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RESEARCH ARTICLE

APPLICATIONS OF SILVER NANOPARTICLES IN PROSTHODONTICS: A NEW APPRAISAL.

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Abstract

Silver (Ag) has been in use in medicine since time immemorial because of its antimicrobial properties. However, due to the emergence of antibiotics, the use of Ag has been declined. Several pathogenic bacteria have developed resistance against various antibiotics. This has led to the reemergence of Ag. Recently, nanoscience and nanotechnology are gaining tremendous popularity. The small size of nanoparticles provides larger surface area and hence increases the effectiveness of nanoparticles. Ag nanoparticles (AgNPs) are used in medical and dental applications ranging from Ag-based wound dressings, Ag-coated medical devices such as catheters, bone cements, in gels, lotions, cosmetics, in dental restorative materials, endodontic cements, dental implants' caries inhibitory agents, and in prosthesis.

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Introduction:-

The synthetic resin used currently in dentistry is based on acrylic resin poly (methyl methacrylate) (PMMA). PMMA polymers were introduced as a denture base material by Wright in 1937, and till date, no other material has been found matching the appearance of oral soft tissues with as great fidelity as acrylic resin. Since the overall performance is satisfactory, it is widely used for the construction of complete dentures⁹.

It has been shown by many researchers that denture base material (PMMA) may act as a reservoir for many microorganisms and have the potential to support biofilm formation. Insertion of a dental prosthesis results in drastic changes in the oral environmental conditions as the prosthesis becomes colonized with various microorganisms¹.

It isolates the underlying mucosa from the mechanical cleansing effect of the tongue and free flow of saliva. Furthermore, the porous surface of denture base material (PMMA) and irregularities on the anatomical surface of prosthesis favor the accumulation of microorganisms⁵. This mainly causes the problem of denture stomatitis.

Denture Stomatitis or Candidiasis

Candida species are human fungal pathogens. They are ubiquitous in nature and capable of initiating a variety of recurring superficial diseases in the oral and vaginal mucosae. Many species of Candida have been involved in pathogenesis, but among them, Candida albicans has been shown to be most opportunistic pathogen causing infection in the oral cavity and to be able to colonize acrylic materials^{11,3}.

Candida species form a biofilm on acrylic denture surfaces. This biofilm is the network of yeasts, pseudohyphae, and hyphae surrounded by an extracellular matrix and lodged into irregularities and a rough anatomical surface of the acrylic prosthesis. Tissue invasion by these species causes infection of the oral mucosa. C. albicans has the

ability to degrade proteins in both yeast and hyphal forms. They can induce a chronic inflammatory response in the oral mucosa, described as denture stomatitis. Denture-induced stomatitis or candidiasis is an inflammatory reaction of the denture-bearing mucosa that affects approximately 60%–70% of complete denture wearers. Medications that lead mainly to xerostomia, nutritional factors, systemic diseases such as hypothyroidism, Sjogren's syndrome, Addison's disease, AIDS, human immunodeficiency virus (HIV), malignancy and cancer therapy, chronic smokers, diabetes mellitus, and denture wearers are the predisposing factors for oral candidiasis¹⁹.

Old and hospitalized patients show candidiasis as the immune system is lowered. These patients are not able to maintain oral hygiene and cleanliness of the denture. Candida infections have received more diligence due to the onset of the retrovirus such as HIV infection. As per Samaranayake, 90% of HIV-infected individuals suffer from oropharyngeal candidiasis. This condition is a key feature in staging HIV disease. Management of candidiasis includes adoption of prophylactic measures by the patients and use of antifungal drugs²¹.

Topical antifungal agents (e.g., nystatin, clotrimazole, and amphotericin B) or systemic oral azoles (fluconazole, itraconazole, or posaconazole) can be used to treat oral candidiasis. However, candidiasis showed resistance to azole group. In addition to these topical or systemic antifungals, antiseptic agents such as chlorhexidine gluconate have been used. In geriatric or hospitalized patients, even denture cleansing might be compromised owing to cognitive impairment (Alzheimer's disease), reduced motor dexterity, and memory loss. Systemic or local antibiotic agents have been prescribed for an elimination of bacterial population. However, with microbial resistance and the health-care costs being inflated, the researching on antimicrobial denture base or antimicrobial tissue conditioner is needed for its prevention and care²⁵.

Thus, denture stomatitis or candidiasis is a challenge for the dental field. Efforts are being made to discover new antifungal agents. For prevention of denture stomatitis, incorporation of antimicrobial agents into denture base resin and in tissue conditioners have been tried. Denture base resin that can prevent adhesion of microorganisms is currently unavailable. However, this review describes oral prosthesis containing silver nanoparticles (AgNPs) that can be used to produce prosthesis with antifungal properties²⁶.

Silver nanoparticles

Richard Feynman in 1959 introduced the concept of nanotechnology. Nanotechnology can be defined as the study of very small materials or structures. The size of the nanostructure is 1–100 nm.

For many years, silver (Ag) has been used in medicines as an antimicrobial agent. However, the use of Ag as an antibacterial agent decreased with the discovery and popularity of antibiotics. However, the antibiotic-resistant pathogens have brought a revival in Ag-based medications. Ag has been widely used in medical and life-care polymers³⁰. It exhibits antimicrobial action against Gram-positive, Gram-negative bacteria, and fungi.

This has stimulated the incorporation of antimicrobials into denture base materials such as Ag. Some researchers used AgNPs in tissue conditioners and denture base materials to make them antimicrobial. Nanoparticles have been introduced as materials used in biological and medical applications². Various nanoparticles and their nanocomposites are used as good antibacterial agents. Antimicrobial action of AgNPs depends on their size, size distribution, shape, and surface chemistry^{8,9}.

The small size of the particles and resulting large surface area can lead to particle–particle aggregation leading to the loss of those properties attributed to the nanoscale nature of the particles. Smaller AgNPs (3 nm) are more cytotoxic than larger particles (25 nm) at a concentration of 10 µg/mL. For better efficacy, size, shape, and morphology are important. In light of the newer advances in the field of nanotechnology, modulation of size and shape of nanoparticles has been made possible.

The AgNPs can be synthesized using physical, chemical, and photochemical methods. AgNPs can be synthesized by chemical reduction of Ag salt using a reducing agent, by photoreduction of the Ag salt in the presence of citrate by ultraviolet (UV) light, by green synthesis method using natural products and avoiding toxic reducing agents, by laser ablation. AgNPs can be prepared by many different ways. Wet chemical reduction method is commonly in use.

AgNPs can be prepared by the reduction of either soluble or insoluble Ag compounds. The use of different reducing agents leads to the formation of AgNPs with various sizes and shapes. The reduction of Ag nitrate by sodium borohydride is one of the strongest reducing agents and therefore very small AgNPs are produced. Milder reducing agents such as saccharides allow preparation of bigger AgNPs with sizes^{21,25}.

The size and shape of metal nanoparticles are measured by analytical techniques such as transmission electron microscopy (TEM), scanning electron microscopy, or atomic force microscopy. AgNPs were characterized by dynamic light scattering and UV/visible spectroscopy techniques and TEM.

Antimicrobial action of silver nanoparticles

Ag has been pursued as an alternative strategy for reducing bacterial adhesion and to prevent biofilm formation. The mechanism of the inhibitory action of AgNPs on microbes is not fully understood. Recently, it has been suggested that the antimicrobial mechanism of AgNPs may also be related to membrane damage due to free radicals that are derived from the surface of the nanoparticles. This bactericidal activity also appears to be dependent on the size, shape, and concentration of the AgNPs.

Two hypotheses were put forward for the bactericidal activity of Ag:

1. AgNPs bind to sulfur-containing proteins in biological molecules, resulting in pore formation in cell membrane or defect in cell membrane through the formation of reactive oxygen species in the vicinity of bacterial cell membrane causing cell permeability and death.
2. It interacts with phosphorus-containing compounds such as DNA and various cellular enzymes such as cytochrome oxidase and NADH-succinate-dehydrogenase that affects cell division process and leading to cell death. Both mechanisms depend on Ag release.

Researchers have studied Ag nanocomposites with antimicrobial, antifungal, and antiviral applications in the medical field. However, as compared to other fields' application of AgNPs in dentistry is less^{4,5,6}.

Applications of Silver Nanoparticles in Dentistry

The main intention of incorporation of AgNPs into dental materials is to avoid or at least to decrease the biofilm formation and microbial colonization. AgNPs are used in dental prostheses, implantology, and restorative dentistry.

Silver nanoparticles in dental implants

Nanotechnology is used for surface modification of dental implants. Titanium (Ti) is a biocompatible material used in medical and dental implants^{1,2,24}.

A common problem with implants is that after implantation bacteria can form biofilms on their surfaces, which can lead to infection, inflammation, and finally to implant rejection. Therefore, surface modification of Ti by coating or adding antibacterial material to reduce the bacterial and microbial infection is an efficient way to increase the prognosis of the treatment. AgNPs is well-known antibacterial, antimicrobial agent, and their integration to Ti surfaces may decrease the risk of implant failure²⁹.

Flores et al. studied the antibacterial activity of AgNPs against microorganisms such as *Pseudomonas aeruginosa*. Their data suggested that the incorporation of AgNPs on Ti implants is a logical method to protect implant surface against the pathogen.

Their findings are valuable for improving the Ti-based implants. As bactericidal action is obtained even with less amount of Ag, which are not detrimental to the cells involved in the osseointegration process. Zhao et al. studied titania nanotubes (TiO₂-NTs) incorporated with Ag nanoparticles fabricated on Ti implants⁶.

The Ag nanoparticles attach to the wall of the TiO₂-NTs prepared by immersion in a Ag nitrate solution followed by UV light radiation. Their results showed that TiO₂-NTs loaded with Ag nanoparticles can kill bacteria in the suspension. Heng-Li Huang et al. used TaN-Ag coatings on Ti dental implants.

Silver nanoparticles in tissue conditioners

Tissue conditioners or soft liners are used to treat an inflamed and abused mucosa supporting a denture and nurturing them back to health. Relining the ill-fitting denture with a tissue conditioner allows tissues to return to normal. The main aim for their use is to aid in the treatment of chronic soreness from dentures. Tissue conditioners are degradable with time and occasionally susceptible to microbial colonization. Thus, incorporation of AgNPs could help in reducing microbial colonization.¹²

Antimicrobial zeolites have been incorporated into tissue conditioner to make it antimicrobial. Zeolites are aluminum silicate crystalline structures. These crystalline structures have empty spaces. Ag and zinc (Zn) have antimicrobial property. Cations of Ag and Zn, which have antimicrobial properties, may be found within the empty spaces of the zeolites. They get exchanged over a period of time with other cations from their environment. The free cations come into contact with the environmental microorganisms, affecting their development by inactivating the vital microbial enzymes, interrupting with the RNA replication, and blocking their respiration by an oxidative process.¹³

Ki Young Nam has incorporated AgNPs into a commercial tissue conditioner. The concentrations used were 0.1%, 0.5%, 1.0%, 2.0%, and 3.0%. This modified tissue conditioner was evaluated against *Streptococcus mutans*, *Staphylococcus aureus*, and *C. albicans* after 24 h and 72 h. Nam has reported that the modified tissue conditioner shows antimicrobial properties even at 0.1% concentration (for *S. mutans* and *S. aureus*) and 0.5% (for *C. albicans*).¹⁴

Matsuura et al. in 1997 studied antimicrobial effect of tissue conditioners containing Ag-zeolite (SZ). Five commercially available tissue conditioners were selected. Tissue conditioners containing SZ showed antibacterial effects. They stated that SZ continuously releases a small amount of Ag ions resulting long-term antimicrobial activity which is not harmful to tissue cells. Therefore, SZ appears to be a suitable material to use with tissue conditioners. Cell viability of five commercially available tissue conditioners was also tested. The results suggest that Shofu Tissue conditioner has the highest cell viability.¹⁶

Nikawa et al. studied antifungal effect of zeolite which was incorporated in the tissue conditioner against *Candida* growth, and they suggested that Zeomic (Ag-Zeolite)-combined tissue conditioner improves the oral environment of denture stomatitis patients. They suggested that an antimicrobial zeolite-combined tissue conditioner would be a potential aid in denture plaque control.¹⁷

Silver nanoparticles in denture base resin

Wady in 2012 evaluated the activity of a AgNP solution against *C. albicans* and then the effect of incorporation of AgNPs on the materials hydrophobicity, *Candida* adhesion, and biofilm formation. However, they concluded that although the AgNPs had antifungal activity, there was no effect on *C. albicans* adherence and biofilm formation.

Acosta-Torres et al. developed a PMMA containing 1 µg/mL of AgNPs and they compared this new compound to PMMA. It has been observed that PMMA-AgNPs specimens demonstrated less *C. albicans* adherence compared to PMMA. Besides that, they evaluated the activity of mouse fibroblasts and human lymphocytes. PMMA-AgNPs compound does not show cytotoxicity or genotoxicity. The flexural properties of the PMMA-AgNPs acrylic resin were studied. They showed the main values were according to ISO-1567. These results suggest that the PMMA incorporated with AgNPs could be developed as an antimicrobial, antifungal, and biocompatible denture base resin.^{18,19}

Monteiro et al. incorporated AgNPs in a commercial denture base resin, in different concentrations. They evaluated a denture base resin containing AgNPs through morphological analysis. They studied distribution and dispersion of these particles in denture base resin. They also tested Ag release in deionized water at different time intervals. It was observed that lower the volume of suspension added, lower the distribution and higher the dispersion of AgNPs in the denture base resin. They also stated that AgNPs particles were not detected in the deionized water.^{20,21}

Li et al. evaluated the effect of PMMA denture base resin incorporated with AgNPs (nano-Ag) on *C. albicans* adhesion and biofilm formation. They showed that bioactivity and biomass of *C. albicans* biofilm successively decreased by increasing the concentration of the nano-Ag solution. Denture base resin incorporated with nano-Ag

did not influence the property of adhesion at low concentrations, but it exhibited antiadhesion activity at a high concentration (5%).^{22,29}

Hamada and Kusai investigated the effect of incorporation of AgNPs on viscoelastic properties of acrylic resin denture base material. They concluded that incorporation AgNPs within the acrylic denture base material can improve its viscoelastic properties.

Castro et al. assessed the antimicrobial activity and the mechanical properties of an acrylic resin embedded with nanostructure Ag vanadate (β -AgVO₃). They concluded that incorporation of β -AgVO₃ can improve the antimicrobial activity in the acrylic resin. At lower concentrations, the mechanical properties were improved; however, at higher concentrations, no changes in the control were detected.

Silver nanoparticles in maxillofacial prosthesis

Maxillofacial prostheses are used to replace lost facial parts. These prostheses are prone to contamination and infection. *C. albicans* infection poses a significant challenge for facial prostheses fabricated out of silicone material. *Candida* causes degradation of the material and infection of the surrounding tissue.

The maxillofacial prosthesis wearer is exposed to medical risks resulting from the fungal infection caused by the *Candida* adherence on the material surface. It has also been noted that *C. albicans* adherence on various commercially available silicon materials regardless of the surface contact angles. Denture-induced stomatitis is often presented in patients using obturator.^{3,4,5}

These maxillofacial prostheses, which are used for nasal, mid-facial, or combinations of facial prostheses which are extended to obturate exposed intraoral defects, are exposed to body fluids such as saliva and nasal secretions. These prostheses are susceptible to surface colonization by microorganisms, with subsequent degradation of the material, resulting in a complex biofilm formation on the prosthesis. The coating of silicone materials with AgNPs could be of great use to prevent fungal infection in those patients using maxillofacial prostheses.^{6,7,8}

Conclusion:-

Ag has been most extensively studied and used as an antimicrobial agent since ancient times. The uses of AgNP are varied and many. They are already entrenched for many commercial applications, certain medical applications, and in dentistry. In prosthodontics, it has been advocated as an antifungal agent used against candidiasis.

AgNPs due to their attributes of antibacterial, antifungal, and antiviral properties possess distinct advantage and great prospective. However, the pitfall of the AgNP is that they can induce toxicity at various degrees. It has been demonstrated that toxicity caused by AgNP increases proportionately with the increase in concentrations of AgNP.

It can cause various health problems. Although a host of in vitro studies have been done, the laboratory conditions used in these studies do not entirely and accurately reproduce oral conditions. Therefore, in vivo studies are of great value and relevance. Use of animal models and clinical studies to get a better understanding of the antimicrobial properties is necessary. AgNPs containing dental materials, especially tissue conditioners and denture base resin, present good antimicrobial properties. This modified material could be an alternative to patients with denture stomatitis, medically compromised geriatric patients, and patients using maxillofacial prosthesis.

AgNPs have also been proved to be biocompatible with mammalian cells. Studies should be carried out to determine the optimal concentration of this Ag compound, to assure the antimicrobial effect without increasing its cytotoxicity, and also to interrogate the Ag ion release and long-term properties of the AgNP-containing dental materials. Researchers must study the most suitable method of Ag incorporation into denture base resin or other materials.

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