

Evaluation of nanomaterials to prevent oral Candidiasis in PMMA based denture wearing patients. A systematic analysis

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ABSTRACT

Purpose: The purpose of this study is the prevention of Candida colonies on PMMA Denture Base by altering the surface and incorporations of Nanoparticles.

Materials and methods: The Pub Med/Medline was searched to identify 100 relevant studies published from 2011 to 2020. The search strategy employed the following keywords related to “use of Nanoparticles in dentistry”, “Antimicrobial agents and PMMA”, “Candidiasis and nanomaterials”, “Prevention of oral Candidiasis”, “Incorporation of antimicrobial agents in acrylic dentures,” “nanoparticles as therapeutic agents for denture stomatitis”, “Nanodentistry” or “Nanotechnology” or “Nanocomposite” or “Nanodrugs” or “Nanomaterials”.

Results: Most of the studies shows that modified PMMA denture base resin containing different antimicrobial coatings and incorporation of metal oxides Nanoparticles and other nanomaterials showed antifungal activity in vitro; however some materials in higher concentration showing altered physical and mechanical properties possibly due to aggregation of Nanoparticles in the lattice of PMMA molecules.

Conclusion: Metal oxides nanomaterials revealed cytotoxicity to Candida and other microbes present in oral biofilm including PMMA denture surface. Nano toxicity may attribute to direct interaction of nanoparticles with cell membrane, hindrance in protein synthesis and early adhesion & interfere with physiology of pathogens.

1. Introduction

Nanotechnology, a technology which deals objects of nanometer size and the particles are called as Nanoparticles (NPs). The term “nano” derived from the Greek word “dwarf.” In recent times, new methods have been developed to manufacture Nanoparticles so that shape and size of different Nanoparticles can be machined as per assigned work. Nanomaterials are presents in various morphologies: Nanorods, Nanotubes, Nanoprisms, Nanosphere, Nanofibers, Nanoplates, Nanoshells, Dendrimers, Nanobelts, Nanorings, Nanocapsules, Fullerenes, Nanowires, Nanobelts, Nanoparticles and nanosheets.¹ The basic idea is to employ every individual atoms and molecules to construct its functional structures. The Nanoparticles can improve the quality of the dental products by adding many functional groups to it.² Nano medicine is the controlled use of nanotechnologies in healthcare leading to new pathways for diagnosis and treatment of diseases.^{3,4}

Nanoparticles are not new entity. NPs were in daily uses even during ancient civilizations like Mesopotamia and Egypt culture. The

Nanoparticles can improve the quality of the dental products by adding many functional groups to it. Similarly many Nanoparticles viz: carbon based nanomaterials, hydroxy apatite, silica, TiO₂, Ag₂O, ZnO, ZrO₂ & CuO have been appreciated as antimicrobial agents for Candida species and other oral microbial species. Some metal oxides Nanoparticles which are ionic in nature have antimicrobial properties, since they have high surface area and different crystalline structure with more number of reactive sites.⁵ Metal Nanoparticles and nonmetal Nanoparticles when combined with PMMA and other polymers or applied to material surfaces have impending relevance to the desired function in dental prosthesis.⁶

Candida albicans is an opportunist fungus found in human mucosa but, under local or systemic conditions, it might invade tissues and become virulent. Candida albicans is the most common species found in oral candidiasis or denture stomatitis, other species are C. tropicalis, C. glabrata.⁷ Oral Candidiasis is a common disease found in elderly dental patients especially in immunocompromised like transplanted patients and those patients who are under chemotherapy.⁸

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The regular antifungal medicine used for local and systemic candidiasis have shown some serious side effects and subsequently leads to development of resistant in *Candida* strains which became a serious health concern.⁹ The toxicity of these antifungal agents is responsible for the resistance to fungi strains and further serious crisis by drug interactions demands more effective treatment with less toxicity.¹⁰ In present scenario, some alternate antifungal therapy is being trying to make effective treatment options for the treatment of Candidiasis like probiotic therapy & many metal Nanoparticles have been considered in the treatment of Candidiasis and have received significant results.^{11–13}

Many Nanoparticles like, gold, silver, copper, titanium, zirconium, zinc oxide, graphene and other carbon Nanoparticles, including chitosan, have been mentioned. In between, alloy Nanoparticles, silica, metal oxides Nanoparticles and iodine have also been intended for their effects on different microorganisms including *Candida*.^{14–17} At present time, antifungal drugs used to treat Candidiasis are in limited use.¹⁸ A special attention is being given to Nanoparticles. Nanoparticles have a higher level of fungicidal effect than conventional antifungal medicines, as they have better penetration in host cells & tissues even in small concentrations. Antimicrobial action of some metal oxide Nanoparticles, such as zinc oxide, copper oxide, and silver oxide, have been proven through many studies.¹⁹ Some metal-oxide NPs, such as TiO_2 , ZrO_2 , Ag_2O and ZnO , have proved their antimicrobial action due to its oxidative stress incited by photo generated reactive oxygen species (ROS). Nanoparticles have greater efficiency in ROS generation than their bulk materials due to their high surface area and high charge density providing them more active sites and positions.²⁰ Titanium dioxide (Titania) is the most common antimicrobial agent used in the biomedical devices. TiO_2 nanomaterial has great opportunity to encounter microbial adhesion on various dental materials and prosthesis including PMMA, Ceramic glass, stainless steel, dental implants.²¹ The application of 1% of Cu–Ti Oxide nanotube coatings in dental implants significantly reduces number of adherent bacteria compared to untreated Ti surfaces.²² Nanoparticles have capacity for attaching and penetrating cell walls of both Gram-positive and Gram-negative microbes through reactive ions.²³ Although The antibacterial action of NPs is not yet clear but broadly their mode of action may be: (1) reaction with peptidoglycan cell wall and cell membrane subsequently cell death; (2) inhibition of protein synthesis; (3) conjugation with bacterial DNA and obstructing DNA replication.²⁴ Most of the fungicidal activity of ZnO NPs was because of bacterial cell wall lysis.²⁵ Graphene as nanomaterials has different active forms like layered graphene (few to multi), reduced graphene oxide, thin and ultra-thin graphite. These all forms have significant antimicrobial effect on oral biofilm.²⁶ Zinc oxide is synthesized with graphene material and producing graphene/zinc oxide (GZNC) Nano composite, it has synergistic antimicrobial effect by producing unique Nano interface but also shown much lower toxicity as compared to ZnO alone.²⁷

2. Materials and methods

The Pub Med/Medline was searched to identify around 100 relevant studies published from 2011 to 2020. The search strategy employed the following keywords related to “use of Nanoparticles in dentistry”, “Antimicrobial agents and PMMA”, “Candidiasis and nanomaterials”, “Prevention of oral Candidiasis”, “Incorporation of antimicrobial agents in acrylic dentures”, “treatment of denture stomatitis through Nanomaterials”, “nanoparticles as therapeutic agents for denture stomatitis” or “Nanotechnology and dentistry” or “Nanocomposites and candida infection” or “Nano drugs as antimicrobial agents” or “Nanomaterials”.

Inclusion and exclusion criteria is given in Fig. 1.

3. Antimicrobial nanoparticles (NPs)

Nanoparticles have all the properties to vanish the microorganism

presents in oral cavity having bacteria and fungi. NPs acts on these microbes by attaching and penetrating into their cell walls, which disturbs cell function by releasing active ions. Therefore, NPs are beneficial for the prevention and treatment of dental diseases including denture stomatitis. PMMA is the most common prosthetic material used for complete dentures, as it exhibits quite poor antimicrobial properties so various nanoparticles are need to incorporated into PMMA to improve its antibacterial activity. The addition of inorganic NPs such as Ag, platinum, Zn/ZnO , Ti/TiO_2 and zirconium oxide (ZrO_2) have shown excellent antibacterial effects.^{28–31}

4. Titanium dioxide- TiO_2 (titania) NPs

TiO_2 NPs have a large spectrum of activity against microorganisms in Gram-negative, Gram positive bacteria and fungi. Incorporation of silica/titania nanoparticle coating in dental prosthesis significantly reduces microbial adhesion.³² As TiO_2 ratio increased in PMMA- TiO_2 it improved the antimicrobial behaviour of PMMA by drastically decreasing bacterial adherence.^{32–33} The integration of TiO_2 Nanoparticles to PMMA reduces the porosity of the denture bases. This finding revealed the aptness of metal oxide Nanoparticles as additives for the improvement of PMMA formulations since high porosities increases the growth of candida hyphae that is accountable for denture stomatitis.³⁴

5. Silver nanoparticles (AgNPs)

Silver nanoparticles (AgNPs) have well know antimicrobial properties, perhaps they were the first in metal NPs using for inhibitions of microbial growth in various dental materials. Incorporation of AgNPs decreases microbial colonization over dental prosthesis and increases oral health.³⁵ The PMMA containing 1 $\mu\text{g}/\text{ml}$ of AgNPs shown significantly less *Candida Albicans* hyphae attachment compared to pure PMMA.³⁶ The synthesis of biologically active silver nanoparticles (AgNPs) have proved potential antifungal activity. This in vitro study shown that the antifungal activity of *Artemisia annua* synthesized AgNPs against three *Candida* species. These AgNPs were effective against all three species with minimum inhibitory concentration (MIC) in order of *Candida glabrata* > *Candida tropicalis* > and *C. albicans*.³⁷ The miniature size of AgNPs facilitate their entry into bacterial cell membrane resulting in rapid bactericidal activity providing interference with DNA replication and protein synthesis, unwinding cell wall and also alters the base pairing of DNA subsequently respiratory failure resulting in cell death.³⁸

6. Zirconium oxide (ZrO_2) NPs

Zirconium oxide nanoparticles (ZrO_2 NPs) have excellent biocompatibility. They are white in color so unlike to other metal oxide NPs, Zirconium Oxide NPs display excellent aesthetics.³⁹ It is proven by many studies that addition of ZrO_2 NPs to PMMA denture base increases the density and decreases porosity which increases its flexural strength, tensile strength, and fracture toughness.⁴⁰ Gad. et al. examined the effect of ZrO_2 NPs on *C. albicans* adhesion of cold-cured acrylic resin and reported that adhesion and proliferation of *C. albicans* were decreased in ZrO_2 -NPs added PMMA specimen due to its less porous and more dense lattice.⁴¹ The findings of Gowri et al., revealed that nano- ZrO_2 almost showed significant inhibition effect against fungal strains by interfering in cell function and causing distortion in fungal hyphae.⁴²

7. Zinc oxide (ZnO) NPs

Zinc oxide is well known antibacterial agent since ages.⁴³ Even in 2000 BC; In the regime of Pharaohs of Egypt historical records confirms the use of zinc oxide as ointments for wound dressings of injuries and

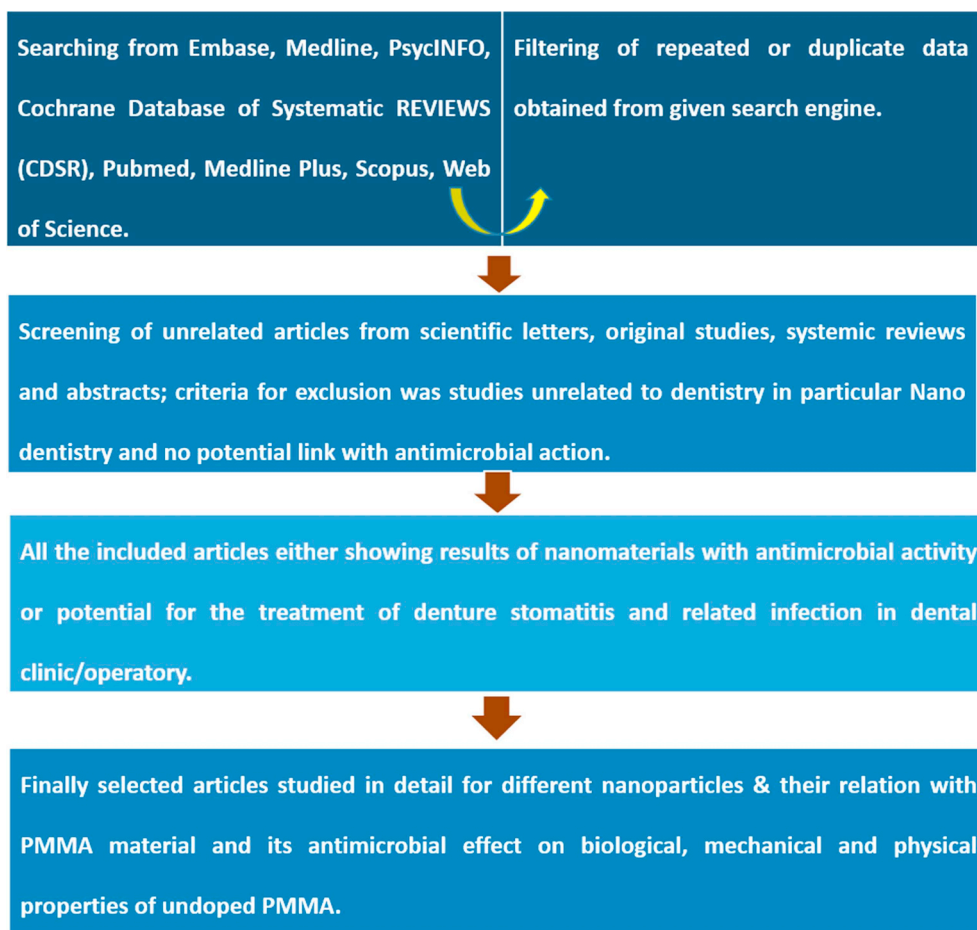


Fig. 1. Inclusion/exclusion criteria and study flow for the systematic review.

boils.⁴⁴ Zinc Oxide nanorod arrays reduced the growth of *Candida albicans* in specimens by continuously releasing metal ions for two months.⁴⁵ Zinc Oxide NPs have shown a significant photo-catalytic effect, which is responsible for their antimicrobial action on bacteria and fungi.⁴⁶ Even in low concentration of 0.01 mg/ml, ZnO NPs showed the significantly antifungal activity against *C. albicans* but surprisingly the efficiency of ZnO NPs was enhanced at 0.01–5.8 mg/ml. This fungicidal action of ZnO NPs was because of damage of fungal cell membrane integrity.⁴⁷

The biofilm staining, XTT analysis and quantitative analysis of adhered *C. albicans* revealed that Composites of PMMA doped with ZnO-NPs in concentrations of 2.5%, 5%, 7.5% by wt. have significant influence on *Candida albicans* solution, These studies proved the antifungal activity of both Nanocomposites PMMA–ZnO-NPs and the effectiveness of sputtering of zinc oxide nanoparticles on the PMMA.⁴⁸

8. Chitosan–silver–copper nanocomposites

This Nanocomposites material provided comparable results to amphotericin B a well-known antifungal agent in vitro. The results shows that this effect was higher for copper–silver–chitosan Nanocomposites than for other nanoparticles studied. Although all these individual NPs have good antimicrobial effect but combined together have synergistic effect and have shown antifungal effects.⁴⁹

9. Copper oxide (CuO) NPs

The study shows the potential antibacterial activity of Copper Oxide NPs on various cariogenic bacteria, these NPs might be good candidate

control agent for preventing cariogenic activity and other dental infections. Moreover, antimicrobial action of Nano copper oxide on all three species of *Candida albicans*, *C. krusei* and *C. glabrata* was not as much of effective as on cariogenic bacteria.⁵⁰

10. Zinc Ferrite Nanoparticles (ZnFe₂O₄NPs)

It is confirmed that the Zinc Ferrite Nanoparticles hybrid nanostructures radially inhibit the biofilm formation of *Candida albicans* cells. This antimicrobial action is due to infiltration of ZnFe₂O₄ NPs into cell membrane and successive interaction of ZnFe₂O₄ NPs with *Candida* cells. These results specify that the Zinc Ferrite Nanoparticles hybrid nanostructures have great potential to be a material of choice to prevent *Candida* infection in denture patients.⁵¹

11. Diamond-like Carbon(DLC) thin film

DLC thin films significantly reduced *C. albicans* biofilm formation on the PMMA specimen surface as compared to control group. The action of DLC was verified after seeing that these thin films were showing same results with undoped and doped with silver NPs. PMMA denture bases coated with thin film of DLC could be an alternative treatment option for the prevention of denture stomatitis.⁵²

12. Curcumin -loaded polymeric Nanoparticles(CUR-NP)

Antimicrobial photodynamic therapy has tested as an alternative treatment for oral candidiasis. In the study encapsulation of curcumin by NPs improves the water solubility of curcumin. Nystatin was used as

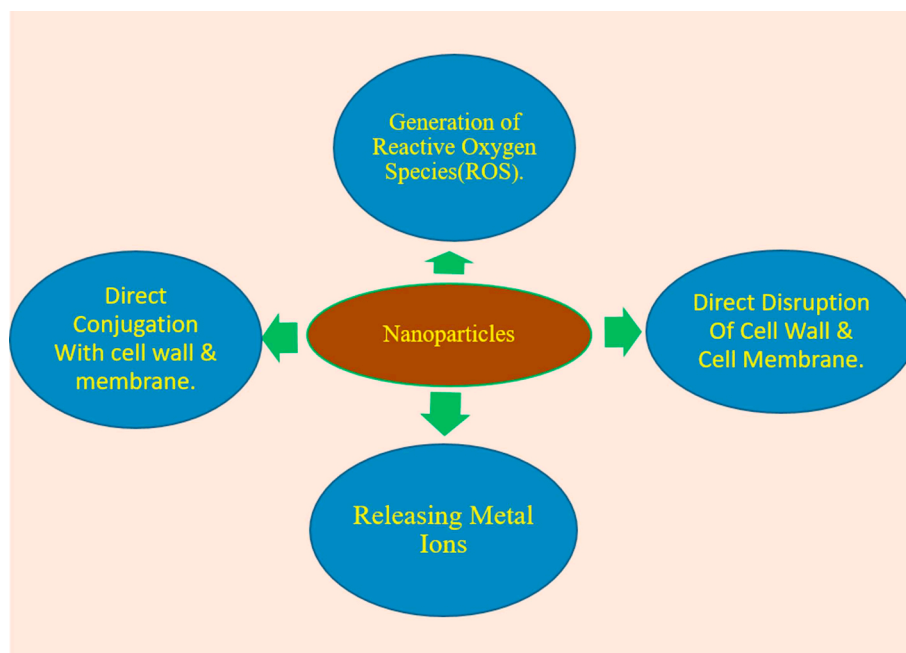


Fig. 2. Mode of action of nanoparticles.

a positive control. Results were encouraging to show the highest reduction of *Candida albicans* in Nystatin group followed by Antimicrobial photodynamic therapy mediated by free curcumin. The cationic and anionic forms of CUR-NP were synthesized. Anionic CUR-NP does not have any significant antifungal effect but cationic CUR-NP diminishes *Candida albicans* hyphae even in dark.⁵³

13. Graphene Oxide(GO) nanosheets

The Antimicrobial effect of GO nanosheets is excellent. In higher concentration, GO nanosheets antimicrobial action was observed more prominent to suppress the viability of microorganisms of oral cavity. GO nanosheets mode of action was due to damage in pathogens cell wall and membrane & followed by cell lysis.⁵⁴

14. Mechanism of action of nanoparticles

All the Nanoparticles have proven action on PMMA biofilm to prevent denture stomatitis. Although their mode of action is little different from each other but common pathway of all nanoparticles is shown in Fig. 2.⁵⁵

15. Conclusion

In this analysis, applications of different Nanoparticles in dentistry are explored. The antimicrobial activities of metal and other nanoparticles are discussed. Our results validated that wide range nanoparticles have shown antimicrobial action on *Candida* species on PMMA denture, dental implant surface, dental prostheses, orthodontics and other dental infections. Most NPs have an exceptional antimicrobial effect, but their actions are largely affected by their shapes, concentration, form and other factors. The common mode of actions of nanoparticles are discussed. In selected doses toxicity of NPs is either unknown or very less. So further more scientific research is needed to deal with mechanism and toxicity as well. Limitation of the study was that only high rated articles were selected and reviewed. As we are comfortable with English language, other languages articles were not reviewed.

Declaration of competing interest

No conflict of interest, necessary references are mentioned in the article.

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