Silver Nanoparticles- a versatile therapeutic and biomimetic intervention in dentistry: A Systematic Review

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Abstract:

Background:

Nanotechnology advances have been changing the face of dentistry with its diverse range of dental applications. Silver nanoparticles (AgNPs) is a relatively newer breakthrough in dentistry. AgNPs, an antimicrobial agent have been incorporated into various biomaterials in order to reduce the biofilm formation and lends a cariostatic effect thus giving a biomimetic.

Aim: This systematic review is aimed to provide an overview of Silver nanopartiocle application in dentistry and its roles as a biomimetic agent in preventing various oral diseases.

Methods: Literature search was done using PubMed and Scopus database between 2010 to 2020 on nanomaterials for dental applications and was systematical and critically reviewed . Accordingly, this review will focus on the current status and the future implications of silver nanoparticle technology in preventive and adhesive dentistry.

Results: Literature search revealed 322 articles on silver nanoparticles in Pubmed and 19 in Scopus. After eliminating the duplicates and additional filtering a total of 9 randomized control trials were reviewed . Silver nanoparticles due to its excellent biological and mechanical advantage can be incorporated in various dental materials either alone or with other nanoparticles for restorative dentistry, in orthodontics, in oral hygiene maintenance, in endodontics, in oral implants and bone regeneration.

Conclusion: Prospective clinical and randomized control studies are required to know the long term beneficial and toxic effects of this material and its biomimetic effectiveness as a therapeutic agent

Keywords: Silver nanoparticles, Nano silver, biomimetic, dentistry

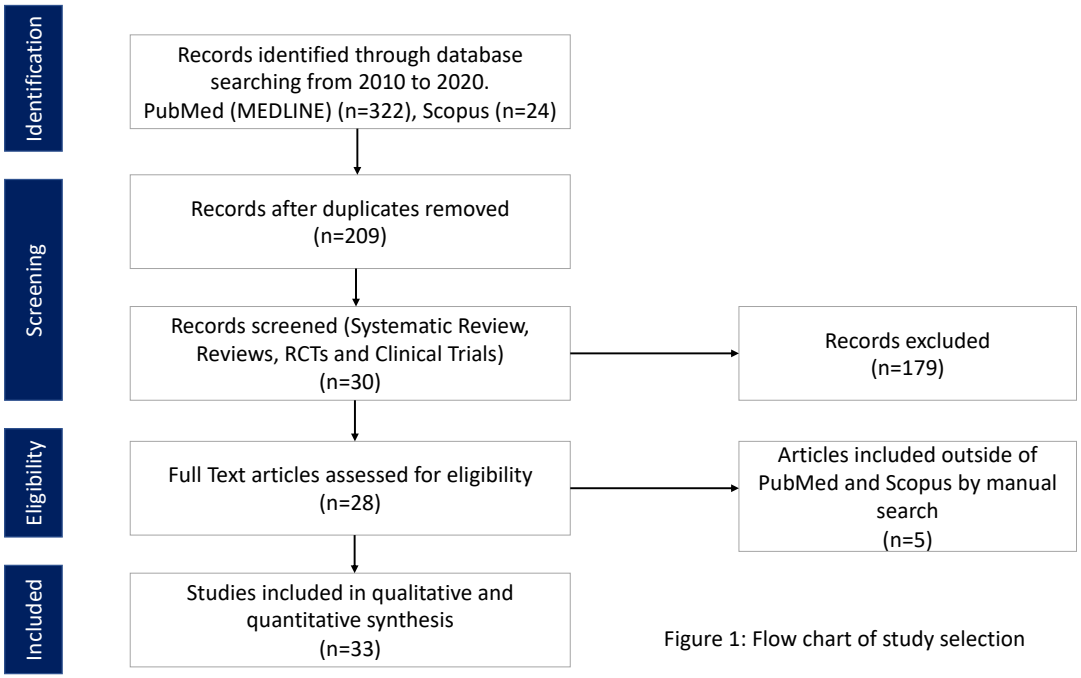

Figure 1: Flow chart of study selection

Silver Nanoparticle- a versatile therapeutic and biomimetic intervention in dentistry: A Systematic Review			
Clinical Question : Is Silver nanoparticle technology an effective therapeutic and biomimetic intervention compared to traditional agents used in dentistry?			
Clinical Bottom Line : Silver nanoparticles is a versatile, antibiofilm and antimicrobial agent which has anticaries potential. It imparts good biomimetic potential to enamel and dentin when used with other nanoparticles such as hydroxyapatite and calcium phosphate which help in remineralization. It has anticaries effect in restorative dentistry and orthodontics, acts as a good disinfection agent in endodontics, antifungal and antimicrobial effect in prosthesis fabrication, implant coating material and for bone regeneration			
Author/Year	**Patient Group**	**Study Type**	**Key Result**
Freire P., Albuquerque A., Sampaio F., Galembeck A., Flores M., Stamford T., Rosenblatt A.(2017)	12 schoolchildren of both genders, aged between 7 and 8 years	Randomized controlled trial, double blind, crossover and prospective.	NSF formulation was effective to arrest active dentin caries in children after one year of application and did not stain teeth. NSF significantly reduced the CFUs four fold in 24 hours. Nano silver fluoride was an effective dental biofilm inhibitor because it reduced the *S. mutans* CFU counts and absorbance values
Dos Santos VE Jr, de Vasconcelos FM, Ribeiro AG, Rosenblatt A (2014)	63 teeth for the NSF group and 67 for the control group. One hundred thirty decayed primary teeth were randomly divided into two (Brazil)	Randomized, controlled	81% of teeth in the NSF group exhibited arrested caries, whereas in controls, no teeth had arrested decay. The NSF formulation is effective to arrest active dentine caries and not stain teeth. Nano-silver compounds do not form oxides when contacting oxygen in the medium.
Baygin O., Tuzuner T., Nagehan Yilmaz 1, Simge Aksoy (2017)	Forty patients aged 12-15 years who were treated at the pediatric clinic	Prospective randomized blinded clinical study	Silver ion-containing toothbrushes exhibited promising outcomes as an alternative to standard oral hygiene strategies applied with dentifrices in teenagers.
Farhadian N., Mashoof R., Khanizadeh S, Ghaderi E., Farhadian M, Miresmaeili A. (2016)	Sixty-six orthodontic patients at the debonding stage were randomly assigned to 2 sex-matched groups with stratified block randomization: group 1 received conventional removable retainers; group 2 received removable retainers containing silver nanoparticles,	Randomized control trial	Intaglio surface of Hawley removable appliances provides an environment for plaque accumulation, leading to enamel demineralization Adding silver nanoparticles to the acrylic plate of retainers had a strong antimicrobial effect against S mutans under clinical conditions. Silver nanoparticles at 500 ppm are safe for clinical use.

Fig 2: Systematic Review Articles

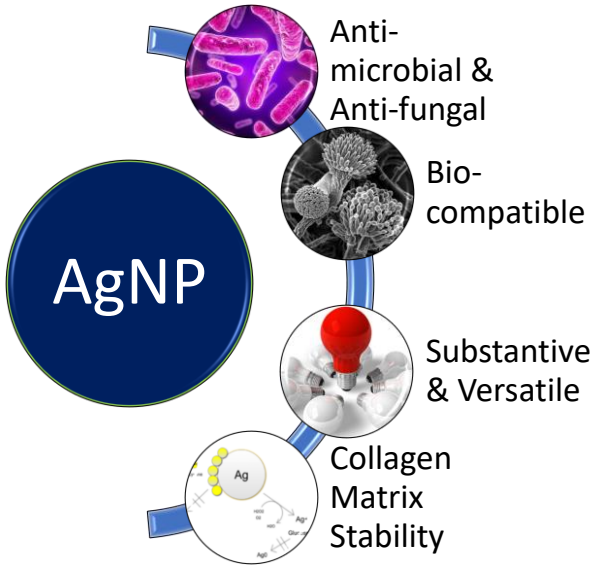

Figure 3: Advantages of AgNP

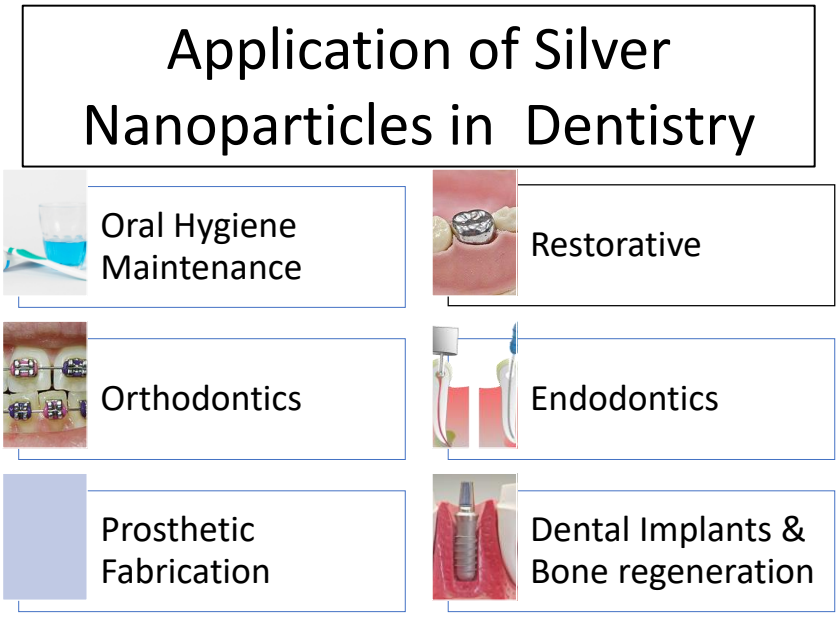

Figure 4: Silver nanoparticle application in dentistry

This review focuses on addition of silver nanoparticles and its application in various materials used in dentistry.

METHODS

For this review a systematic review was performed using a comprehensive literature search using PubMed (MEDLINE) and Scopus was done.

Inclusion Criteria:

Potentially eligible publications were searched electronically, and titles and abstracts were screened. Articles with full texts of the remaining publications were identified. Articles published before January 2010 were excluded from the search. Studies about case reports, non-English articles, and irrelevant studies were excluded. Duplicate articles were removed. The keywords used in the search of the selected electronic databases were silver nanoparticles, Nano silver, biomimetic and dentistry. Studies that met the following criteria were selected in this systematic review: the study type is clinical trial on adults and children and the outcome measurement of the studies should be evaluating the effectiveness of Nano silver particles in different materials used in dentistry.
Randomized control trial and clinical trials were searched in PubMed and Scopus Studies that met the criteria above were included for data analysis.

RESULTS

Study Identification and Selection:

The initial electronic search retrieved 346 citations in PubMed and Scopus. In first screening 209 articles were selected on the basis of title, abstract and full text. Finally, 9 randomized control studies and clinical trials were selected but 4 were included in this review as full texts were not found.

Characteristics of the included studies:

All the included studies in this systematic review were randomized clinical trials.

Appraisal of Evidence and quality of evidence in included studies:

There is consensus amongst the available literature in the vitro studies that the activity of AgNPs enhances the antimicrobial effect of different biomaterials and it is a versatile material. No metanalyses were found for this topic. The number of clinical studies done is low. There is need for prospective clinical studies to know more about long term implications of this nanoparticles. Assessment of risk of bias for individual study was done under the following domains: selection bias and attrition bias. In all the four studies, adequate concealment method is used and all relevant outcomes are measured in a standard, valid and reliable way.
The studies do not clearly mention how much attrition occurred in each group

Discussion

Caries is a dynamic process caused by plethora of oral microbiota that inhabit the biofilm. Streptococcus mutans is regarded as the main bacterium related to the initiation of dental caries. Biomimetics refers to materials or process that can simulate natural processes. In biomimetics, biological evidence-based solutions are developed to resolve problems arising in oral cavity due[1]. Various biomimetic interventions have been developed over the years to help in prevention of carious lesion and to treat them.
Molecular units of 0.1 to 100 nm in diameter are usually categorized in nanoparticles. Nano silver are clusters of silver atoms in diameter from 1 to 100 nm. Nanoparticles have a wide range of uses and different synthetic bioactive nanoparticles are used to develop dental materials. These are hydroxyapatite, bioglass, titanium, zirconia, and silver nanoparticles.[2]

Anti-microbial Effect: Silver Nanoparticles have unique advantages of being nanosized, have a large ratio of surface area & volume and increased chemical reactivity[2]. The silver nanoparticles penetrate the bacterial cell walls, and increase the cell membrane permeability. In the process, they produce reactive oxygen species which interrupt deoxyribonucleic acid replication by releasing silver ions[3]. Silver can interfere with DNA and proteins, alters the base pairing, DNA unwinding, cell wall synthesis and respiratory processes [4,5].
As it disrupts the respiratory chain and leaks through the openings in cell wall, it ultimately results in cell death[6]. The nanoparticles bond strongly to one another and to other materials dues to the high surface free energy[7]. In vitro studies have demonstrated that silver nanoparticles have effective antifungal and antiviral activity. Apart from the antimicrobial effect exerted by the nanosilver has been shown to have anti-inflammatory effect as well. AgNP have been incorporated into various dental biomaterials due to the small particle size and greater surface to volume ratio[8]. In this review, we will explore the multiple biomimetic applications of AgNP in dentistry from its use in dentifrices, dental restorative materials, dental prosthesis, orthodontics, endodontics and dental implants.

Restorative Dentistry

Secondary caries is a critical issue and results in restoration failure. Despite using high quality polishing systems, composites tend to accumulate form a biofilm on them and subsequently results in microbial adhesion onto surfaces. This results in leakage of microbes through the dental biofilm around the margins of the restoration on tooth surfaces[9].
Over the years, to reduce the leakage around the margins various nanoparticles system including AgNP have been incorporated into composites, bonding and priming materials. Each nanoparticle system has an additive effect on the longevity of the restorations and tooth structure. In an experimental bonding system study, monomer dimethylaminododecyl methacrylate (DMADDM) was combined with nanoparticles of silver (NAg) and nanoparticles of amorphous calcium phosphate (NACP) and compared with Scotch Bond Multipurpose primer and adhesive system(SBMP)[10]. The nanoparticle bonding system readily flowed into dentinal tubules to form resin tags showed no bond strength loss in the first 6 months, a strong antibacterial activity during 6 months of water-aging. The nanoparticle system resulted in decreased biofilm colony forming Units (CFU), metabolic activity and lactic acid production.
Nanoparticles of silver (NAg) and amorphous calcium phosphate (NACP) can also reduce acid production in dental plaque and enhance remineralization[11]. The combination of NACP with AgNP helps NACP calcium/phosphate ions to promote remineralization and also adds to an antibacterial effect through toxicity of Ag to some cellular enzymes. Overall, Ag nanoparticles when incorporated into resins does not affect the bond strength and material color[12]. Similarly, both silver along with fluoride ions are important for enamel remineralization as silver ions infiltrate into carious lesions and precipitate resulting in enamel hardening[13].
An critical side-effect of silver from esthetic perspective while restoring with composite is the ability to darken then tooth structure and leave a residue. The nano silver fluoride formulation is effective to arrest active dentine caries and not stain teeth[14].
Dentin blocks impregnated with S. mutans were treated with antibacterial bonding agents and composites containing a quaternary ammonium dimethacrylate (QADM) and nanoparticles of silver (NAg). They have shown promising results in inhibiting the S. mutans and inhibit caries thus showing a potential pliable application of AgNP in adhesives, cements, selants and composites[15]. Due to the ease of handling and cost-benefit it could be also be a good replacement for NAF varnish does not stain the teeth[14].

Another important application of AgNP is its use as a disinfecting agent as a preventative step for the secondary caries before restorative materials are placed in the preparation. According to a study he disinfection liquid proved to be biocompatible. Antibacterial effect of AgNP with glass ionomer cement (GIC) in a total etch system was assessed in a vitro study against Streptococcus mutans, Streptococcus salivarius and Lactobacillus acidophilus. AgNP's interfered with the total-etch bonding system in terms

of vitality, which may have serious clinical implications. The study results showed an incomplete polymerization of the polymer resins combined with AgNPs, along with the increase of the release of the unbound monomers, have been found[16].
The ability for silver to for agglomerates and its ability to interfere with the bonding ability of dentin is the main concern when it comes to incorporating AgNP into various dental biomaterials. It is biocompatible with low toxicity[17].

Another in vitro study by[18] was done to evaluate the effect of cavity disinfection with 2% chlorhexidine (CHX) and Gold(Au)- Silver(Ag) nanoparticles on microleakage and resin tag penetrability of composite restoration. The results were promising which showed that sealing ability and resin tag penetrability of composite resin in permanent molars was unaffected by Ag–Au nanoparticles when compared with 2% CHX. More randomized clinical trials are needed to further evaluate the longevity of teeth treated with AgNP disinfectant. Silver has shown to improve the long term intrafibrillar mineralization by improving the crosslinking and secondary structure of demineralized dentin collagen[19]. The Dynamic-Mechanical and Raman Analysis by Osorio et al. highlighted that undoped silver NP improved collagen matrix structure and stability however the mineralization and crystallinity was low.

Oral Hygiene Maintenance:
Toothpaste: When it comes to dentifrices, various nanoparticles have been incorporated into toothpastes, mouthwashes and even on bristles of toothbrushes. Toothpastes incorporated with AgNP show a high antibacterial efficacy against S. mutans when compared to fluoride and chitosan containing toothpaste[20]. Dentifrices containing NSF presented a lower MIC and higher statistically significant results compared to NaF dentifrices with respect to preventing bacterial adhesion and pH decreases. Nanosilver fluoride (NSF) combination is also effective compared to NaF dentifrices in preventing bacterial adhesion and pH decreases. NSF containing dentifrices presented a lower MIC and higher statistically significant results compared to NaF dentifrices. NSF and NaF had similar effectiveness in preventing caries by avoiding enamel demineralization (Teixeira JA). NSF presented a lower minimal inhibitory concentration (MIC), and higher statistically significant results compared to NaF dentifrices. Remineralization at dentin was not produced after Ag-NPs application, though improved crystallinity may lead to increase stability of the apatite that was generated at the dentin surface[17].

Mouthwashes:
In a vitro study, Ag nanoparticple solution was compared to chlorhexidine against five S. mutans, S. oralis, L. acidophilus, L. fermentum and Candida albicans. The results highlighted higher anti-bactericidal and bacteriostatic potential of silver nanoparticle containing solution compared to CHX [22]. Another study by Al-sharani et al., with nanosilver mouthwash was comparable to the CHX mouthwash in terms of reducing plaque, gingival and papilla bleeding scores, however CHX was better in decreasing laque scores than NS[23]. Another study investigating the toxicity of Ag, silica and titanium nanoparticles against the oral pathogenic species of Streptococcus mutans, compared to the routine disinfectant, chlorhexidine concluded that AgNP is a better disinfectant than chlorhexidine. And suggested improvements to the MIC assay[24]. High antimicrobial potential of AgNP may help it to serve as good alternative to conventional mouthwash especially in immunocompromised cancer patients and for preoperative patients at high risk for nosocomial pneumonia. As it is alcohol free it is comfortable and non-irritating to patients with inflamed and sensitive mucosa.

Orthodontics
In orthodontics, nanocoated orthodontic bracket is effective in reduction of smooth surface caries and in the inhibition of S.mutans thus resulting in reduced white spot lesion after fixed orthodontic treatment[25].

Endodontics:

Ag nanoparticles microbial activity was investigated against yeast, Escherichia coli, and Staphylococcus aureus and its application in diverse medical devices[26]. The study results suggest that AgNP are effective growth inhibitors for these microorganisms. The anti-biofilm activity of AgNP results in 95% reduction of microorganism and can be effectively used to treat Pseudomonas Aeroginosa and Staph species[27]. Gutta-percha coated with silver nanoparticles had antibacterial and antifungal properties and was as effective as conventional gutta-percha in preventing bacterial leakage[14]

Effective antimicrobial and biofilm anti-adhesion activities of poly (vinyl alcohol)-coated silver nanoparticles (AgNPs-PVA) and farnesol against Enterococcus faecalis, Candida albicans or Pseudomonas aeruginosa, showing a potential adjunct use of silver nanoparticle in endodontic treatment. It could be used as auxiliary procedure for root canal disinfection or to inhibit biofilm formation and preventing bacterial leakage[28,29]. Yin et al., highlighted that addition of silver nanoparticles to MTA can enhance the antibacterial potential against anaerobic microbes. Similarly, AgNP also improved the antifungal potential against Candida Albicans[2] . The antimicrobial effect as previously described is due to the small size of the NSF nanoparticles (3.2 ± 1.2 nm) and their spherical shapes potentiate the antimicrobial effect by increasing the contact surface .

Prosthetic Fabrication: An effective antimicrobial effect could be attained by incorporating Silver nanoparticles can be incorporated in the polymethylmethacrylate(PMMA) denture resin to help control common infections caused by oral pathogens on the denture supporting oral mucosal tissues in complete denture wearers[31]. Denture stomatitis due candidiasis is a common finding especially in patients lacking proper oral and denture hygiene. As AgNP is used in lower concentration, it minimizes the unpleasant taste and reduces the toxicity[32].

Implants

Titanium oxide treated with coating containing calcium, phosphorus and Ag nanoparticles has revealed that the coating containing Ag nanoparticles has more significant antibacterial effectiveness against Staphylococcus aureus and Escherichia coli compared to a coating that does not contain silver[33]. Another study by Flores et al., exhibited that modified implant surface with AgNP-Ti/TiO(2) surface a good resistance to colonization by Pseudomonas aeruginosa.

Bone Regeneration and Alveolar Reconstruction

Bone healing could be enhanced if collagen barrier membrane in guided bone regeneration and alveolar reconstruction used in anti-bacterial and anti-inflammatory potential. Chen et al. study highlighted AgNP-coated collagen membrane has exhibited excellent anti-bacterial effects against Staphylococcus aureus (S. aureus) and Pseudomonas aeruginosa (P. aeruginosa) with limited cellular toxicity. Silver nanoparticles demonstrated effective anti-inflammatory effects by reducing the expression and release of inflammatory cytokines including IL-6 and TNF-alpha.

CONCLUSIONS

Dental materials are constantly evolving due to developing technology and to provide quality dental care to patient needs. Nanotechnology and particularly nanoparticle have shown tremendous momentum. Various studies have shown promising results supporting therapeutic and biomimetic potential of AgNP. There is not enough conclusive clinical data, to ascertain the effectiveness of AgNP compared to some of the conventional preventive measures. It antimicrobial potential to treat caries producing bacteria and antifungal potential along with its versatile nature has shown tremendous results. Nano silver helps in collagen matrix stability but does not help in remineralization. When used with other nanoparticles such as hydroxyapatite, and calcium phosphate helps in remineralization of tooth structure. More research is needed to know its efficacy and potential drawbacks of this nanotechnology.

Future Implications
More clinical trials with larger sample size would be required.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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