beneficial effects, AgNPs incorporation in these materials can solve the issues arising from microbial colonization particularly oral *Candida* infection.

4.2. Composite resins

AgNPs are combined with different materials due to their antimicrobial effect which decreases biofilm formation and maintenance of better oral health [56,57].Due to its smaller particle size, AgNPs penetrates through cell membranes more readily, resulting in damage and inactivity[58]. In order to avoid biofilm build up over composite and in the restorations margins, few researchers tried to evaluate the effect of AgNPs incorporated restorative materials composite resins [59–61] and adhesive systems [62–64].

Vazquez-Garcia et al.; 2016 evaluated the effect of addition of AgNPs on mechanical and antibacterial properties of calcium silicate cements like Mineral trioxide aggregate (MTA) and Portland cement (PC) associated with zirconium oxide (ZrO2). Results observed were that the PC/ZrO_2 + AgNPs had higher resistance for compression. This could be because of incorporation of AgNPs leading to decrease porosity. Both, MTA + AgNPs and PC/ZrO_2 + AgNPs depicted enhanced mechanical properties. Even at the end of 15 hours' period both showed higher reduction of test bacteria. Thus, addition of AgNPs showed favourable outcomes with calcium silicate cements [65].Composite resin containing silver ions have antibacterial effects on various oral bacteria e.g. *S. mutans* [66]. Ag^+ also influence the mechanical properties of various adhesive systems used with these composites [67]. However, the influence of these Ag^+ on polymerisation of these materials is scarce. Durner et al. observed the influence of AgNPs in composite resins on the production of elutable substances from light cure polymerisation hardened specimens. The amounts of these elutable components were roughly proportional to amount of AgNPs. Exception to this was the material with 0.05% of AgNPs. Thus the study concluded that AgNPs does have an influence on formation of these elutable ingredients during the light cure polymerisation method and this could be explained due to different mechanisms like photon reflection and scattering, electron interaction of AgNPs and light initiators, absorption and emission of photons by AgNPs, different complex of silver ions [17]. In comparison to other restorative materials, composites exhibit more biofilm formation on its surface in-vivo [68]. These biofilms are major reasons for secondary caries formation at the margins of the restoration which leads to failure [69]. To combat these, formulation of adhesive systems have been developed with antibacterial agents to prevent the issue of secondary caries[70]. Similarly, Li F et al., 2013 investigated a novel bonding agent with quaternary ammonium dimethacrylate (QADM) to a bonding agent having AgNPs for antibacterial activity. They also were evaluated for contact and long-distance inhibition. AgNPs resins depicted inhibitory action against *S.mutans* on its surface as well as at a longer distance compared to QADM bonding agent showing only contact inhibitory action. Fibroblast cytotoxicity and microtensile bonding strength were not affected by both the agents. Thus these novel agents demand more research validation and can find valuable applications as agents incorporated in restorative cements and carious preventive agents [71].Similar observations were done by Zhang K et al., 2012 who observed AgNPs and QADM containing adhesive attained strong antibacterial actions against biofilms without any effect on bond strength [72].

Another novel combination of AgNPs and amorphous calcium phosphate (NACP) was evaluated by Melo et al., 2013 for antiplaque efficacy and effect on bond strength. Viability of microcosm biofilm was reduced by this unique combination without any impact on its dentin bond strength. Thus rationale of having this combination is to have antibacterial action of AgNPs by reducing the acid production by microorganisms and remineralizing action of NACP which release of calcium and phosphate ions causing remineralisation of the affected dentin [62]. Zhang et al. 2013 studied the effects of biocompatibility of AgNPs for use as a restorative material. They incorporated AgNPs at 0.05% by mass, to a primer and an adhesive and tested it for human gingival fibroblast viability. It was observed that incorporation of AgNPs does not affect the cytotoxicity of primer and adhesive. Thus it can be used clinically as a biocompatible antimicrobial agent [73].

Cheng et al.; 2012 described the incorporation of AgNPs at different concentrations to a composite resin to investigate its effect on mechanical properties and biofilm formation. AgNPs with mass fractions of 0.028, 0.042, 0.088, and 0.175% were incorporated in composites. Mechanical properties of composites containing 0-0.042% of AgNPs matched those of a commercial composite without antibacterial activity. The amounts of dead microorganism were more with AgNPs incorporated composites. Lactic acid production of 0.042% AgNPs was 1/3 and colony forming unit counts (CFU) for total organisms were 1/4 respectively compared to those of commercial composites .This data suggests that AgNPs added composites are favourable for dental restorations with remineralizing and antibacterial capabilities especially at low concentrations [61] .

To have a have a maximum interaction with prokaryotic cell membrane and minimum with eukaryotic cells, it is important to immobilise AgNPs with biocompatible film of polymers. Thus lactose-modified chitosan also known as Chitlac can be one of the polymers which is used in minute concentrations for stabilisation of AgNPs [74]. Cataldi A et al., 2016 investigated adhesive and proliferation performance of human gingival fibroblasts (HGF) on triethylenglicoldimethacrylate (TEGDMA) and Bisphenol A glycidylmethacrylate (BisGMA) substrates with and without coating of AgNPs. It was observed that HGF had definite attachment with Chitlac-nAg and Chitlac. They also showed antibacterial activity in presence of AgNPs. Thus it could be concluded that this nanocomposite formulation can be used for surface coating various dental devices to prevent their failures due to infections [75].

Evidences suggest that microleakage on restoration margins provides gaps for the colonization by oral bacteria, resulting in secondary caries. This leads to restorative failure and need for restoration replacement. Problem can be averted by incorporation of antimicrobial agents like AgNPs to composite resins and adhesive systems **(Figure 3)**. However, question arises that whether incorporation of these nanoparticles affects the mechanical and biological properties of the composites? Data reveals that AgNPs incorporation to composite resins does not influence its mechanical and biological properties and it imparts notable antimicrobial property, even at low concentration. Thus, incidence of development of recurrent caries under composite resins due to microleakage can be reduced by the antibacterial effects of AgNPs-containing restorative materials.

4.3. Endodontic materials

Successful root canal treatment depends on elimination of bacteria [76] , materials used in its treatment should be able to eradicate these bacteria [77,78] to better the outcome of endodontically treated teeth [79]. Gutta-percha is the most preferred filling materials in root canal therapy [76].

Shantiaee et al., 2011developed gutta-percha with nanosilver coating and tested their microlekage in obturated teeth. Although the results were comparable to normal gutta-percha, nanosilver coated showed marginally less leakage than control [80].The main step to prevent recontamination of canal space is complete elimination of microorganisms with the diseased pulp tissue. Even though the use of cleaning instruments attempts to disinfect the canal, it still may not completely clean certain anatomy of the root canal system[81].Due to these shortfalls, different irrigants like sodium hypochlorite (NaOCl), Ethylenediaminetetraacetic acid (EDTA), Chlorhexidine (CHX) can supplement along with mechanical instrumentation for having a complete clean sterile canal. Various studies have proposed use of nanoparticles as irrigation systems for lavage of root canals[82,83]. Lotfi et al.; 2011 compared the antibacterial effect of AgNPs solution and sodium hypochlorite (NaOCl) against *E. faecalis*. It showed that in lower concentrations, AgNPs solution would possess the bactericidal effect similar to 5.25% NaOCl, so it can be a used as a new intra-canal irrigant [19]. Moghadas et al., 2017 also tested AgNPs based irrigant with NaOCl for antimicrobial efficacy. The novel concept with this AgNPs based irrigant was other than AgNPs, other two constituents added were sodium hydroxide (helps dissolve the pulp tissue with removal of smear layer enabling deeper penetration of AgNPs) and ethanol (decreases the surface tension facilitating ingress of AgNPs in the later canals and tubules of dentin). The potency of this AgNPs based irrigant was similar to 5.25 % NaOCl in elimination of *S. aureus* and *E. faecalis*. Thus AgNPs based irrigation solution can be used for root canal irrigation due to its deeper penetrating antimicrobial effect [84].

Abbaszadegan et al., 2015 formulated AgNPs having diverse surface charges and analyzed their antibacterial potential in comparison to CHX and NaOCl. Of all the tests agents, positively charged AgNPs exhibited lowest inhibitory concentration against *E. faecalis*. Also, in minor concentrations its activity was superior to other tested agents and depicted highly cytocompatible results. This showed that surface charge does play a significant role for antibacterial activity and can serve as a capable vehicle for root canal decontamination [85].

MTA finds varied application in pulp therapies, repair of perforations and furcation's, apical root sealers [86,87]. MTA even though effective against many organisms, may lack its activity against strict anaerobes. Few studies mention about antimicrobial result of MTA against certain microorganisms[78,88–90]. With the aim to improve antimicrobial potential Samiei et al.,2013 tested antibacterial effect of modified MTA by adding AgNPs, at 1% weight. Its effect against different bacteria and *C.albicans* were assessed. Results have showed that AgNPs-containing MTA possesses higher antimicrobial effect against bacteria and fungi compared to unmodified MTA[18]. Zand et al., 2016 similarly tested biocompatibility of white MTA in vivo by adding AgNPs to MTA and compared to white MTA without AgNPs by observing inflammatory reaction to both. Both test agents were implanted subcutaneously in connective tissues of rats. The overall inflammatory reaction was similar at the end for both groups. Thus author concluded that, addition of AgNPs (1%) to MTA does not affect *in vivo* reaction of inflammation.[91]

Recently Alabdulmohsen et al. evaluated a novel medicament of calcium hydroxide [$Ca(OH)_2$] and AgNPs as a combination in comparison to AgNPs and $Ca(OH)_2$ medicaments alone against *E. faecalis* in root canal therapy. It was observed that $Ca(OH)_2$ alone showed better results in comparison to AgNPs alone or AgNPs + $Ca(OH)_2$. The conclusion from this experiment was antibacterial efficacy of AgNPs was inferior to $Ca(OH)_2$ or AgNPs + $Ca(OH)_2$. The reasons for these results could be influenced by different methods of application, varied concentrations, and diameter of the particles. Also, one agent (AgNPs) may be antagonizing the action of other agent Ca $(OH)_2$. González-Luna et al., 2016 investigated the bactericidal outcome of irrigation solution having AgNPs as a final irrigant in instrumented canals. It was observed in this study that *E. faecalis* like previous study was eliminated by AgNPs based solution with similar potency to NaOCl. But in this experiment NaOCl at 2.25% was comparative in action to AgNPs irrigants compared to NaOCl with

5.25% in previous study. The authors observed that even though both these solutions were efficient in terms of their antibacterial activity, irrigants with AgNPs showed added benefit of smear layer removal which may potentiate the penetration action of the irrigants. The novel part of this study was that uniradicular teeth used were used in a protocol similar to the one used in actual clinical set-up. This helps enhanced observational analysis of bacterial performance and their actions [92].

Above studies have demonstrated that residual bacteria in root canal are associated with potentially higher rates of treatment failure. Thus, elimination of bacteria in root canals is a key to the treatment success. Since most of endodontic materials do not possess any antimicrobial activity [96, 97], incorporation of AgNPs in root canal filling materials and intra-canal irrigation could be explored further.

4..4. Periodontology

Biofilms of oral cavity exists as polymicrobial communities of bacteria, yeasts resulting in infections of the gums and teeth [93]. Biofilms consists of mix of aerobic and aanaerobic species responsible for dental caries and periodontal disease and abscess [94,95].Removal of these biofilms will prevent the periodontal infections and future tooth loss. Mechanical therapy can be complemented by adjunctive antimicrobial agents [96]. Due to structural integrity of these biofilms , they provide resistance to antimicrobials[97]. Thus, there is an urgent need for developing agents which possess antibacterial properties without generation of resistance. As AgNPs have shown to have antibacterial action against gram negative organisms[98,99] , this review will discuss the studies of AgNPs in periodontal infection prevention and its influence on tissue healing for periodontal regeneration.

Frankova et al., 2016 investigated the effects of AgNPs on fibroblasts, keratinocytes and also on interleukins, growth factors and matrix metalloproteinases. The study found that

AgNPs reduced inflammatory cytokines like IL-12,NF-α and growth factors (vascular endothelial growth factor) after 1-2 days and reduced COX-2 after one day only at maximum concentration of AgNPs [49]. Panácek et al., 2016 investigated bactericidal effect of AgNPs combined with selected antibiotics. The study revealed that there was synergistic effect when AgNPs are combined with antibiotics; resulting inreduction of MICs of the antibiotics at concentrations below 1 mg/L. In addition, antibiotics ineffective against multi-resistant bacterial strains showed bactericidal effect when combined with AgNPs. [100]

Velusamy et al. investigated anti-bacterial, anti- biofilm effect of carboxymethyl cellulose and sodium alginate capped AgNPs. The study demonstrated that carboxymethyl cellulose capped AgNPs were more effective at preventing the growth of gram negative organisms compared to gram positive bacteria while sodium alginate AgNPs exhibited more inhibition for gram positive in comparison to gram negative [101]. Thus, AgNPs can prove to be effective against periodontal infections which are predominantly caused by gram negative bacteria. Lu et al., 2013 investigated influence of size of AgNPs on its antibacterial activity. Different particle size of AgNPs had diverse antibacterial activity against oral anaerobic bacteria; with 5-nm size AgNPs having the best antibacterial activity [102]. Ibrahim HMM; 2015 aimed to synthesize AgNPs from an extract derived from banana peel waste and observe its antimicrobial effect on human pathogenic organisms. AgNPs were more effective against gram negative bacteria *(E. coli and P.aeruginosa*) than the Gram positive bacteria *(B.subtilis and S. aureus*). AgNPs also had synergistic effect on the antimicrobial activity of levofloxacin against Gram-positive and Gram-negative bacteria.[103] Rani et al., 2015 conducted a study to investigate the colonization and penetration of specific bacteria [*S. mutans, Aggregatibacter actinomycetemcomitans (A.a), F. nucleatum and Porphyromonas gingivalis*] on AgNPs impregnated guided tissue regeneration membranes. Results showed that mean bacterial adherence scores and CFUs were lower with these membranes and statistically significant [104].

Habiboallahet al., 2014 investigated the effect of AgNPs synthesized by chemical reduction method incorporated in periodontal dressing on gingival wound in white adolescent female rabbits. Periodontal dressings A (25% v/v) and B (50% v/v) of AgNPs concentrations were used to analyze the optimum concentration of AgNPs dosages on healing of periodontal wounds post-surgery. Untreated wound was taken as controls for the study. Histologic changes for evaluation of repair and regeneration changes were observed at after 4 and 7 days. Compared to controls, AgNP group exhibited relatively less inflammatory cell infiltration and new collagen synthesis with marked neovascularization. As AgNPs have biocompatibility, they can be safely administered in the form of local drug delivery, or incorporating it in periodontal dressing, GTR membranes etc. However, more *in vitro* and *in vivo* studies are required with long term follow ups for evidence based applications.[105]

4.5. Porcelain for crowns and bridges

Dental porcelain is the most popular material used for fixed prosthesis due to good biocompatibility, mechanical durability and aesthetics similar to natural teeth [106]. However, on application of excessive masticatory force, it may chip or fracture due to lack of malleability or ductility. Reinforcing porcelain with metal particles have been recommended to enhance fracture toughness and prevention of crack propagation. This could be due to exchange of ions between reinforced metal particles with porcelain[107].This review attempts to highlight effect of incorporation of AgNPs on mechanical properties of dental porcelain**.**

Fujieda et al., 2012 studied the effect of silver and platinum nanoparticles on fracture resistance of porcelain. Fracture toughness and young’s modulus increased with addition of both nanoparticles [108]. They also investigated the influence of AgNPs on the behavior of subcritical crack growth of porcelains by post-indentation method. Study discovered that with increased concentration of AgNPs, the fatigue parameter increased. Also time required for slow crack growth to occur became shorter and crack growth amount also reduced.[109] Uno M et al., 2012 investigated introduction of silver and potassium ions on the mechanical properties of computer-aided design & computer-aided manufacturing (CAD/CAM) blocks by a commercial staining slurry. They got improved while crack length decreased[110].Mohsen C et al., 2015 evaluated effect of AgNPs on color and fracture strength of ceramics. It concluded that addition of AgNPs increased the fracture strength but adversely affected the color of dental ceramic [111]**.**

Thus, studies have demonstrated that incorporation of AgNPs inside porcelain improves its mechanical properties. It improves its fracture resistance and decreases length of the crack. This simply implies that AgNPs have a potential to tackle problems associated with porcelain.

4.6. Titanium dental implants

Dental implant is one of the most predictable treatment options for replacement of missing teeth and is preferred over traditional removable prosthesis or fixed bridges. Mechanical and biological factors play a key role in long-term success of implant therapy[112]. In spite of being biocompatible, titanium implants can still fail due to biofilm formation along the implant surface. It is known as peri-implant infection which may cause discomfort to the patient [113]. Thus, strategies like antibacterial films needs to be developed on titanium surface to prevent adhesion of the bacterial colonies eliminating peri-implant diseases. Implementation of AgNPs coatings have been performed in various experiments as a source of bioactive material for implant surfaces.

Cao et al., 2011 investigated role of silver plasma immersion ion implantation (Ag-PIII) on commercial pure titanium to control and assess its actions of AgNPs on *S. aureus* and *E. coli* bacteria and osteoblast-like mammalian cell lines e.g.MG63. One-step silver plasma immersion ion implantation process, embedded AgNPs in titanium which precipitate on and underneath the titanium surface. Samples prepared by this process showed higher inhibition potential against both S. aureus and E. coli strains. At the same time, it also promoted proliferation of the osteoblast- like cell line MG63. These may be due to the micro-galvanic couples that are formed by the AgNPs and titanium matrix. This in turn must have played an important role in the potential interaction between nanoparticles and the attached cells. The present study demonstrated a novel technique of the AgNPs application and their concurrent biological activity. This is important as surface cytotoxicity is directly dependant on the physico-chemical characteristics of the AgNPs.[114]

Wanget al., 2013 evaluated bactericidal effect of unique silver nanostructure on the metallic titanium surface using in situ model. The study demonstrated that AgNPs filled hydrogen titanate ($H_2Ti_3O_7$) nanotube-layered titanium foils exhibited high bacteriostatic activity of 99.99% also showing long-term silver ion release capability. AgNPs located in hydrogen titanate nanotubes have shown to release enough Ag^+ to impart the long-term bactericidal action. In comparison to the pure titanium, titanium foil with AgNPs hydrogen titanate nanotube layers demonstrated increased osteogenic potential and good cytocompatibility. The presence of OH- molecules on the surface potentially provided excellent cytocompatibility and high osteogenic potential to the nanotubes. This showed that unique AgNP-filled H2Ti3O7 nanotube coating can impart antibacterial activity as well as excellent cell biocompatibility to the titanium surfaces [115].

Marsich et al., 2013 investigated the antimicrobial potential of Chitlac–nAg system. In addition to that it was tested for its potential property to prevent the developed biofilm on the surface of BisGMA/TEGDMA samples coated with Chitlac–nAg in comparison with uncoated ones. The third objective of the study was to observe the long-term stability of the potential antibacterial activity of coated material, after samples were immersed in physiological saline solutions. The antimicrobial activity was tested against *S. aureus* and *P. aeruginosa* for the fact that they the most prevalent in biofilm-associated infectious diseases. The study was able to demonstrate that Chitlac–nAg system has a moderate antibacterial property against the tested microbes. Also, the anti-biofilm action is not affected by conditioning layer formed by the proteins on the Chitlac–AgNP coated surface. Even though washing the Chitlac–nAg-coated samples with normal saline caused a steady release of silver from the coating, it still showed a significant antimicrobial activity for at least 3 weeks. This time-span is important for short-term protection from perspective of early peri-implant infections. Having acceptable biocompatibility and no significant adverse bone reaction, this novel material has a potential for certain clinical applications especially in situations where conventional metallic implants are contra-indicated [116]. Zhu et al., 2015 investigated potential antimicrobial of sandblasted large grit and acid etched (SLA)treated titanium to produce micro/nanostructural surfaces coated with AgNPs against the commonly suspected oral pathogens. Additionally, their biocompatible properties were also tested on rat bone marrow mesenchymal stem cells (r-BMSCs). Immobilized AgNPs on acid etched titanium surfaces demonstrated no cytotoxicity. At same time these nanoparticles were able to inhibit the growth of both *F.nucleatum and S. aureus*. Having comparatively less rigid cell wall structure, *F.nucleatum* showed an elevated susceptibility to AgNPs. Antibacterial efficiency of the materials remained unaffected even after incubation in PBS for 1 month or exposure to several cycles of bacteria. This implies that the antimicrobial activity of immobilized AgNPs was independent of silver release. Results of this study suggested that titanium implants with hierarchical micro/nanostructures possess balanced antibacterial and osteogenic functions.

This makes them safe for the clinical applications [117]. Zong et al., 2016 investigated the long-term biocompatibility and antimicrobial efficacy of AgNPs-containing multilayer coating on the phase-transited lysozyme-primed Titanium surfaces. Authors suggested that their strategy of coating titanium surface using phase-transited lysozyme (PTL) can provide an extremely facile, green and powerful approach in contrast to conventional time-consuming chemical synthesis and costly processing titanium surface preparation strategies. Thus, authors concluded with the layer of PTL strategy, it is possible to fabricate multilayers loaded with osteogenic growth factors, cytokines or functional components and antibacterial agents on titanium surfaces. This in turn help in preventing implant associated infection and promote early osseointegration of an implant. This also aids in fabricating AgNP coatings on various medical devices by use of the substrate-independent PTL as the base layer[118]. Chenget al., 2016 investigated the role of controlled release of Silver (Ag) and Strontium (Sr) from the nanotubular (NT) assembly loaded with both Ag and Sr (NT–AgSr). Further its role in ossteointegration and new bone formation both in a bone defect model and osteoporosis condition and as well as potential long-term antibacterial properties was assessed. Anodized and hydrothermally treated titanium implant surfaces to deposit nanotube coatings loaded with Sr and Ag exhibited prolonged Sr and Ag release from the NT–Ag.Sr samples showing no apparent cytotoxic effects. These surfaces also displayed excellent and long-lasting antimicrobial and anti-adherent properties against methicillin-resistant S. aureus as well as Gram-negative bacteria such as E. coli and methicillin-sensitive S. aureus. The accelerated bone fill by Nt-Ag.Sr was observed owing to properties like ability to repair the damaged cortical bone and increase in trabecular microarchitecture. Fabrication of titanium implants with NT–Ag.Sr surfaces is can possess potential clinical use as bone implants as they possess excellent osteogenic and antibacterial properties[119].

AgNPs incorporation to implant surface has demonstrated the long-term beneficial effects by virtue of its antibacterial properties. Additionally, AgNPs coatings have shown least cytotoxicity. In fact, it possesses a proliferative effect on osteoblasts opening up a whole new avenue for its role in osseointegration.

4.7. Orthodontic cements and adhesives

Patients undergoing orthodontic therapy are more prone for white spot or caries formation. This is due to plaque formation around the orthodontic brackets due to ineffective self-cleaning ability and accumulated acidogenic oral flora. [120] This oral biofilm can also cause caries or demineralisation around the brackets.[121] The major treatment aspect to deal with this problem is the mechanical removal of plaque biofilm along with use of antimicrobial agents and fluoride.[122] Due to its antimicrobial action, AgNPs have been used in Orthodontics either to prevent demineralization of enamel or adhesion of microorganisms. These have been used as coating on orthodontic brackets and in cements or adhesives to improve bond strengths and prevent caries or white spot formation.

Ahn et al., 2009 investigated the consequence of adding various concentrations of AgNPs to composite adhesive having silica nanofillers. Based on observations from this study, incorporation of AgNPs considerably reduced the adhesion of streptococci to orthodontic adhesive in comparison to conventional adhesives, without altering shear bond strength.[123] Moreira et al., 2015 developed a novel cement with AgNPs as an antimicrobial agent for orthodontic band. The major rationale was to observe efficacy to prevent formation of white lesions. The AgNPs were generated in-situ in the resins. AgNPs incorporated resin showed bacterial inhibitory action due to sustained release of Ag^+ ions. The mechanical properties were not affected with exceptional biocompatibility. Thus AgNPs incorporated cements could be used for orthodontic cases to prevent white spot lesions [124]. Sodagar et al., 2016 similarly tested antimicrobial effect of combination of AgNPs with hydroxyapatite

(HA) amalgamated in adhesive used for orthodontic application. AgNPs have shown to have antibacterial effect but the reason to choose HA in this experiment is its remineralizing potential of initial lesions of the enamel[125]. Three different concentration of combinations were tested (1%, 5%, 10% w/w). Of all three, 5% w/w AgNPs/HA exhibited superior most antimicrobial action against tests bacteria. Thus, addition of 5% composite (AgNPs/HA) to adhesives used in orthodontic intervention decreases cariogenic microbes and prevents biofilm formation [126]. Previous study by Akhavan. A et al., 2013 investigated effect of same combination of AgNPs/HA on shear bond strength (SBS) of adhesive used for orthodontic treatment. It was observed that 1% and 5% AgNP/HA increased and maintained shear bond strength respectively whereas 10% decreased SBS. This indicates that 5% AgNPs/HA offer appropriate antimicrobial and mechanical properties for orthodontic adhesives [127].

Although application of AgNPs in orthodontics is still at primitive stage, there is a huge potential for the research in this area including incorporation of them in orthodontic bonding material for its antimicrobial action, possible nano-vector for gene delivery for mandibular growth stimulation. With more studies coming up we hope that these technologies will demonstrate actual clinical applications soon. This is important as these clinical applications can improve quality of orthodontic treatment as well as reduce the cost of it for orthodontist and patients alike.

4.8. Anticancer treatment

Off all the malignancies diagnosed, 6% is by head and neck squamous cell carcinoma [128,129]. Almost 40% of these are from the tongue or floor of mouth. Those with advanced tumors or metastases have poor prognosis [130]. The incidence of cancer and mortality has not improved appreciably in spite of early diagnosis, combinations of radiotherapy, surgical interventions and chemotherapy [131]. The oral squamous cell carcinomas cause functional disability and severely affect the aesthetics of orofacial areas [132]. Radiotherapy and chemotherapy also has adverse effects on various systems affecting the homeostasis [133]. For similar reasons adjunct treatment options needs to be explored to overcome the drawbacks caused by these anticancer therapies. Different types of nanoparticles have been used in medicine and dentistry however their role in treatment of malignant tumors still lacks complete validation. For cytotoxic effects of AgNPs, they are able to cause DNA damage and apoptosis. They may also affect the normal cells [134,135]. However, evidence of AgNPs for cancer therapy is still lacking. AgNPs potential for tumor therapy at various concentrations needs further research.

Venkatesan et al., 2017 developed chitosan-alginate-AgNPs composites to observe the anticancer efficacy. Results showed there was a considerable increase in apoptotic cell levels with chitosan-alginate-AgNPs composite compared to controls. This indicates that there must have been apoptosis induction by the AgNps within the composite. The reasons for causing apoptosis could be due to initiation of reactive oxygen species or increase of oxidation stress. Thus, AgNP showed a great potential to be utilized for anticancer treatment [136]. Dziedzic et al., 2016 evaluated effect of low dosages of AgNPs on malignant oral epithelial cells and tested *in vitro* for their viability and proliferation efficiency along with berberine. The viability of cancer cell line was reduced by AgNPs at low doses. The natural product berberine decreased the proliferation of these cells. These findings shows that AgNPs along with berberine could serve as a potential composite for anticancer therapy[137].

Different methods have also been used for formulation of AgNPs [138]. Surface alterations permit precise targeting of tumor cells. Muazzam et al., 2011 synthesized stable and biocompatible AgNPs from silver nitrate in sucrose solution and were tested for anticancer potential. The novel methodology of green route methodology for AgNPs showed immediate inhibitory effect on cancer cells. The normal cells remained unaffected. Thus

AgNPs synthesized with this novel method can be an innovative therapies of tumors [139]. The data suggests that the targeted AgNPs based drug delivery system to cancer affected site can prove beneficial as it will reduce turmoil to the patient. These molecules can also be used for the early detection of the cancer and thus physician will have a significant option to start treatment immediately. Most importantly, as nanocarrier specially targets the cancerous cell, the normal cells are not affected thus minimizing the side effects associated with conventional chemotherapy.

5. Studies of AgNPs in relation to animal models

Various studies have been performed to assess the in vivo effect of AgNPs in relation to various animal models. Boudreau MD et al., 2016 investigated the distribution patterns of AgNPs and Silver acetate (AgOAc) of varied particle sizes in rats. Irrespective of the form or particle size, Ag+ ions were discovered in tissues with similar pattern of distribution. AgOAc showed higher affinity for extracellular membranes while AgNPs for cells. Female rats showed higher accumulations in kidneys and liver.[40]. Jeong GN et al., 2010 investigated the effects of AgNPs on the histological structure of intestinal mucosa of rats. Dose dependent higher amounts of AgNPs was detected in small and large intestines. It was concluded that AgNPs stimulate the release of mucus granules in goblets cells of intestines. [41]. Zand V et al., 2016 carried out a study to assess inflammatory response of MTA with and without AgNPs by connective tissue of rat. Addition of AgNPs (1%) did not have any major impact on inflammatory reaction on subcutaneous tissues of rats.[91]. Habiboallahet al., 2014 investigated the effect of AgNPs containing periodontal dressing on gingival wound in white adolescent female rabbit's models. Periodontal dressing A (25 % v/v) and dressing B (50 % v/v) of AgNPs were evaluated against control (wound without any dressings) on gingival wound healing. Incorporation of AgNPs proved to have a better effect on healing of gingiva. Thus, AgNPs incorporated dressings can be used post periodontal surgery due to biocompatibility.[105]. Takamiya AS et al., 2016 investigated the connective tissue reaction of rats to various types of AgNPs. These AgNPs were formulated with polyvinylpyrrolidone or ammonia with average particle size of 5nm. Both types of AgNPs at concentrations of 25ug/ml or lower were nontoxic and histologic examination revealed similar response compared to controls.[48] Even though AgNPs have shown promising results in animal models, further investigations establishing complete biocompatible profile is highly recommended.

6. Conclusions

AgNPs display distinctive biological properties unlike other biomaterials routinely used in dentistry and can serve as a novel application in restorative dentistry, prosthetic dentistry, endodontics, implantology, oral cancers and periodontology. AgNPs holds immense potential due to their antimicrobial, antiviral, antifungal actions. Incorporation of AgNPs prevents biofilm build up over composite avoiding microleakage and secondary caries. It enhances the mechanical properties of a restorative material and improves overall bonding between dentin and biomaterial affecting the bond strength. AgNPs decreases the microleakage in root canal system and can be used as canal irrigant similar to sodium hypochlorite. Its use with acrylic resins have shown its antifungal property and decreased chances of denture stomatitis. Can be favorably used to form antibiocidal surface coating over titanium implants preventing periimplantitis and has shown potential for osteogenic differentiation. Experiments have revealed that AgNPs possess anticancer activity. AgNPs incorporated adhesive systems can be used in orthodontic treatments to prevent white spot lesions. *In vitro* research depicted that these nanoparticles prevent crack propagation and improves the fracture toughness with dental ceramics which will negate the cracking of porcelain restorations with crowns and bridges and veneers. Periodontal diseases can be prevented by use of AgNPs action against gram negative bacteria and stimulate regeneration as they have been revealed to be biocompatible with mammalian cells. Even though AgNPs have shown to be effective for its incorporation with dental biomaterials, most of the studies done are in vitro experiments. For AgNPs to be actually used in clinical applications, in-vivo results with long-term data are necessary. In spite of benefits of AgNPs, research on long-term in-vivo results, methods of AgNPs incorporation and characterization and data on its long-term antibacterial action is the need of the hour for its clinical applications.

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Figure captions:

Figure 1. Applications of silver nanoparticles used for biomaterials.

Figure 2. Steps of antimicrobial action of silver nanoparticles. (A) AgNP diffusion and uptake into the bacterial cell: Accumulation and dissolution of AgNPs at plasma membrane cause cell leakage. (B) Destabilization of Ribosomes: denatures ribosomes inhibiting protein synthesis and plasma membrane degradation. (C) Enzyme interaction: AgNPs bind with the thiol group (-SH) in the respiratory enzymes and deactivate them. (D) Interruption of electron transfer chain: AgNPs interfere with electron transport affecting signaling pathway. (E) Reactive oxygen Species(ROS): Mitochondrial damage induces ROS which oxidizes proteins. (F) DNA Damage. AgNP binds with DNA preventing its replication and multiplication causing apoptosis. (G) Cell Death: Formation of pits and perforations in cell membrane leads to release of cell organelles and cell death.

Figure 3: Incorporation of AgNPs to Composite resins and Adhesive system eradicates the biofilm organisms and prevents loss of tooth structure. It prevents the microleakage increasing the longevity of restoration.

Table caption:

Table 1- Application of Silver Nanoparticles for various biomaterials used in dentistry

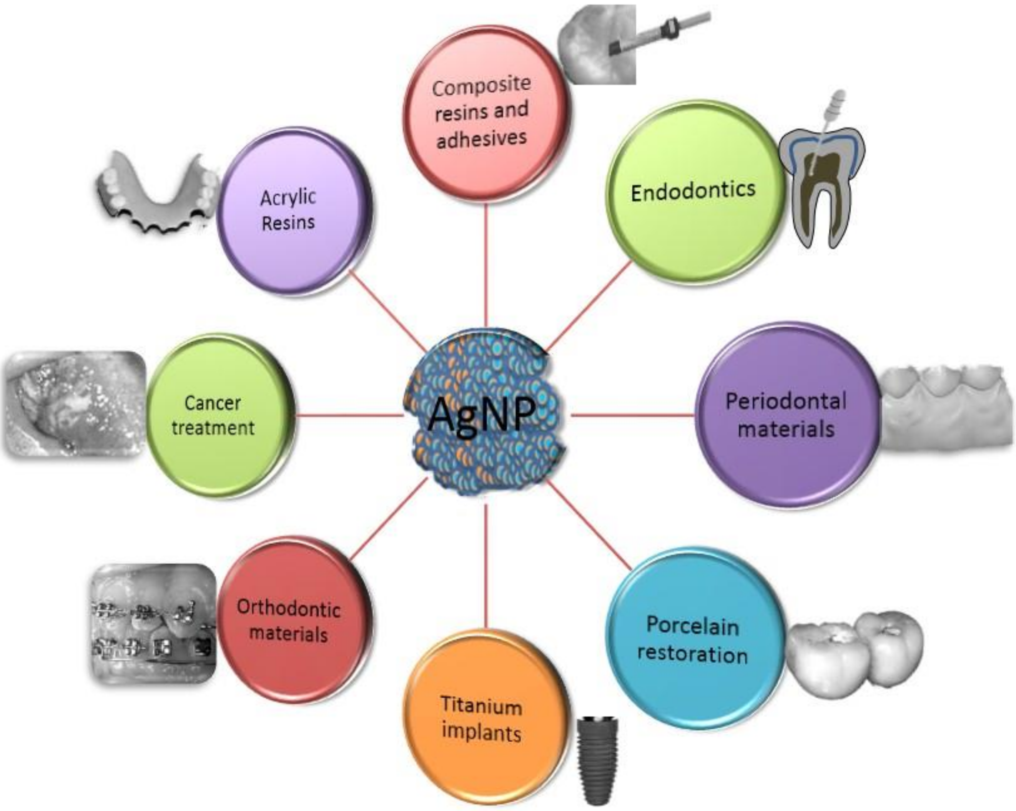
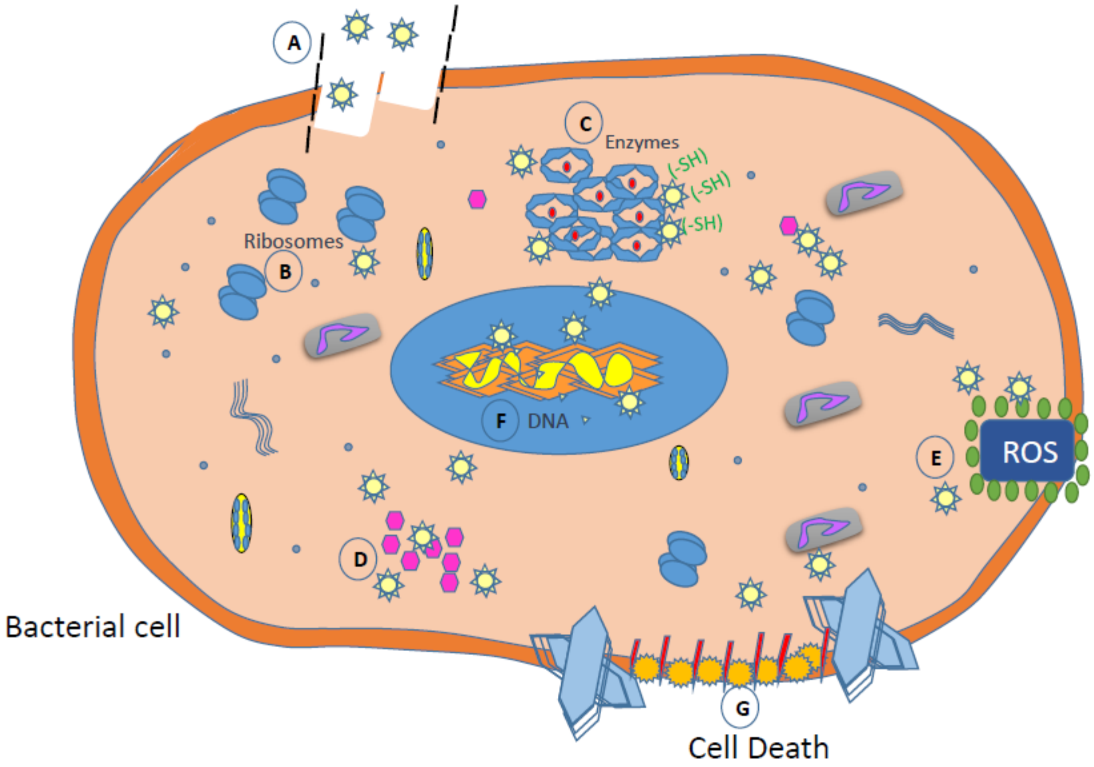

Composite resins and adhesives
Endodontics
Acrylic Resins
Cancer treatment
AgNP
Periodontal materials
Orthodontic materials
Titanium implants
Porcelain restoration

Figure 1


A
Enzymes
C
(-SH)
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Ribosomes
B
F
DNA
E
ROS
D
Bacterial cell
G
Cell Death

Figure 2

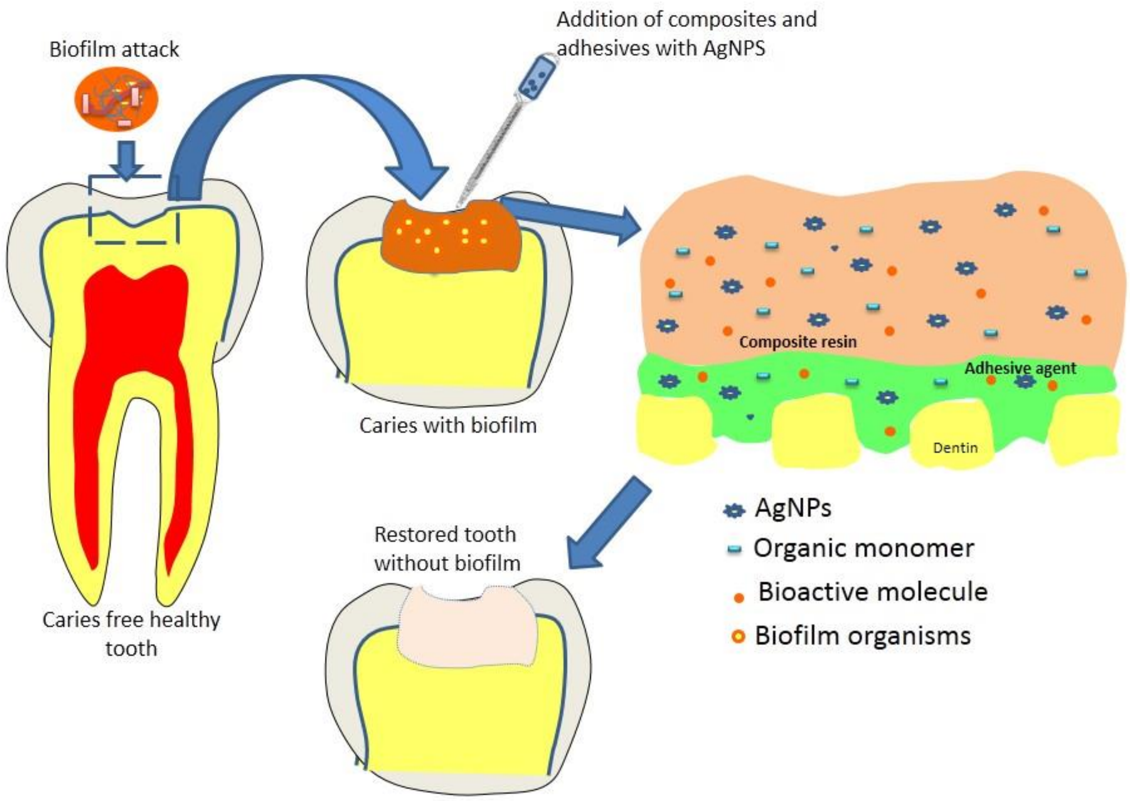
Biofilm attack
Addition of composites and adhesives with AgNPS
Caries with biofilm
Composite resin
Adhesive agent
Dentin
AgNPs
Organic monomer
Bioactive molecule
Biofilm organisms
Restored tooth without biofilm
Caries free healthy tooth

Figure 3

Table 1- Applicationof Silver Nanoparticles for various biomaterials used in dentistry

Objective	Type of study	Method of Preparation	Characterization parameters	Concentration of AgNP (in % or ugs) influencing mechanical, antimicrobial and antifungal properties of materials.	Inferences	Ref.
1] Acrylic resins for dentures						
To investigate the effect of silver nanoparticles on mechanical properties of conventional heat polymerized acrylic resin and microwave polymerized acrylic resin	*In vitro*	Prepared by Turkevich method using thermal and microwave irradiation polymerization.	TEM analysis showed that prepared AgNP were Spherical in shape with average diameter of 68 nm. Presence of AgNP in microwave polymerized resins significantly decrease elastic modulus and flexural strength. Similarly, thermal analysis revealed decrease in intra and inter molecular forces within polymeric matrix.	**Mechanical properties** Microwave-polymerized resins with *0.3 wt%* of AgNPs showed highest flexural strength and elastic modulus Heat-polymerized resin with 0.6 wt% AgNPs showed lowest values. While adding 0.8 nd 1.6 wt% AgNPs in the microwave-polymerized resin significantly decreased and elastic modulus	Incorporation of 0.8 and 1.6 wt% AgNPs decreased flexural strength and elastic modulus for resin group but no effect on heat polymerized resin group. Addition of AgNPs decreased the glass transition temperature for both groups without any affecting the impact strength.	[52]
To explore the effect of	*In vitro*	Light-cure and chemical-	Durometer hardness	**Antibacterial** AgNP-	Addition of	[53]

AgNPs incorporated in PMMA on mechanical and antimicrobial properties.		cure systems were used to synthesize AgNP-PMMA denture resin.	and Ultimate Transverse Strength (UTS) study showed that AgNP-PMMA was softer and lower UTS compared to PMMA control. Ag release was studied for 28 days; however, plateau was observed after 7 days.	PMMA resins with *1% w/w* AgBz (silver benzoate) and extra benzoyl peroxide (B) and dimethyl-p-toluidine (D) [1.5B:0.5D] and [1B:1D] showed long term *in vitro* antimicrobial activity.	AgNPs lead to improvement in the mechanical and anti-bacterial properties of PMMA.	
To observethe outcome of AgNPs incorporated in PMMA on biocompatibility and anti-fungal properties.	*In vitro*	AgNP was prepared by reducing $AgNO_3$ via plant infusion and incorporated in during PMMA synthesis by suspension polymerization technique.	TEM results showed spherical nanoparticle with the size range of 10-20nm. A flexural strength test showed Mean flexural modulus (GPa) and flexural strength (MPa) of AgNP-PMMA was higher than commercial acrylic resin, Nature Cryl^{TM}.	**Antifungal property** Concentration of 1 µg/mL of silver nanoparticles in PMMA-silver nanoparticle discs was found to have antifungal activity without any cytotoxicity and genotoxicity.	Addition of AgNPs lead to decreased adherence of *C. albicans* and exhibited no cytotoxicity and genotoxicity.	[32]
To observe the effects of AgNPs in tissue conditioners on antimicrobial properties, minimum bactericidal concentration and minimum fungicidal concentration of silver nanoparticles.	*In vitro*	Silver nanoparticles were prepared by gamma irradiation using $AgNO_3$ and polyvinyl pyrrolidon (stabilizer).	TEM analysis showed average size of AgNP was in the range of 100-120nm.	Weight percentages *Ag^+: 2.5 wt%;* Zn^{2+} : 14.5 wt%; $NH4^+$: 2.5 wt%, H_2O: 16-18 wt%	tissue conditioners containing SZ have antimicrobial effects on *C. albicans* and nosocomial respiratory infection-	[23]

					causing bacteria, *S. aureus* and *P. aeruginosa*, and that this effect may be found *in vitro* after four weeks of immersion in saliva	
To investigate whether a modified method can produce AgNP in-situ in resins and release silver ions to produce antibacterial action.	*In vitro*	AgNP synthesized in-situ inlight cure (LC) and chemical cure (CC) dentalresin via curing method.	The colours of dental resin become darker due to presence of AgNP. Rockwell hardness of CC was not affected by presence of Ag while hardness of LC was decrease with increase in Ag concentration. Nanoparticles cluster was observed in LC resin while nanoparticles distributed evenly with less cluster in CC. In CC the release of Ag was detected at every concentration while in LC Ag was detected when resin made with 0.1% of AgNPs.	**Mechanical properties** Concentration of *0.15% (w/w)* Ag benzoate(AgNBz) was the maximum which could be light-cured and for specimens for chemicaly curable resins, concentration of 0.6% (w/w) AgBz was the highest. Hardness of light cured resins decreased with concentrations AgBz reaching 0.1% (w/w) and above. Chemical cured resins were harder than the light cured resins above *0.2%* AgBz. For LC specimens, Ag+ ion release with light cured	The study demonstrated that the modified process generated AgNPs in- situ using the resin's own curing process. Silver ions release was detected but it gradually diminished overtime. The silver nanoparticles loaded resins also demonstrated antibacterial activity against *S. mutans*.	[55]

				resin was easurable only resins made with *0.1%* AgBz. Resin having *0.5%* AgBz inhibited 97.5% and those made with *0.2%* AgBz inhibited 52.4% of the growth of S. mutans		
2] Composite Resins						
To analyse the consequence of adding AgNPs to calcium disilicate cements' mechanical properties.	*In vitro*	AgNP was synthesized by chemical reduction method using NaBH4 and capped with polyvinyl alcohol. These capped nanoparticles were incorporated in dental cements (PC 70%/ZrO2 30% or to WMTA)	Radiopacity of PC/ZrO$_2$ and WMTA/AgNPs was higher, the lowermost radiopacity wa sdetected for PC/ZrO2/AgNP. Compressive strength of dental cements was increased by incorporation of AgNP.	AgNP particle size was 4-11nm.	Incorporation of AgNPs to these cements improved their mechanical and physiochemical properties	[65]
To evaluate effect of AgNP incorporated in composites on formation of elutable substances from light cure polymerisation process.	*In vitro*	Commercial AgNP was dispersed in Tetric Flow and polymerize using an Astralis 10® light source.	Not available	**Polymerization process of composites:** 0.0125, 0.025, 0.05, 0.1 and 0.3% by weight silver nanoparticles were added to composite. 24 hours later the elutable compounds were detected	Addition of AgNP to light cure polymerized composites may cause increase in elutable substances.	[17]

				with *0.3%* AgNP.		
To analyse bonding materials having quaternary ammonium dimethacrylate (QADM) and compare with bonding material having AgNP for cytotoxicity and antibacterial properties.	*In vitro*	Quaternary ammonium dimethacrylate (QADM) was synthesized by modified Menschutkin reaction. Silver 2-ethylhexanoate salt was dissolved in 2-(tert-butylamino) ethyl methacrylate and then added to Scotchbond Multi-Purpose bonding system (SBMP) primer. Finally added to adhesive to make composite.	TEM results showed uniform dispersion of Ag in dentin with the particle size of 2.7nm. Presence of Ag doesn't affect the microtensile bond strengths of composites.	**Antibacterial property:** AgNP filler levels of *0.05%* in primer and adhesives presented strong antibacterial properties without decreasing microtensile dentin bond strength.	The AgNP containing adhesive exhibits long distance as well as contact inhibitory effect whereas QADM-adhesive exhibits inhibition of organisms on its surface only. Fibroblast cytotoxicity and microtensile bonding strength remained unaffected by both the adhesives.	[71]
To investigate antibacterial efficacy and bond strength of adhesive with AgNP and amorphous Calcium phosphate	*In vitro*	Silver 2-ethylhexanoate salt was dissolved in 2-(tert-butylamino) ethyl methacrylate and then added to SBMP primer. Nanoparticles of amorphous calciumphosphate (NACP) was prepared by	Dentin shear Bond strength of AgNP containing primer and adhesive similar to control while presence of NACP increase the bond strength. SEM images revealed that prepared resins	**Antibacetrial property** Mean particle size of AgNP was 2.7nm. AgNP were added at *0.1%* by mass into adhesive and primer which reduced the metabolic activity of biofilm by 50% without reducing the dentin bond	Biofilm viability was substantially reduced by this novel combination without affecting the bond strength	[62]

		spray drying method by using dicalcium phosphate anhydrous and calcium carbonate. Finally, the NACP was mixed with adhesive containing AgNP.	were well filled and nanoparticles well filtered into dental tubules.	strength		
Evaluation of effects of biocompatibility of AgNPs for use as a restorative material	*In vitro*	12-methacryloyloxydodecyl pyridinium bromide (MDPB) and AgNP was incorporated into SBMP primer.	Dentine shear bond strength was not affected by incorporation of MDPB and AgNP.		Can be used as a biocompatible and antimicrobial agent	[73]
To explore the influence of AgNPs on dental plaque and properties of nanocomposite material.	*In vitro*	Spray drying method was used to fabricate NACP. NACP was incorporated into TEGDMA (triethyleneglycol dimethacrylate and BisGMA(bisphenolglycerolatedimethacrylate) resin. Similarly, QAS and AgNP was also incorporated in resin and finally the resins were photo- polymerized.	Particle size of formulated NACP and AgNP was 116nm and 2.7 respectively. TEM analysis showed uniform distribution of nanoparticles in resins. The resin with NACP showed lower flexural Strength.	**Antibacterial and cytotoxicity** AgNP were added at *0.05%* by mass fraction with the primer had potent antibacterial activity without affecting the bond strength. Also, fibroblasts viability was 100% proving it to be biocompatible.	AgNPs decreased biofilm formation and improved the mechanical properties of nanocomposites	[60]
						[75]
3] Endodontic materials						
Comparative analysis	*In vitro*	Ag NP was produced by catalytic chemical	Prepared nanoparticle are spherical with 35nm	**Antibacterial action and**	In lower	[19]

between AgNP, chlorhexidinegluconate (CHX) and sodium hypochlorite (NaOCl) for antibacterial action.		vapours deposition procedure and then dispersed into water.	average diameter.	**cytotoxic levels as intracanal irrigant in endodontics** AgNP in concentration of 50 *µg/ml (0.005%)* can be considered for intracanal irrigant.due to antibacterial action whereas those above 80 *µg/ml* concentration could be considered cytotoxic levels. The silver particle size used in this experiment was 35nm.	concentrations, AgNPs solution can have the bactericidal effect similar to 5.25% NaOCl, so it can be a used as a new intracanalirrigant. .	
To analyse the bactericidal action of AgNPs as a irrigation solution in root canal therapy.	*Ex vivo*	AgNP was synthesized by reduction method using AgNO3 and gallic acid.	AgNP have spherical structure with 10 nm diameter. The surface plasmon resonance is narrow and located at 420 nm.	**Antibacterial action** AgNP particle size around *10nm* with a showed antibacterial effect on E. faecalis	The antibacterial potency of AgNP based solution was similar in antibacterial action as an irrigant compared to 2.25% of NaOCl.	[92]
To evaluate the effect of adding AgNP (1%) to MTA antibacterial properties.	*In vitro*	Used commercially AgNP	Not available	**Antibacterial action** Addition of AgNPs by *1%* weight with particle size *<150um* to MTA improved	Addition of AgNP to adding MTA enhanced its antimicrobial	[18]

				its antimicrobial (E. faecalis, C. albicans, and P. aeruginosa).	efficiency.	
To investigate bactericidal efficacy of AgNP + Ca (OH)2 medicament vs.AgNP and Ca (OH)2 alone.	*In vitro*	Used commercially available AgNP gel	Not available	**Antibacterial action** Concentration of AgNP in gel used used was of *20 ppm* with an average diameter of *2 nm* particle size.	Antibacterial outcome of AgNP was inferior to Ca (OH)2 or combination of both materials.	[140]
4] Periodontology						
Examine the effects of AgNPs on human dermal fibroblasts, human epidermal keratinocytes and also on interleukins, growth factors and matrix metalloproteinases.	*In vitro*	AgNP was prepared by reducing AgNO3 via $NaBH_4$.	Particle size of AgNP was found to be 10 ± 5 nm with -22mV zeta potential and 7.1 pH.	**Biocompatibility of AgNPs** AgNPs were spherical in structure with average size of 10 nm. The production of IL-12 was by human epidermal keratinocytes (NHEK) after 24 hours was increased by AgNPs (2.5 and 0.25 ppm) whereas they decreased (at 25ppm) expression of COX-2 in normal human dermal fibroblasts(NHDFs). Also the levels of MMP-1 were increased after 24-48 hrs.	The study observed AgNPs reduced cytokines like TNF-α, IL-12 and growth factors (vascular endothelial growth factor) after 1-2days and dreduced COX-2 after 1 day at the maximum concentration of AgNPs only.	[49]
Analysis of bactericidal	*In vitro*	AgNP was prepared by	The prepared NP was	**Antibacterial property**	Synergistic	[100]

effect of AgNPs along with selected antibiotics) against multiresistant *Enterobacteriaceae.*		reduction of complex cation [Ag (NH3)2] + by D-maltose in the presence of NaOH also known as Tollens process.	28nm in diameter with narrow size distribution.	AT concentration of 0.8mg/L , AgNPs demonstrated the strongest antibacterial. At lowest concentration of $MIC_{Ag}/16$, AgNPs potentiated the effect of antibiotics. The strongest enhancement of antibacterial activity was seen at AgNP concentrations of $MIC_{Ag/2}$ and $MIC_{Ag/4}$ at which the MICs of the antibiotics being as much as 100-fold lower. **Biocompatibility** AgNPs, antibiotics alone and AgNPs–antibiotics combinations at concentrations of 4 mg/L and 2 mg/L, respectively, did not exhibit any cytotoxic effects.	effect when AgNPs are combined with antibiotics; resulting in a reduction of MICs of the antibiotics. In addition, antibiotics became bactericidal when combined with AgNP.	
Investigated anti-bacterial anti- biofilm effect of carboxymethyl cellulose (CMC) and sodium alginate (SA) capped silver	*In vitro*	Biopolymers (sodium alginate SA and carboxymethyl cellulose CMC) capped AgNP was prepared by microwave irradiation method.	SEM results showed polygon shape CMC coated NP with the size range of 50-100nm while the size range of SA coated NP was 100-	**Antibacterial activity** AgNPs in conc. (15 µg/mL) with CMC@AgNPs and SA@AgNPs were effective in inhibiting growth of	Carboxymethyl cellulose capped AgNPs exhibited more potency in reducing growth	[101]

nanoparticles (AgNPs)			150 nm without any aggregation.XRD and FTIR data indicated the characteristic peaks of silver nanocrystals.	Gram-positive and Gram-negative bacteria.	of Gram –ve as compared to Gram+ve bacteria. While results was exactly reverse for sodium alginate AgNPs.	
To explore whether size of silver nanoparticles had any effect on the anti-bacterial activity against oral anaerobic pathogenic bacteria.	*In vitro*	AgNP were produced by using a hydrothermal method or simple reduction method.	The XRD results showed no diffraction in characteristic peak of AgNP which indicated high purity of sample. Particle size of NP ranges from 3 to 8 nm with spherical shape prepared by reduction method while size of NP synthesized by hydrothermal method was found in the range of 30-80nm. Stability study revealed that NP are highly stable without any significant change in structure and size.	**Antibacterial activity** AgNPs with particle size 5-nm shows the best antibacterial activity.	Different particle size of AgNPs had different antimicrobial action against anaerobic bacteria; with 5-nm size AgNPs having the best antibacterial activity.	[102]
Effect of silver nanoparticles containing periodontal dressing on inflammatory and repair stages of healing of	*In vivo (animal model)*	AgNP was fabricated by chemical reduction method and incorporated into periodontal dressing.	Histologic findings The histologic picture with periodontal dressing applications	**Antibacterial property** Periodontal Dressing A had 25% v/v concentration of AGNPs and Periodontal Dressing B had 50% v/v	Silver nanoparticles containing periodontal dressing showed	[105]

gingival wound.			showed more improved healing parameters compared to controls. There was less inflammatory cell infiltration , decreased edema and well aligned collagen fibres after one week of gingivectomy.		marked reduction in oedema with moderate inflammation and prominent neovascularization on 4th post-operative day; it also showed complete wound healing on 7th post-operative day.	
To synthesize silver nanoparticles from an extract derived from banana peel waste and its antimicrobial effect on human pathogenic organisms.	*In vitro*	AgNP was synthesized by chemical reduction method using banana leaf extract as capping and reducing substance.	Formulated nanoparticles were spherical in shape with mean diameter of 23.7 nm. EDX analysis and FT-IR showed typical absorption peak of silver nanocrystals which confirms the formation of AgNP.	**Antibacterial property** The antibacterial effect was tested against B. subtilis, S. aureus, P. aeruginosa and E. coli, i. Minimum inhibitory concentration (MIC) was observed at 6.8, 5.1, 1.70 and 3.4 mg/ml of silver nanoparticles respectively whereas the minimum bactericidal concentration (MBC) of AgNPs were found to be 10.2, 10.2, 5.1 and 5.1 mg/ml, respectively.	Silver nanoparticles were more effective against Gram negative than the Gram-positive organisms. Silver nanoparticles also had synergistic effect on the antibacterial action of levofloxacin against Gram-positive and	[103]

					negative bacteria under study.	
Study to investigate the colonization and penetration of specific bacteria (*Streptococcus mutans, Aggregatibacteractinomycetemcomitans, Fusobacteriumnucleatum and Porphyromonas gingivalis*) on silver nanoparticle impregnated guided tissue regeneration membranes.	*In vitro*	Silver nanoparticles as a colloidal solution (0.1 mg/mL) in water (PlasmaChem GmbH, Berlin, Germany; 100 mL; average particle size: 10 nm) was utilized in this study to prepare GTR-NS membranes.	The concentration of silver nanoparticles used was 100 µg/mL (0.1 mg/mL);	**Mechanical properties** Stress-Strain behaviors of membranes were calculated. GTR-NS showed significantly higher tensile strength (10.01 ± 0.92 MPa; p ≤ 0.001) in comparison with GTR-C (8.02 ± 1.2 MPa) and GTR-DOX (8.01 ± 1.4 MPa) and	Results showed that mean bacterial adherence scores and colony forming units were lower statistically significant	[104]
5] Porcelain for crowns and bridges						
Analyze the effect of silver and platinum (Pt-NS) nanoparticles on fracture resistance of porcelain	*In vitro*	10 nm of average diameter of Ag particles and 5 nm of average diameter of platinum (Pt) particles were separately dispersed in water. Noritake Super Porcelain AAA powder was mixed with silver or platinum NP dispersed solution. Then the slurry was dispensed into a metal mold using a vibrational	The addition of metal NPs increased the mechanical strength of porcelain. Inclusion of both the metals increased the fracture toughness and Young's modulus whereas increased of the fracture toughness was more with Ag NPs than Pt NPs.	**Mechanical properties** Vickers hardness and crack length of sintered specimens was significantly higher with AgNPs (622.3; SD: 14.1) compared to Pt-NS (515.4, SD: 15.0) and control (503.4, SD: 33.8). Also, the fracture toughness, KIC, of AgNPs	Addition of both the nanoparticles enhanced the fracture toughness and Young's modulus.	[108]

		mixer. Green pellet was prepared using hydraulic press then fired in porcelain furnace.	Pt NPs did not show any effect on the median crack length and Vickers hardness.	(1.54 MPa·m1/2, SD: 0.05), was significantly higher than Pt-NS (1.42 MPa·m1/2, SD:0.02) and control (1.36 MPa·m1/2, SD: 0.03)		
						[110]
Evaluation of influence of silver nanoparticles on Vickers hardness, crack length, Young modulus and toughness of the porcelain.	*In vitro*	Average diameter of 10 nm Ag NPs were dispersed in purified water. Noritake Super Porcelain AAA (NS porcelain) powder was mixed with Ag NP dispersed solution and the slurry was poured into a 20nm diameter cylindrical metal mold using a vibrational mixer. Green pellet was prepared using hydraulic press then fired in porcelain furnace.	Inclusion of Ag NPs resulted significant increase of the fracture toughness and Vickers hardness of NS porcelain. UV-Vis and FT-IR analyses revealed that some of the Ag NP countered with the matrix compositions and were converted to silver ions whereas remaining stay as Ag NPs form itself.	The concentration of silver (Ag) in the solution (water carboxymethyl cellulos) and was adjusted to 100, 200,500, and 1000 ppm. Vikers hardness Hv of Ag1000 (641, SD: 38.5) was significantly greater (P<.01) than that of Ag200 (547.3, SD: 24.2) or Ag100 (526.3, SD: 23.5). The median crack length was higher in Ag200 (113.7 µm, SD: 6.5), Ag100 (117.6 µm, SD: 5.7) compared to Ag500 (104.5 µm, SD: 11.9) and Ag1000 (100.0 µm, SD: 5.5) (P<.01) .	Decreased crack length while other mechanical properties increased due to incorporation of silver nanoparticles.	[141]
To analyse the consequence of silver	*In vitro*	Average diameter of 10 nm Ag NPs of different	Addition of Ag NPs to porcelain increased the	Four different concentrations of silver	Fatigue parameter	[109]

nanoparticles on the subcritical crack growth behavior of dental porcelains by post-indentation method.		concentration of Ag were dispersed in purified water in presence of carboxy methyl cellulose as dispersing agent. NS porcelain powder was mixed with Ag NP dispersed solution. and the slurry was poured into a 20nm diameter cylindrical die using a vibrator. The slurry was compressed in the die using hydraulic press then fired in porcelain furnace followed by rapid cooling.	fatigue parameter which further improved with increase concentration of Ag. Increased fatigue parameter means higher resistance to its subcritical crack growth behaviour.	nanoparticle were used: 100 ppm, 200 ppm, 500 ppm, and 1,000 ppm	increased with increased amounts of AgNPs. The resistance to crack growth was also enhanced by AGNPs.	
6] Titanium Dental Implants						
Evaluation of bacteriostatic effect of AgNPs layer on titanium surface.	*In vitro*	By an alkaline hydro-thermal HCl immersion method, hydrogen titanate nanotube layer was created on a titanium surface, and subsequent absorption of silver nitrate by immersing the dried nanotube layer into silver nitrate solution and	Uniform distribution of 10–12 nm diameter single crystalline nanotubes on the surface of the titanium foil sample with hydrogen titanate nanotube layer (NT-Ti) was observed in SEM and TEM analysis. The TEM analysis of	**Ag ion release for antibacterial activity** After 15 days, the Ag ion released concentration for AgNPs-NT-Ti, was 50ppb which was enough to have antimicrobial action compared to AgNO3-NT-Ti which dropped to zero. Compared to AgNO3-NT-Ti, AgNP-NT-Ti possesses	Silver nanoparticles located in hydrogen titanate nanotubes have shown to release enough Ag ions to impart the long-term bactericidal	[115]

		lastly, in-situ growth of AgNPs in the hydrogen titanate nanotube channels was achieved by reducing Ag ions using glucose.	AgNP-NT-Ti shows that the nanotubes still maintain their morphology, but there are some nanoparticles of Ag with size of 3 to 8nm inside the nanotubes. Invitro release study demonstrated that the effective silver release from AgNP-NT-Ti can extend to more than 15 days.	a long-term Ag ion release for enhanced antibacterial effect.	action and excellent biocompatibility	
Investigation of antibacterial efficacy and biocompatibility of AgNPs multilayer coating on the phase-transited lysozyme-primed Titanium surfaces.	*In vitro*	Phase-transited lysozyme-functionalized titanium substrates were obtained by dipping into a mixture of lysozyme and tris (2-carboxyethyl) phosphine. To develop multilayer coatings on titanium Substrates, hyaluronic acid and chitosan loaded with AgNP coating was performed via layer-by-layer self-assembly onto the precursor layer of phase-transited lysozyme.	The results of XPS and SEM represented that the necklace-like phase-transited lysozyme and self-assembled multilayer were successfully immobilized on the titanium substrates.	The average concentration of released Ag from AgNPs nanoparticles-loaded Ti discs was 0.70±0.14 μg/ml.	The PTL priming technique offers a promising technique for producing long-term antimicrobial multilayer coatings to prevent implant related infections.	[118]
7] Orthodontic cements						

and adhesives						
To develop a novel AgNP antimicrobial cement for orthodontic bands for prevention of white lesions by release of AgNPs in situ	*In vitro*	AgNP-loaded Opal Band Cement (OBC) was developed using in-situ developed Ag NPs.	AgNP-loaded Opal Band Cement had similar mechanical strength measured in terms of modulus, hardness, and ultimate transverse strength values to those of the control group. Upto 4 months, controlled and sustained Ag+ ion release was observed. Further, release of Ag+ ion increased with increased Ag loading.	**Biocompatibility** 0.5% AgNP-OBC was not cytotoxic or mutagenic.	The novel AgNP in-situ released cement showed a excellent antibacterial action which will prevent white spot formation with unaltered mechanical properties compared to controls	[124]
To investigate antibacterial outcome of orthodontic adhesive with 1%,5%,10%w/w of AgNP/HA	*In vitro*	Ag-doped hydroxyapatite NPs were developed by gamma irradiation and Hyaluronic acid (HA) used as a carrier. Transbond XT pastes Ag/HA NPs were developed by precisely mixing appropriate amounts of Ag/HA NPs and composite paste. Composites was filled in 5-mm diameter of	----	Antibacterial property composite discs having 5 and 10 % silver/hydroxyapatite nanoparticles shows better antibacterial properties against biofilms.	5 % Ag/HA decreased cariogenic bacterial growth, without affecting the non-cariogenic bacteria.	[126]

		circular metal molds. Thereafter composite discs were taken out and sterilized by gamma-rays.				
8] Anticancer treatment						
To observe the anticancer efficacy of composite of alginate, chitosan, and biosynthesized silver nanoparticles (AgNPs)	*In vitro*	Biosynthesized AgNPs using aqueous extract of Eckloniacava were added into the prepared chitosan-alginate polyelectrolyte solution and frozen and lyophilized. Thereafter scaffold was regenerated using 1 % CaCl2 solution followed by 1 % NaOH solution and water wash. The washed scaffold was frozen and lyophilized.	Presence of strong chemical interaction between alginate and chitosan was observed in FT-IR spectra whereas, UV–vis spectroscopy and XRD results assured the presence of AgNPs in the composite. SEM analysis revealed that the nanocomposites have a porous structure and AgNPs were dispersed uniformly in the porous membrane.	The IC50value of chitosan-alginate-AgNPs composite tokill MDA-MB–231 cells were 4.6 mg	Chitosan-alginate-AgNPs composite depicted an enormous potential for anticancer treatment.	[136]
To synthesize AgNPs by novel green route method and tests its anticancer potential	*In vitro*	Sucrose stabilized Ag NPs was developed by adding AgNO3 to transparent sucrose solution followed by overnight stirring at room temperature.	UV analysis represent the surface plasmonresonance band for spherical AgNP at 420nm. XRD and Electron diffraction analysis confirmed that particles were of pure Ag with a	50% Growth Inhibition Dose (ID50) was observed at 3.6 µM for AgNPs against human cancer cell lines HT144 (malignant skin melanoma) and H157 (squamous cell lung carcinoma).	AgNPs formulated by Green route method showed instant action against cancer cell line without damaging the	[139]

			face centered cubic (fcc) structure. TEM analysis revealed that particle size was within the range of 10 to 20nm.		host cells.	

Highlights:

- Nanoparticle applications have become useful tools for various dental applications.
- AgNPs have been widely used in dentistry due to its antimicrobial properties.
- Application of AgNPs into various biomaterials used in different dental applications are discussed.