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Article

The Antibacterial and Anti-biofilm Efficacy of Nanoparticles Against Multi-Drug Resistant Bacteria Associated with Periodontitis Disease.

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Abstract: -

Periodontitis is defined as a long-lasting multifactorial inflammatory disease include the breakdown of the tooth's supportive tissues, such as the bone, soft tissues, and periodontal ligament .its initiation and progression is related to biofilm formation, unhealthy meals characterized by high carbohydrate intake, smocking ,hormonal changes and poor oral hygiene .it is considered as the most important leading cause of tooth loss so it is necessary to improve the treatment of

periodontitis . the traditional management of periodontitis is local or systemic antibiotic, mouthrinse, dentifrices, along with scaling and root planning.

Nanoparticles (NPs) have been increased interest in dentistry in the last few years. Their favorable biological and physicochemical characteristics can increase periodontitis diagnosis, prevention, and therapy. NPs have demonstrated antibacterial activity against pathogens that cause periodontal disease. Additionally, nanoparticles can limit the generation of exopolysaccharides by oral cavity bacteria and prevent biofilm development.

Keywords: nanoparticles; bacteria; biofilm formation; periodontal diseases.

Introduction: -

In its most restrictive definition, the phrase "periodontal disease" encompasses both gingivitis and periodontitis. A direct immunological reaction to dental microbial plaque accumulation on teeth, gingivitis is an inflammatory disease of the gingiva, the soft tissues that surround teeth. Following gingivitis, periodontitis includes the breakdown of the tooth's supporting tissues, such as the bone, soft tissues, and periodontal ligament [1].The prevalence of periodontal disease has been observed to range between 20% and 50% worldwide[2].Periodontitis is a serious global communal well-being concern, with almost 62% collective occurrence in dentate adults, according to research conducted between 2011 and 2020. The collective occurrence for moderate to severe cases was 53.2%, while for severe periodontitis it was 23.6%[3].A novel classification of periodontal and peri-implant diseases was proposed in 2017 by the American Academy of Periodontology and the European Federation of Periodontology. This novel sorting divides periodontitis into 3 groupings: necrotizing periodontal diseases, periodontitis itself, and periodontitis as a symptom of systemic diseases. In the latter group, some immunosuppressive conditions or syndromes lead to the advancement of periodontal disease, increasing the risk of developing periodontal disease [4].

The variety of the oral microbiota and the complex way in which oral microbes can produce dental plaque on tooth, implant, and oral mucosal surfaces have been described [5]. Over 700 bacteriological classes have been identified in the human

mouth. Saliva encompasses 10^8 to 10^9 germs per milliliter, and some of them stick to the teeth and commence creation of a dental biofilm, previously known as dental plaque, which is the major cause of periodontal disease [6].G-ve anaerobic bacteria, such as Porphyromonas species, Treponema species, Tannerella species, and Aggregatibacter species, are the most common bacteria linked to periodontal disease[7].G+ve bacteria might exacerbate inflammation in periodontal disease with alveolar bone damage [8].

Staphylococcus aureus is thought to be essential for the disease's exacerbation, while Staphylococcus epidermidis has also been found to be highly prevalent in periodontal pockets and subgingival areas in PD patients [9].Biofilm generation, immune response, and microbiota imbalances have been related to the commencement and subsequent evolution of periodontal disease [10].The formation of biofilm nearly invariably results in a significant rise in resistance to antimicrobial drugs (e.g., amoxycillin, doxycycline, metronidazole), including those used in dentifrices and mouth rinses such as chlorhexidine. Resistance can be caused by the creation of inactivating enzymes, and there is evidence of rather high levels of antibiotic-inactivating enzymes [11].

Affected persons are commonly given antibiotics as a anticipatory provision after hazardous periodontal procedures. However, treatment resistance in gum disease patients has grown in recent years, which is consistent with the contemporary tendency of human microorganisms fetching antibiotic-resistant. Antibiotics are less effective against these bacteria because of the particular circumstances in the gum area and how biofilm forms. We require creative techniques to indulgence periodontal disease [12].In the last few years, the application of nanotechnology and nanoparticles (NPs) combination and synthesis have taken new opportunities to the combat against MDR bacteria, with the NPs facing remarkable interest for their development as potential antibacterial drugs [13]. Nanotechnology is the technology of today for future and current insistent challenges. Nanotechnology applications a good and proper choice in dentistry. These newly produced NPs exhibit the ability to emulate the surface as well as contact properties of tooth tissues closely [14].

The advance and application of NPs/ Nano carriers, nanotechnology has become extensive use through several disciplines. Due to their minor size 1–100 nm, have

various properties, for example, a considerable surface-to-volume ratio can be readily able to pass through biological and structural barriers [15]. Nano biomedical information has also been explored for its potential uses in imaging and early disease diagnosis and for its efficient delivery applications for drugs, genes, and therapeutic composites to targeted organs or cells [16].

Nanoparticles have potential applications in preventive dentistry, restorative dentistry, endodontics, implantology, prosthetic dentistry, oral cancers, and periodontology [17,18]. So, the treatment for persistent periodontitis needs antioxidant-based therapeutics to reduce the inflammatory response. The function of antioxidant materials involves preventing or inhibiting the function of reactive oxygen species or free radicals by stabilizing them using electrons. The nanoparticles may be in the form of metals, metal oxides, or functionalized using natural antioxidant materials. This assists in preventing oxidative stress through reducing free radicals or scavenging reactive oxygen species in sites where periodontitis occurs[19]. The antibacterial property along with antioxidant property of nanoparticles such as zinc oxide, chitosan, titanium dioxide, silver, copper and curcumin has been broadly researched for use in dental applications. These nanoparticles may reduce oxidative stress, prevent the formation of biofilms, and regulate bacterial growth [20].

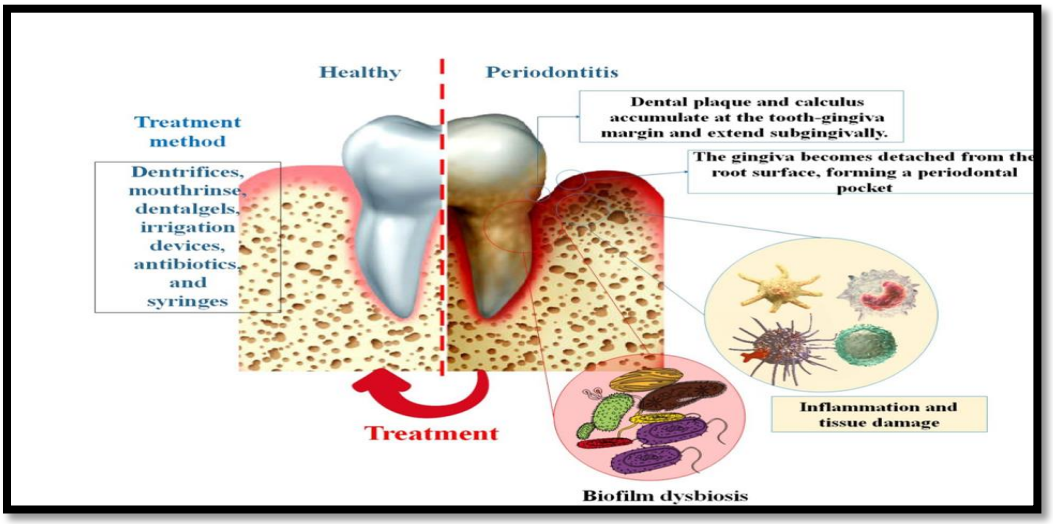

Fig. 1: Periodontal disease-causing factors include biofilm dysbiosis, unchecked gingival and periodontal inflammatory responses (21)

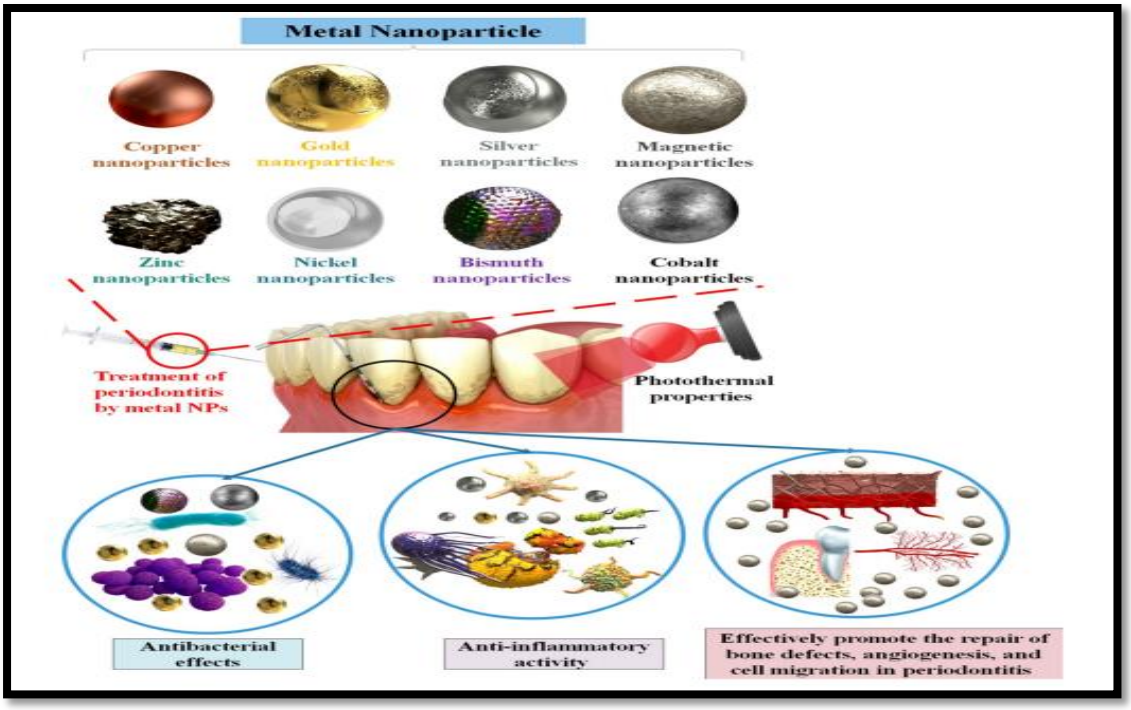

Fig. 2: Different mechanisms of treatment periodontitis by the metal NPs (22)

Materials and Methods

This study reviews **20 research papers** focusing on periodontal disease. It begins with a comprehensive definition of the condition, encompassing both gingivitis and periodontitis. Furthermore, it details the classification of periodontal diseases and explores the critical role of the oral microbiome in their pathogenesis.

Furthermore, this study elucidates the composition of dental plaque, focusing on the role of Gram-positive and Gram-negative bacteria. It also details the stages of biofilm formation, a key driver of disease initiation. Given the increasing resistance to antibiotics, this research explores the critical need for alternative treatments. Consequently, we discuss a wide range of nanomaterials, including zinc oxide, titanium dioxide, silver, copper, curcumin, and chitosan, highlighting their emerging applications in the medical and industrial fields. By evaluating their impact on periodontal pathogens and the oral microbiome, this study aims to determine the efficacy and limitations of nanomaterials in periodontal disease management.

Results

All the data that the researchers reached in their results are in Table (1).

Table 1: Summary of researches in therapeutic effects of metals and their oxide nanoparticles in periodontitis disease.

Nano particles	Nanoparticle effect on causative bacteria	characterization of nano.	references	Result
AuNPs	*S. aureus and E. coli*	The uptake of AuNPs with 3 distances (five, thirteen, forty-five nm) were imaged by TEM.	23	The 45 nm AuNPs may enhance the inflammatory milieu for periodontal tissue revitalization by controlling favorable inflammatory response, macrophage split, and macrophage cytokine production. According to these results, AuNPs may be a practicable medication possibility for periodontal tissue engineering and periodontitis treatment.
TiO2 nanotubes	A. actinomycetemcomitans, T. forsythia, and Campylo bacter	The surface morphologies were investigated using a scanning electron microscope (SEM) with a 25 kV acceleration voltage. The thin films' microstructures, were seen using a field emission scanning electron microscope	24	TiO2 nanotubes doped with Ag exhibited a prominent peak before annealing. Bacterial mortality rates against A. actinomycetemcomitans and T. forsythia. As-annealed Ag-doped TiO2 nanotubes were efficient against C. rectus, indicating their antibacterial properties.

		(FESEM at 5 and 10 kV acceleration voltages and magnifications. With diameter of 70-100nm.		
AuNPs (AuDAPT)	P. gingivalis	The fragments were layered with gold and witnessed by SEM at a magnification of 10 × 103 and 20 × 103 and a fast-tracking voltage of 5.0 kV. The diameter used in this study was 6 mm.	25	When it came to P. gingivalis, the coated aligners had good antibacterial action. This article describes a novel approach to curing oral P. gingivalis by applying 4,6-diamino-2-pyrimidinethiol-modified AuNPs (AuDAPT) to aligners. This approach typically provides benefits over existing therapies for both periodontitis and associated systemic disorders.
NiNPs	Staph. aureus, Staph. epidermidis and E. coli	Before being used, Ni-NPs were obtained from Sigma-Aldrich in the structure of nano powder, overhanging in TSB (Merck), and ultrasonicated for two hours. Nanoparticles (NPs) are gatherings of fragments, ions, or atoms with diameters in the array of 1–100 nm	26	-ve antiseptic properties stayed perceived in the 0.01, 0.05, 0.1, and 1 mg/mL of Ni–NPs concentrations of Ni-NPs. Absent relations between anti-bacterial and anti-biofilm effects of Ni-NPs in the tested concentrations.

CuNPs	A. Actinomycetemcomitans	the CuNP was spotted over the outward plasmon resonance determined by Ultraviolet-Visible Spectrophotometry (UV-Vis). The dimensions and geomorphology of CuNP were surveyed by scanning electron microscopy (SEM) with a Jeol JSM 5410 microscope with diameter of1.5 mm	27	The spherical nanocomposites demonstrated a sustained liberation of copper (Cu) at levels effectual against bacteria and were more stable in saliva. . These compounds inhibited the growth of A. Actinomycetemcomitans. The findings of this study suggest that CuNP/chitosan nanocomposites are promising systems for the creation of localized periodontal treatments in the future.
CoNPs	Staph. aureus and E. coli	The depiction revisions of created nanoparticles were steered via innumerable ordinary techniques like particle size analyzer (PSA), transmission electron microscopy (TEM) and scanning electron microscopy (SEM) with diameter nanoparticles of 150–250 nm.	28	CoNPs' zone of inhibition was more effectual against E. coli than S. aureus.

BiNPs	S. mutans	The figure, dimensions, and spreading of synthesized BiNPs have been exemplified by the high-resolution trans mission electron microscopy (TEM)	29	BiNPs inhibited biofilm production in S. mutans, also BiNPs could inhibit cell bacterial growth.
Ag/ZnO NPs	S.mutans	The characterization of Ag/ZnO nanocomposite by scanning electron microscopy (SEM) appear rod-like morphology length:300–500 nmwidth:10–20 nm and UV–visible absorption spectrum displayed a sharp peak with a maximum absorption at 424 nm	30	Potentially effective as antibacterial agents on S. mutans
platinum nanoparticles (PtNPs)	S. mutans, Enterococcus faecalis, Porphyromonas gingivalis	The PtNPs were displayed particle size is 2–19 nm were tested by transmission electron microscope (JEM-1200EX II,).	31	PtNPs exhibited bactericidal efficacy towards dental-related bacteria within a range of concentrations (1, 5, 10, 20 µg/mL) andproteolytic ability to degrade proteins and LPS, which is considered a main inflammatory factor inducing periodontal diseases.

Au NPs	Streptococcus oralis	The characterization of the Au NPs by AFM showed the average size of the particles to be 43 nm, and the Au NPs had polycrystalline structures. The Au NPs were also characterized by UV-visible absorption spectroscopy, which showed the plasmon peak in the near vicinity of 538 nm. The Au NPs crystal structure was established through XRD and gave sharp diffraction peaks at 12.3°, 21.8°, and 51.8°, which represented crystal planes for (110), (200), and (220), respectively.	32	The antimicrobial properties of the Au NPs were tested against S. oralis using the Agar well diffusion method with variable concentrations of Au NPs (100, 50, 25, 12.5, 6.25, 3.125, 1.562, 0.781, 0.391ppm).
AuNPs	Escherichia coli, pseudomonas aeruginosa and proteus ssp	The structure of gold nanoparticles was characterized through various methods include (XRD), (TEM), (AFM), and absorption spectra of AuNPs (UV-Vis) spectra.	33	Gold nanoparticles showed antibacterial activity with a concentration of 100 µg/mL in well diffusion, with an average inhibition zone of 26-37 mm for each Escherichia coli, Pseudomonas aeruginosa, and proteus ssp. Nevertheless, MIC units of gold

				nanoparticles showed the value at 73 µg/mL for P. aeruginosa. And 75 µg/mL for Proteus sp. and 53 µg/mL was found to be the lowest concentration of AuNPs to inhibit E. coli.
Fe3O4NPs	S. sanguinis, P. gingivalis, and F. nucleatum	Fe_3O_4 NPs displayed spherical phases indicates at 8 nm in diameter were characterized by the TEM.	34	Fe3O4 has excellent anti-biofilm action against pathogens linked to periodontitis and antibacterial properties that kill bacteria. Fe3O4 combined with a magnetic field enabled the targeting of infection sites.
MgO NPs	Staphylococcus aureus	MgO NPs characterized by UV-visible spectroscopy has a peak at 285nm and FESEM was used to determine the morphology and size of MgO particles. Well distributed and spherical shaped MgO nanoparticles were a size of between (59.55 – 82.27 nm).	35	The antibacterial activity of MgO nanoparticles at different concentrations (100, 200, 300, and 400 µg/ml) against S. aureus demonstrated that the inhibition zones increased with the concentration of MgO nanoparticles.

Staphylococcus aureus, *E. coli Escherichia coli*, AuNPs Gold Nanoparticles, Aggregatibacter actinomycetemcomitans, T. forsythia tannerella forsythia, (SEM) scanning electron microscope, (FESEM) field emission scanning electron microscope, TiO2 titanium dioxide, C. rectus = Campylobacter rectus, P. gingivalis Porphyromonas gingivalis, Au-DAPT gold nanoparticle–assisted antimicrobial

photodynamic therapy, Staph. Aureus Staphylococcus aureus, Staph. Epidermidis Staphylococcus epidermidis, Ni-NPs nickel nanoparticles, TSB Tryptic Soy Broth, CuNPs copper nanoparticles, UV-Vis Ultraviolet-Visible Spectrophotometry, CoNPs Cobalt Nanoparticles, PSA particle size analyzer, TEM transmission electron microscopy, BiNPs Bismuth Nanoparticles, S. mutans Streptococcus mutans, Ag/ZnO NPs silver (Ag) and zinc oxide (ZnO) Nanoparticles , PtNPs platinum nanoparticles , LPS Lipopolysaccharide , AFM Atomic Force Microscopy , XRD X-ray Diffraction , *Proteus spp*. *Proteus species* , AFM Atomic Force Microscopy , P. aeruginosa, Fe_3O_4 NPs = Iron Oxide Nanoparticles , *S. sanguinis* Streptococcus sanguinis , P. gingivalis Porphyromonas gingivalis, F. nucleatum Fusobacterium nucleatum , MgO NPs Magnesium Oxide Nanoparticles , FESEM = Field Emission Scanning Electron Microscopy.

Discussion:

Periodontitis is a critical oral health illness clarified by the inflammation and demolition of the auxiliary structures of the teeth. Its primary cause is a mixed bacterial colonization in the oral tissues, forming a complex biofilm. also, periodontitis primarily stems from poor oral hygiene, certain factors like diabetes, smoking, and conditions like leukemia can increase one's risk [36].Accumulation of biofilm on dental plaque of the main cause of periodontal diseases is the dental and gingival surface, which is further synchronized with the unclean behavioral factors of the internal position of the oral surface. It induces the immune responses that cause destruction to the gingival surface, leading to resorption of bone, making it the most predominant keystone pathogen of the periodontal biofilm, which is Porphyromonas gingivalis. [37]. Biofilm is a heterogeneous ecosystem wherein bacteria form collections inside a matrix-forming self-synthesized extracellular polymeric substances (EPS). The process of plaque formation encompasses multiple stages beginning through the development of a pellicle. The pellicle is mainly made up of salivary glycoproteins. This coats the tooth surface that binds to oral bacteria and finally forming plaque biofilms [38].The periodontitis considered a very risky disease because it may progress to the teeth loss and also can cause systemic disease. Zhu et al. mentioned that when the disease developments, cause destruction of the periodontal tissues, leading to loss of the teeth, which will affect the patient's life due to difficulties in speaking, eating, speaking clearly, or even affect the aesthetic value due to the loss of the teeth [39]. Antibiotics are commonly prescribed preventively for patients undergoing invasive periodontal procedures. Nevertheless, antibiotic resistance has risen in recent years among periodontal

patients, reflecting the modern trend of increased antimicrobial resistance among human pathogens. This phenomenon necessitates the exploration of innovative therapeutic alternatives, such as nanoparticle-based systems, to combat recalcitrant oral biofilms [40].

It is difficult for a single material to meet various requirements in multiple domains, like safety and antibacterial properties, because of the complex and dynamic oral environment. However, compound materials can rely on material synergy to develop low-concentration antibacterial properties and improve biosafety. Additionally, they can use the advantages of multiple materials to produce multifaceted uses. At present, nano-antibacterial combination compositions account for most of the nanocomposites. Nanoparticle metal oxides have been interest in the field of antibacterial applications. Because they may be made with a very large surface area and a rare crystal form with many edges, corners, and reactive sites.

Metallic nanoparticles have shown their effectiveness against *E. coli, S. aureus and B. subtilis,* and they might replace conventional antibacterial. However, it has been recognized that three major mechanisms, including the generation of reactive oxidative species (ROS), the release of ions, and the interaction between NPs and the cellular membrane, might be responsible for the antibacterial activities of metallic NPs. In processing bacterial infections, metallic nanoparticles are much capable than their corresponding salts. Most dominant factor affecting the mechanism of antibacterial activity is the size of NP dimensions [41].

Metallic nanoparticles include Gold, Copper, Silver, Titanium, and Zinc, which have gained special attention with varied properties, such as antimicrobial agents, each different from the others. Various oral preparations, toothpastes especially, combine powdered (micron-sized) zinc citrate or acetate as a control measure for dental plaque and powdered titanium dioxide, which is generally present as a whitener in toothpaste [42]. These NPs generate ROS, which are toxic to microorganisms due to their potential to degrade cellular components, including DNA, RNA, proteins and cell wall. Among the other nanometals, ZnO NPs exhibit excellent photocatalytic activity, enhancing their antibacterial efficiency, and ZnO NPs are also capable of generating ROS upon exposure to UV light (43). Recently, the researchers record A big obstacle in the treatment of periodontitis because of antibiotic resistance. This is established may be as a result of antibiotic abuse or bacterial mutation. As a result of this reason، scientists directed to develop nanoparticles as a clinical trial to develop periodontitis treatment.

Conclusion

The comprehensive investigation into the effects of nanoparticles against Gram-positive and Gram-negative bacteria that causes periodontitis and this review illuminates a promising landscape for combating bacterial infections and addressing antimicrobial resistance. This review contributes to a comprehensive analysis of the efficacy of several types of nanoparticles in their ability to inhibit or disrupt the production of biofilms by diverse bacterial species. The review elucidates the optimal strategies and most auspicious nanoparticles for preventing and eradicating biofilms. Furthermore, it highlights the potential of nanoparticles as a viable substitute for conventional antibiotics in healthcare environments and in addressing the issue of antibiotic resistance.

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