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NOVEL PLANT- MEDIATED NANOPARTICLES AGAINST ORAL CAVITY DISEASES: SYNTHESIS, CHARACTERIZATION AND APPLICATION

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Abstract
Oral diseases are dominant in both rural and urban centres, children, youth and among the aged in Nigeria, and range between 39% - 57%. The use of existing or orthodox antibiotic agents to treat oral diseases are not without a number of challenges, varying from potential for long – term adverse effect through biotic resistance, lack of antidote for the drug, balance between cost and effectiveness, among others. The application of nanotechnology in medicine has led to the beginning of multidrug resistance to various conventional antibiotics, and the increased financial burden due to medical-care expenses has been gaining a renewed interest among researchers to develop new and effective antimicrobial agents. Metal nanoparticles synthesized using different plant extracts to prevent activities of oral infection were developed. The use of silver nanoparticles has been well thought of for a

Introduction:
The term *"nanotechnology"* was produced by Norio Taniguchi of Tokyo University in 1974 to describe the manufacture of materials with nanometre tolerances, but its foundation dates back to Richard Feynman's 1959 talk: "There's Plenty of Room at the Bottom", in which he proposed the direct manipulation of individual atoms as a more powerful form of synthetic chemistry. Eric Drexler of MIT expanded Taniguchi's definition and popularised nanotechnology in his 1986 book "Engines of Creation: The Coming Era of Nanotechnology".
Nanoscience is the study of

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range of biomedical applications, including, within the dental field, an antibacterial factor in dental gum composites. The specific use of nanomaterials with antimicrobial properties and/or as a drug carrier system has been considered as a new line of defence against various pathogens and the application of MNPs in medicine and technology is the hope for future in oral infection diseases.

Keywords: Nanoparticles, Oral infection, sliver-nanoparticles, plant - mediated, nanotechnology

Phenomena and manipulation of materials at atomic, molecular and macromolecular scales, in order to understand and exploit properties that differ significantly from those on a larger scale. Nanotechnologies are the design, characterisation, production and application of structures, devices and systems by controlling shape and size on nanometre scale. Modern industrial nanotechnology had its origins in the 1930s, in processes used to create silver coatings for photographic film; and chemists have been making polymers, which are large molecules made up of nanoscale subunits, for many decades (*Burda et al., 2005;* Chityal, 2016).

Nanotechnology has assisted humans with the capacity to understand, control, design and manipulate matter with the skill of a craftsman at the simplest level of atoms and molecules. It is a technology that enables working with atoms and molecules that are sized on a nanometre (nm) scale with dimensions less than 100nm-these are the nanoparticles. The particles are being produced using different physical techniques such as lithography, laser ablation, sputtering deposition, pulsed electrochemical etching, vapour deposition, laser pyrolysis, plasma or flame spraying synthesis and chemical processes (sol gel processing) (Azeez, et al. 2020). In some years past, a lot of studies have demonstrated the synthesis of metal nanoparticles using different biological systems such as bacteria (Ojo, et al. 2016; Narayanan, et al. 2010 and Lengke, et al. 2007), fungi (Rautaray, et al. 2003 and Elegbede, et al. 2018), plants and their metabolites (Azeez, et al. 2017; Lateef, et al. 2016b; Lateef, et al. 2016c; Lateef, et al. 2016d; Shankar, et al., 2004; and Philip, 2011), insects and their metabolites (Lateef, et al. 2016e; Lateef, et al. 2016f;

Eranga et al. 2017 and Ghosh, et al. 2012); cobweb (Lateef, et al. 2016f), honey (Eranga et al. 2017) and earthworm (Kim et al. 2013) to mention a few. A detailed analysis of different methods of green synthesis, biological systems used and the special attributes of the synthesized particles have been compiled (Lateef, et al. 2016e)

Nanomaterials with characteristic dimensions in the nanometre regime find importance in nanoscience and nanotechnology. Despite the fact that nanoscience and nanotechnology as disciplines are new, mankind has been exposed to the use of nanomaterials since antiquity. Red colloidal gold tinctures were used as the first alchemical drugs for longevity, the so-called "Jin Tu" in China and "Makaradhwaja" in India (*Mahdihasan, 1985; Hayat, 1989). Noble nanomaterials were used from an ecological sense for both aesthetic and curative purposes, since ancient times. The Lycurgus Cup dating back to fourth century AD is an outstanding example of nanotechnology used by Roman glass-makers to manufacture this exotic goblet. This Roman goblet exhibited a dichronic effect due to the presence of colloidal metal particles of silver and gold; resembling jade with an opaque greenish-yellow tone in reflected light and when light transmitted through the glass it turned ruby red (Freestone et al., 2007). During the seventeenth century, noble metallic nanomaterials were used to make different clour preparations for staining glass windows of cathedrals throughout Europe and* by the Chinese for colouring ceramic vases and other ornaments, and similar applications are being practiced even today *(Trindade et al., 2001; Burda et al., 2005).*

In recent years, tremendous developments have occurred in the area of nanotechnology that has crossed the lab boundaries, and new applications have been identified that have geared to change our lifestyles. The rapid worldwide development of nanotechnology is a testimony to the transformative power of identifying a concept and laying out a vision at the synergistic confluence of diverse research areas. This has influenced several sectors ranging from healthcare, agriculture, environment, energy, to consumer products. It has built great expectations not only among the academic community but also among investors and industries. The global nano-product market is estimated to reach $3 trillion by the year 2020 **(Roco,**

2011). To meet this remarkable global demand, the synthesis of nanobiomaterials of specific size, shape, and composition for diverse applications has been a burgeoning area of research in the field of nanotechnology. In recent years, the increase in drug resistance in bacteria and the emergence of resistant bacterial infections have compelled the search for new antimicrobial agents. The unique physicochemical properties of nanomaterials along with the ability to inhibit microbial growth have led to the recent upsurge of research in the synthesis and application of nanobiomaterials for antimicrobial therapy (*Dunn and Edwards- Jones, 2004).*

Application of nanotechnology in medicine

In medicine, nanotechnology helps predict the major diseases that are likely to develop in an individual. The goal would be to routinely and cheaply analyze several hundred substances in a patient's blood and estimate disease risks with a relatively high degree of accuracy. This would also provide a window on a person's overall state of health. Several research groups are in fact working on developing a "labon-a-chip" device, using nanotechnology to perform a comprehensive analysis of a drop of blood. This analysis would alert the doctor to early precursors of disease that reflect both genetic predispositions and environmental factors, such as diet, exercise, stress and exposure to air pollution. In pre-emptive medicine, it focuses on early intervention, but it also requires early diagnosis. It is to help detect treatable diseases earlier so that they can help patients pre-empt the full-blown development of illness or at least manage it effectively over a lifetime. Nanotechnology can enhance the development of sensitive diagnostic tests, as well as devices for health monitoring and disease management (Schavan, (2011) cited in Bankole, *et al.,* (2014).

Oral health

Oral health is vital for overall health. Dental diseases are recognized as a disease of modern civilization and major public health problem globally (Adapa, et al. 2018). Oral diseases in Nigeria range between 39% and 57% among the ages 1-39. At age 1-15 it was 39% and 25–39 it was 57% (Akpata, 2004). In the past decades, microbiologists, taxonomists, molecular biologists, biochemists, epidemiologists, and dental scientists – led to the identification of the presumed pathogens of human dental caries and periodontal disease/s. The primary etiologic agents of dental caries are the *Streptococcus mutants* and *Streptococcus sobrinus* secondarily implicated are the *Lactobacillus* species. In chronic periodontitis, the species primarily implicated include *Porphyromonas gingivalis* (Pg), the spirochetes (including *Treponema* and *Selenomonas* species), and secondarily *Campylobacter*, *Fusobacterium*, and *Bacteroides* species, as reviewed by Liljemark, Bloomquist (Liljemark, 1996 cited in Adapa, 2020). Micro–organisms play a significant role in oral diseases, and control of their activities prevents oral diseases.

In recent time, the World Health Organisation (WHO) published a worldwide review of oral health which emphasized that, despite great developments in the oral health of populations in several countries, serious global problems still persisted (Petersen PE. World Health Organization global policy for improvement of oral health – World Health Assembly 2007). The human oral cavity harvests a diverse ecosystem including over 700 species of microorganisms, including bacteria, archaea, fungi, and viruses. Increasing evidence indicated that the microorganism contributes to infectious oral diseases including caries, periodontal diseases, endodontic infections, etc (He, et al. 2015).

Dental caries and periodontal diseases are the most prevalent bacteria-infectious oral diseases in humans worldwide. Severe periodontal diseases (periodontitis) are the leading cause of multiple tooth loss and edentulism in adults. Dental caries is the most prevalent chronic disease of childhood. The data from the Global Burden of Disease Study in 2010 showed that the worldwide burden of periodontal diseases, oral cancer, and caries increased markedly, by an average of 45.6% from 1990 to 2010 (Murray, et al. 2012). For example, pulpitis was caused by bacteria and their products entering the pulp through a deep caries lesion or a leaked filling (Haapasalo, et. al. 2005). Moreover, in apical periodontitis, bacteria could invade and colonize the entire root canal system (Haapasalo , et al. 2005). In addition, with the infective microorganisms residing in the main canal, the bacteria could penetrate from the main root canal into dentinal tubules, lateral canals, and other canal irregularities, leading to secondary endodontic infections (Haapasalo, et al. 2005). Indeed, studies have shown that dentin invasion occurred in 50–80% of the teeth with apical periodontitis (Peters, et al., 2000) Antibiotics is usually applied in the treatment of such oral infectious diseases. However, it was shown that the minimal concentration of antibiotics for the eradication of bacterial biofilm was difficult to reach in vivo (Hengzhuang, et al., 2011). Furthermore, there was an increasing concern on the abuse of antibiotics due to bacterial drug-resistance. Currently, antimicrobial photodynamic therapy (aPDT) was investigated as a promising antibacterial therapeutic modality to eliminate the aforementioned shortcomings.

Photodynamic therapy (PDT) was discovered over 100 years ago by observing the killing of microorganisms when harmless dyes and visible light were combined in vitro (Dai et al., 2009), since then, it was primarily developed as a treatment for cancer. Unlike traditional therapies (surgery, chemotherapy, and radiotherapy), PDT did not have severe side effects and could often be repeated (Hopper C. 2000), recently the interest in the antimicrobial effects of PDT was revived. PDT was proposed as a therapy for a large variety of localized infections,(Hamblin, 2016) and it was described as antimicrobial or antibacterial PDT, or photodynamic inactivation (PDI). aPDT employed appropriate excitation light in combination with photosensitizers (PSs) and oxygen, and allowed the non-specific attack against microorganisms by generating cytotoxic, especially singlet oxygen (Carrera, et al., 2016). Singlet PS was extremely unstable and could instantaneously release the energy, returning to the triplet state. The released energy was absorbed by the tissue oxygen to form ROS, which had a strong oxidation and high reactivity, thus causing rapid lipid oxidation of the bacteria. This led to the destruction of the vulnerable membrane lipids and eventually the bacterial death (Carrera, et al. 2016).

The major disadvantage of PSs was hydrophobic and poorly soluble in water. Therefore, a promising approach to enhancing the performance of PSs was to encapsulate them in nanostructured materials. The application of these nanocarriers would improve the drug availability for parenteral administration, by increasing the nanoparticle (NP) uptake for greater therapeutic efficacy(Van der Ouderaa, 1991). Therefore, the present article focuses on several synthetic routes of nanobiomaterials, their characterization, and their application of novel plant- mediated nanoparticles against oral cavity diseases. Also, the new developments in nanomaterial-based aPDT and the applications in dentistry, focusing on the bioactive and therapeutic effects against several key oral and dental infectious diseases. The aPDT researches attracted tremendous attention recently as an alternative approach to combating the drug-resistant microorganisms.

The emergence of multidrug resistance to various conventional antibiotics, and the increased financial burden due to medical-care expenses, has been gaining a renewed interest among researchers to develop new and effective antimicrobial agents. There is a profuse enthusiasm with regard to the materialization of nanomedicine; with many expectations to replace conventional antibiotics. In the present context, the specific use of nanobiomaterials with antimicrobial properties and/or as a drug carrier system has been considered as a new line of defence against various pathogens. The nanomaterial systems have great potential since they are able to change poorly soluble, weakly absorbed and labile biologically active molecules which can find use as antimicrobial drug delivery agents. Considering the prospects of nanotechnology in antimicrobial therapy, it is believed that these nanobiomaterials contribute to the concept "big dreams with small stuff," which will impact the biomedical sector in the future.

Synthesis of nanoparticles (NPs)

NPs are synthesized from metals such as platinum (Pt), silver (Ag), gold (Au), cadmium (Cd), cobalt (Co), iron (Fe), copper (Cu), and zinc (Zn). These NPs have distinctive sizes, shapes, surface areas, and density. Numerous technologies are involved in the fabrication of nanomaterials from various sources such as physical, chemical, and biological materials, and different strategies are used to maximize the production of nanomaterials such as the use of different raw materials, temperature, and pH (Muniyandi, *ET AL.,* 2019).

The confirmation of reducing agents that are widely distributed in the biological systems led to the evolution of green synthesis of AgNPs. The plant extract obtained from leaves, barks, roots, flower and seeds contain the *essential biomolecules: amino acids, proteins, enzymes, polysaccharides and vitamins that could efficiently reduce silver ions (Ag+ ions) to the AgNPs (Velayutham et al. 2013; Shaik et al. 2018). They may also act as capping agents for the colloidal stabilization of AgNPs (Kumar and Yadav 2009; Chung et al. 2016; Banerjee et al. 2014). Reportedly, the plant metabolites: terpenoids (Mashwani et al. 2016), alkaloids (Almadiy et al. 2017), and polyphenols (Jacob et al. 2008) mediate the bio reduction of metal ions to nanoparticles (Mittal et al. 2013; Makarov et al. 2014). An added advantage of the plant-mediated synthesis of AgNPs is that the plant extract customarily plays a dual role of reducing agent as well as that of a stabilizer (Roopan et al. 2013). Additionally, the most favoured solvent is water in most cases. However, reports have also validated the use of organic solvents like methanol, ethanol and ethyl acetate for the same purpose (Sadeghi et al. 2015; Rahimi-Nasrabadi et al. 2014; Logeswari et al. 2015). Table 1 presents a brief description of the plant extract mediated synthesis of AgNPs and their morphology. In these examples, the plant extract plays a dual role of a reluctant as well as the colloid stabilizer of MNPs.*

Table 1: Metal nanoparticles synthesized using different plant extracts to prevent activities of microbes.

Plant Source	*Metal Used*	*Average Size (nm)*	*Plant Phytochemicals*	*Application*	*References*
Neem (Azadirachta indica)	*Au*	*50-100*	*Ployhenols, terpentoids*	*antimicrobial*	*Shanikar et al. (2004)*
Cinnamon zeylanicum	*Ag*	*20-30*	*Polyphenols*	*antimicrobial*	*Sathishkumar et al. 2009*
Acalyphaindica	*Ag*	*2-20*	*flavonoids*	*antimicrobial activity*	*Krishnaraj et al. (2010)*
Cochlospermum gossypum	*Ag*	*3*	*Polysaccharides*	*antimicrobial*	*Kora et al. 2010*

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Sesuvium portulacastrum	*Ag*	*5-20*	*Flavonoids and terpenoids*	*antimicrobial activity*	*Nabikhan et al. 2010*
Citrus Sinensis	*Ag*	*25-30*	*Polyphenols*	*antimicrobial activity*	*Kavlya et al. 2011*
Sweet sorghum (Sorghum bicolour (L) Moench) syrup	*Ag*	*11.2±2.06*	*reducing sugars*	*antimicrobial activity*	*Kumar et al. (2012a)*
Tephrosia pumpurrea	*Ag*	*6.6*	*Polyphenols*	*antimicrobial activity*	*Rajathi and Sridhar (012)*
Tinospora cordifolia	*Ag*	*8.5*	*Polyphenols*	*antimicrobial activity*	*Rajathi et al. 2012*
Rhizophora mucronata	*Ag*	*4-26*	*Alkaloids*	*antimicrobial activity*	*Umashankan et al. 2012*
Terminalia chebula	*Au*	*6-60*	*Hydrolysable tannins*	*Antimicrobial activity*	*Kumar et al. (2012b*
Eucalyptus chapmaniana	*Ag*	*60*	*Flavanoids and terpenoids*	*Antimicrobial, anticancer activities*	*Sulaiman et al. (2013)*
Trigonella foenum graecum	*Ag*	*48*	*Saponins, coumarin, fenugreekine, nicotinic acid,*	*Antimicrobial activity*	*Pooloth (2013)*

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			phytic acid, scopoletin, and trigonelline		
Fermented soybean (Glycine max)—garlic (Allium sativum)	*Au*	*21.8*	*Flavonoids, polyphenols, and protein*	*Antimicrobial activity*	*El-Batal et al. (2013)*
Sterculia foetida	*Ag*	*30-50*	*Flavonoids, alkaloids, and polyphenols*	*Antimicrobial activity*	*Singh and Vidyasagar (2014)*
Wattakaka volublis	*Ag*	*30-40*	*n.s.*	*Antimicrobial activity*	*Gokak and Taranath (2014)*
Aerva lanata	*Ag*	*15_20*	*Flavonoids, terpenoids*	*Antibacterial activity*	*Balashanmugam et al. (2014)*
Pistacia atlantica seed	*Ag*	*27*	*Flavonoids and polyphenols*	*Antibacterial activity*	*Sadeghi et al. (2015)*

Source: Sujitha, et al. 2016

As several pathogenic bacteria are developing antibiotic resistance, silver nanoparticles (AgNPs) are the new hope to treat them. In general, particles with a size <100 nm are referred to as nanoparticles. Entirely novel and enhanced characteristics such as size, distribution and morphology have been revealed by these particles in comparison to the larger particles prepared (Ahmad and Sharma, 2012 and Banerjee, et al. 2014). The bactericidal activity of AgNPs against the pathogenic, multi-drug resistance (MDR) as well as multidrug susceptible strains of bacteria was studied by many scientists, and it was proved that the AgNPs are the powerful weapons against them (Rai, et al. 2012).

The nano-size of material results in specific physicochemical characteristics that are different from those of the bulk materials or larger particles. This effect is mainly credited to high surface-area-to-volume ratio, which results in increased reactivity; hence, the nano-scale materials are more advantageous than their bulk materials. The metallic nano-particles such as copper, titanium, magnesium, zinc, gold, and alginate have a strong bactericidal potential owing to their large surface-area-to-volume ratio. Among all, AgNPs have proved to be the most effective antimicrobial agent against bacteria, viruses and other eukaryotic microorganisms (Gong, et al., 2007).

Table 1 shows how nanoparticles (NPs) inhibit activities of microbes. Since the oral diseases are majorly caused by these microorganisms therefore, NPs will be the best option against oral diseases. Also, in a study conducted by Lu *et al*. (2013), stable Ag NPs with different sizes (~5, 15, and 55 nm mean values) were synthesized by using a simple reduction method or hydrothermal method. The antibacterial activities were evaluated by colony counting assay and growth inhibition curve method, and corresponding minimum inhibitory concentration (MIC) against five anaerobic oral pathogenic bacteria and aerobic bacteria *E. coli* were determined. The results showed that AgNPs had apparent antibacterial effects against the anaerobic oral pathogenic bacteria and aerobic bacteria. The MIC values of 5-nm Ag against anaerobic oral pathogenic bacteria *Aggregatibacter actinomycetemcomitans* (Aa), *Fusobacterium nucleatum* (Fn), *Streptococcus mitis*, *S. mutans* and *Streptococcus sanguis* were 25, 25, 25, 50, and 50 μg/mL, respectively. The aerobic oral bacteria were more susceptible to AgNPs than the anaerobic bacteria. The results showed a potential role of AgNPs in the inhibition of oral microbial infections.

Similarly several studies have demonstrated that bacteria are the main etiologic agent of pulpal infection and peri-radicular lesion formation (Byström, and Sundqvist, 1981 copied as referenced by Adapa, 2020). Various materials have been used as root canal fillings, among which gutta-percha is one of the most used (Shantiaee, et al. 2011). Since elimination of bacteria in root canals is the key to treatment success, endodontic materials should ideally provide some antimicrobial activity. Iranian researchers (2008) (Dianat and Atale, 2008) have introduced nanosilver gutta-percha, as an attempt to improve the antibacterial effect of gutta-percha. The new material, which is standard gutta-percha coated with AgNPs, has demonstrated significant effect against *E. faecalis*, *S. aureus*, *C. albicans*, and *E. coli*.
Aiming to improve antimicrobial potential of mineral trioxide aggregate (MTA), Samiei *et al.* (2013) modified MTA by adding AgNPs, at 1% weight. Its effect against oral bacteria and fungi species was assessed. Results have showed that AgNPs-containing MTA possesses higher antimicrobial effect against *E. faecalis, C. albicans*, and *Pseudomonas aeruginosa*, compared to unmodified MTA. In study performed by Zhao *et al.* (2011) AgNPs were incorporated into titanic nanotubes (TiO_2-NTs) on Ti implants, in a process involving silver nitrate immersion and UV radiation. The antibacterial effect against *S. aureus* was assessed, and results have shown the inhibition of planktonic bacteria during the first several days. Moreover, AgNPs-coating Ti implants have presented ability to prevent bacteria adhesion for up to 30 days, which are considered sufficient time to prevent post infection in early stages. AgNPs-containing dental materials present good antimicrobial properties. However, much is still to be discovered.

Table 2: Antimicrobial effectiveness of silver nano-particles in dental materials

Material studied	AgNPs concentration	Antimicrobial effectiveness	Reference
Composite resin	0.028 weight %, 0.042 weight % 0.088 weight%, 0.175 weight %	Good inhibitory activity against *S. mutans*, at 0.042 weight %	Cheng, et al. (2012

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Adhesive system	0.05 weight % 0.1 weight %	Reduction of CFU and acid lactic production for *S. mutans* Reduction of CFU for total microorganisms, total streptococci, and *S. mutans*	Li, et al. (2013)
Primer and adhesive	0.05 weight %	Good inhibitory activity against total microorganisms, total streptococci, and *S. mutans*	Zhang, et al. 2013
Acrylic resin	1 µg/mL 0.05 volume %, 0.5 volume % and 5 volume %	Reduction on *C. albicans* adherence Good efficacy against *C. albicans*, at 5 volume %	Monteiro, et al. 2012
Tissue conditioner	0.1%, 0.5%, 1.0%, 2.0% and 3.0%	Antimicrobial properties against *S. mutans* and *S. aureus* at 0.1% and against *C. albicans* at 0.5%	Nam, 2011
Intracanal irrigant	0.005%	Bactericidal effect against *E. faecalis*	Lotfi, et al. 2011
Gutta-percha	-	Significant effect against *E. faecalis*, *S. aureus*, *C. albicans* and *E. coli.*	Dianat et al. (2008)
MTA	1 weight %	High antimicrobial effect against *E. faecalis*, *C. albicans*, and *P. aeruginosa*	Samiei, et al. (2013)
Titanium implants	0.5 M, 1.0 M, 1.5 M, 2.0 M 3.16×10−2 mg Ag/mL	Prevention of *S. aureus* adhesion for up to 30 days Reduction of *P. aeruginosa* adhesion	Zhao, 2011; Flores, et al 2010

Source: Adapa, 2020

Dental caries and periodontal diseases, the majority widely increased diseases affecting mankind, occupy the devotion of microbes and expansion of biofilm on the natural and restored tooth surface equally. In this framework, a biofilm can be classed as an aggregate of bacteria in which cells stay to each other and to an outside (Marsh and Martin 2009). Nanostructured materials are a technically significant object that possesses optical and electrical properties that depend powerfully on the size and shape of the nanoparticles. This is due to confinement of the charge carriers in the narrow space of the nanocrystal (Dameron, et al., 1989; Steigerwald and Brus, 1990). Semiconductor and other nanoparticles are currently being combined by polymers or coated onto surfaces which may have a multiplicity of potential antimicrobial applications with the oral cavity (Hannig, *ET AL.,* 2007; Monteiro, *ET AL.,* 2009). In addition to that, II-VI semiconductor nanoparticles are playing attention in enormous fields due to their excellent and unique optical and electrical properties which present a major advantage over their mass counterparts (Loukanov, *ET AL.,* 2004; Speiser, *ET AL.,* 2008). Polymers are also excellent host materials as capping agents and stabilizers since they prevent agglomeration and precipitation of the particles. Sulphide is a semiconductor nanomaterial processing a lot of interesting physical properties and potentially used in mesoscopic electronic (Stanley, 1975 cited in Malarkodi, et al., 2013) bio-labelling (Elghanian, *ET AL.,* 1997) and photo-catalysis (Malarkodi and Annadurai, 2013). Metals have been used for centuries as bactericidal agents; silver, copper, gold, titanium, and zinc have attracted particular attention, each having various properties and spectra of activity (Vanaja, *ET AL.,* 2013).

Various oral foods, including toothpaste, now integrate powdered zinc citrate or acetate to control the development of dental plaque (Giertsen, 2004). Powdered titanium oxide is also generally used as a whitener in toothpastes (Malarkodi, et al, 2013). The antibacterial, antifungal, and antiviral actions of sulphide nanoparticles have been broadly investigated in comparison with other metals.

The use of silver nanoparticles has been well thought of for a range of biomedical applications, including, within the dental field, an antibacterial factor in dental resin composites (Rajeshkumar, *ET AL.,* 2013). The anticipation of dental caries and periodontal infection is usually targeted at automatic or nonspecific control of the plaque biofilm; biofilms are part of our daily life, for example, when brushing our teeth (Hans-Curt and Grill, 1990). The use of bactericidal agents represents an expensive balance to mechanical plaque control (Baehni and Takeuchi, 2003). However, real periods of exposure to antimicrobial agents through tooth brushing and mouth rinsing can be present especially short, amounting to 30 seconds (Van der Ouderaa, 1991).

Conclusion

In conclusion, the presence or emergence of multidrug resistance to various conventional antibiotics, and the increased financial burden due to medical-care expenses, has been gaining a renewed interest among researchers to develop new and effective antimicrobial agents. There is a profuse enthusiasm with regard to the materialization of nanomedicine; with many expectations to replace conventional antibiotics. In the present context, the specific use of nanomaterials with antimicrobial properties and/or as a drug carrier system has been considered as a new line of defence against various pathogens. In this review, we provided an account of the biological methods for MNPs (green nano) synthesis, as well as their most promising applications in biomedical devices and in oral infection diseases. Presently, nanomedicine and nanotechnology are the hope for future, although if nanotechnology and nanomedicine have to be the key to the future, they should be developed with sustainability in mind from the outset.

Recommendations

Based on the major application of nanotechnology discussed above, the technology has been established to be useful and functional in many other areas. The overall benefit derived from nanotechnology will revive the economy of any nation. There is the need for the government of African countries to understand the impact that nanotechnology can have in all the sectors of the economy for improved standard of living of the populace. Therefore, government should support the researchers financially in all areas of nanotechnology. Also, government agents and individual populace should encourage the researchers in tertiary institutions and national research centres to carry out more investigation into medical nanotechnology, since health is wealth. Government can also encourage and sponsor seminars, workshops, short courses, post-graduate courses and conferences in the discipline. Adequate and appropriate research facilities should also be provided for those in the field to sustain trained personnel and graduates to check brain drain or diversion of research interest.

References

Adapa, S. B. (2020). A Review on silver nanoparticles-The powerful nano-weapon against oral pathogens. *Int. J Oral Health Sci*. **10**:6-12.

Adapa, S. B., Sushanth, V. H., Prashant, G. M. (2018). *Mohamed I. In vitro antimicrobial activity of Spinacia oleracea against Streptococcus mutans and Lactobacillus acidophilus*. *J Indian Assoc. Public Health Dent.* **16**:251-5.

Ahmad N, Sharma S. (2012). Green synthesis of silver nanoparticles using extracts of *Ananascomosus.* Green Sustain Chem 2:141-7.

Akpata Kuwait, E. S. (2004). Oral health in Nigeria. *International Dental Journal,* **54**: 361-366

Almadiy, A. A., Nenaah, G. E., Shawer, D. M. (2017) Facile synthesis of silver nanoparticles using harmala alkaloids and their insecticidal and growth inhibitory activities against the khapra beetle. *J Pest Sci*. **91**:727–737. https ://doi.org/10.1007/s1034 0-017-0924-2.

Azeez, M. A. Durodola, F. A. Lateef, A. Yekeen, T. A. Adubi, A. O. Oladipo, I. C. Adebayo, E. A. Badmus, J. A. and Abawulem, A. O. (2020). Green synthesized novel silver nanoparticles and their application as anticoagulant and thrombolytic agents: A perspective, *IOP Conf. Ser.: Mater: Sci. Eng:* 805 012043

Azeez, M. A., Lateef, A., Asafa, T. B., Yekeen, T. A., Akinboro, A., Oladipo, I. C., Gueguim-Kana, E. B. and Beukes, L. S. 2017 Biomedical applications of cocoa bean extract-mediated silver nanoparticles as antimicrobial, larvicidal and anticoagulant agents. *J. Clust. Sci.* **28** 149-164.

Baehni, P. C. and Takeuchi, Y. (2003). "Anti-plaque agents in the prevention of biofilm-associated oral diseases," *Oral Diseases*, **9**, (1), 23–29.

Banerjee, P., Satapathy, M., Mukhopadhyay, M., Das, P. (2014). Leaf extract mediated green synthesis of silver nanoparticles from widely available Indian plants: synthesis, characterization, antimicrobial property and toxicity analysis. *Bioresour Bioprocess* 1:3. https ://doi.org/10.1186/s4064 3-014-0003-y

Bankole, M. T. Jimoh, O. Tijani, I. A. Mohammed and Abdulkareem A. S. (2014). A review on nanotechnology as a tool of change in Nigeria **9**(8), 213-223, http://www.academicjournals.org/SRE

Burda, C., Chen, X., Narayanan, R., El-Sayed, M. A. (2005). Chemistry and properties of nanocrystals of different shapes. Chem. Rev. **105**, 1025 -1102.

Carrera, E., Dias, H., Corbi, S. 2016). The application of antimicrobial photodynamic therapy (aPDT) in dentistry: a critical review. *Laser Phys*. (26):123001. doi:10.1088/1054-660X/26/12/123001 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

Chityal, G., Kumar, S. P., Yedla, P. and Sankalp, V. A. (2016). Synthesis, characterization, and applications of nanobiomaterials for antimicrobial therapy Nanobiomaterials in Antimicrobial Therapy. DOI: CSIR—Indian http://dx.doi.org/10.1016/B978-0-323-42864-4.00004-X Elsevier Inc.

Chung, I. M., Park, I. Seung-Hyun, K., Thiruvengadam, M., Rajakumar, G. (2016). Plant-mediated synthesis of silver nanoparticles: their characteristic properties and therapeutic applications. Nanoscale Res Lett 11:40. https ://doi.org/10.1186/s11671-016-1257-4

Dai, T., Huang, Y. Y., Hamblin, M. R. (2009). Photodynamic therapy for localized infections – state of the art. *Photodiagn Photodyn*. **6**(3–4):170–188. doi:10.1016/j.pdpdt. 2009.10.008 (PMC free article) (PubMed) (CrossRef) (Google Scholar)

Dameron, C. T. Reese, R. N. Mehra, R. K. (1989). "Biosynthesis of cadmium sulphide quantum semiconductor crystallites," *Nature*, **338**, (6216), 596–597.

Dianat, O., Ataie, M. (2008). Gutta-Percha Coated With Nanosilver Particles. Invention Registered Number: 56019.

Dunn, K., Edwards-Jones, V. (2004). The role of acticoat with nanocrystalline silver in the management of burns. Burns **30**, S1-S9.

Elegbede, J. A., Lateef, A., Azeez, M. A., Asafa, T. B., Yekeen, T. A., Oladipo, I. C., Adebayo, E. A., Beukes, L. S. and Gueguim-Kana, E. B. (2018). Fungal xylanases-mediated synthesis of silver nanoparticles for catalytic and biomedical applications. *IET Nanobiotechnol*. **12** (6) 857-863.

Elghanian, R., Storhoff, J. J., Mucic, R. C., Letsinger, R. L. and Mirkin, C. A. (1997). "Selective colorimetric detection of polynucleotides based on the distance-dependent optical properties of gold nanoparticles," *Science*, **277**, (5329), 1078–1081.

Eranga, R. B., Chanika, D. J., Uthpala, A. J., Ranasinghe, W. D., Ruwanthika, R. M. and Pretti, V. U. (2017). Honey mediated green synthesis of nanoparticles: New era of safe Nanotechnology. *J. Nanomater.* http://doi.org/10.1155/2017/5919836.

Freestone, I., Meeks, N., Sax, M., Higgitt, C. (2007). The lycurgus cup—a roman nanotechnology. Gold Bull. **40**, 270-_277.

Ghosh, S., Patil, S., Ahire, M., Kitture, R., Gurav, D. D., Jabgunde, A. M., Kale, S., Pardesi, K., Shinde, V., Bellare, J., Dhavale, D. D. and Chopade, B. A. (2012). *Gnidia glauca* flower extract mediated synthesis of gold nanoparticles and evaluation of its chemocatalytic potential. *J. Nanobiotechnol.* 10 17. https://doi.org/10.1186/1477-3155-10-17.

Giertsen, E. (2004). "Effects of mouth rinses with triclosan, zinc ions, copolymer, and sodium lauryl sulphate combined with fluoride on acid formation by dental plaque *in vivo*," *Caries Research*, **38**(5), 430–435.

Gong, P., Li, H., He, X., Wang, K., Hu, J., Tan, W. *(*2007). Preparation and antibacterial activity of Fe3O4@Ag nanoparticles. Nanotechnology **18**:604-11.

Haapasalo, M., Endal, U., Zandi, H., Coil, J. M. (2005). Eradication of endodontic infection by instrumentation and irrigation solutions. *Endod Topics*. **10**(1):77–102. doi:10.1111/j.1601-1546.2005.00135.x (CrossRef) (Google Scholar)

Hamblin, M. R. (2016). Antimicrobial photodynamic inactivation: a bright new technique to kill resistant microbes. *Curr Opin Microbiol*. 33:67–73. doi:10.1016/j.mib.2016.06.008 (PMC free article) (PubMed) (CrossRef) (Google Scholar)

Hans-Curt, F. and Grill, G. G. (1990). "Biofouling and biocorrosion in industrial water system," in *Proceedings of the International Workshop on Industrial Biofouling and Biocorrosion*, 200, Springer.

Hannig, M. Kriener, L. Hoth-Hannig, W. Becker-Willinger, C. and Schmidt, H. (2007). "Influence of nanocomposite surface coating on biofilm formation *in situ*," *Journal of Nanoscience and Nanotechnology*, **7**(12): 4642–4648.

Hayat, M. A. (1989). Colloidal Gold: Principles, Methods and Applications. Academic Press,

New York.

He, J., Li, Y., Cao, Y., Xue, J., Zhou, X. (2015). The oral microbiome diversity and its relation to human diseases. *Folia Microbiol*. **60**(1): 69–80. doi:10.1007/s12223-014-0342-2 (PubMed) (CrossRef) (Google Scholar)

Hengzhuang, W., Wu, H., Ciofu, O., Song, Z., Høiby, N. (2011). Pharmacokinetics/ pharmacodynamics of colistin and imipenem on mucoid and nonmucoid *Pseudomonas aeruginosa* biofilms. *Antimicrob Agents Ch*. **55**(9): 4469–4474. doi:10.1128/AAC.00126-11 (PMC free article) (PubMed) (CrossRef) (Google Scholar)

Hopper, C. (2000). Photodynamic therapy: a clinical reality in the treatment of cancer. *Lancet Oncol*. **1**(4):212–219. doi:10.1016/S1470-2045(00)00166-2 (PubMed) (CrossRef) (Google Scholar)

Jacob, J. A., Mahal, H. S., Biswas, N., Mukherjee, T., Kapoor, S. (2008). Role of phenol derivatives in the formation of silver nanoparticles. Langmuir **24**:528–533. https ://doi.org/10.1021/la702 073r

Kim, H. K., Choi, M., Cha, S., Koo, Y. K., Jun, S. H., Cho, S. and Park, Y. (2013). Earthworm extracts utilized in the green synthesis of gold nanoparticles capable of reinforcing the anticoagulant activities of heparin. *Nanoscale Res. Lett.* **8** 542. https://doi.org/10.1186/1556-276X-8-542.

Kumar, V. and Yadav, S. K. (2009). Plant mediated synthesis of silver and gold nanoparticles and their applications. *J Chem Technol Biotechnol* **84**:151–157. https ://doi.org /10. 1002 /jctb.2023

Lateef, A., Akande, M. A., Azeez, M. A., Ojo, S. A., Folarin, B. I., Gueguim-Kana, E. B. and Beukes, L. S. (2016d). Phytosynthesis of silver nanoparticles (AgNPs) using miracle fruit plant (*Synsepalum dulcificum*) for antimicrobial, catalytic, anticoagulant, and thrombolytic applications. *Nanotechnol. Rev.* **5**(6): 507-520.

Lateef, A., Azeez, M. A., Asafa, T. B., Yekeen, T. A., Akinboro, A., Oladipo, I. C., Gueguim-Kana, E. B. and Beukes, L. S. (2016f). Cobweb as novel biomaterial for the green and eco-friendly synthesis of silver nanoparticles. *Appl. Nanosci.* **6:** 863-874.

Lateef, A., Azeez, M. A., Asafa, T. B., Yekeen, T. A., Akinboro, A., Oladipo, I. C., Azeez, L., Ojo, S. A., Gueguim-Kana, E. B. and Beukes, L. S. (2016b). Cocoa pod husk extract-mediated biosynthesis of silver nanoparticles: Its antimicrobial, antioxidant and larvicidal activities. *J. Nanostruct. Chem*. **6** (2): 159-169.

Lateef, A., Ojo, S. A. and Elegbede, J. A. (2016e). The emerging roles of arthropods and their metabolites in the green synthesis of metallic nanoparticles. *Nanotechnol. Rev.* **5** (6): 601-622.

Lateef, A., Ojo, S. A., Folarin, B. I., Gueguim-Kana, E. B. and Beukes, L. S. (2016c). Kolanut (*Cola nitida*) mediated synthesis of silver-gold alloy nanoparticles: antifungal, catalytic, larvicidal and thrombolytic applications. *J. Clust. Sci.* **27:** 1561-1577.

Lengke, M. F., Fleet, M. E. and Southam, G. (2007). Biosynthesis of silver nanoparticles by filamentous cyanobacteria from nitrate complex. *Langmuir* **23**(5): 2694-2699.

Loukanov, A. R. Dushkin, C. D. Papazova, K. I. Kirov, A. V. Abrashev, M. V. and Adachi, E. (2004). "Photoluminescence depending on the ZnS shell thickness of CdS/ZnS core-shell semiconductor nanoparticles," *Colloids and Surfaces A*, **245** (1–3): 9– 14.

Liljemark, W. F., Bloomquist, C. (1996). Human oral microbial ecology and dental caries and periodontal diseases. Crit Rev Oral Biol Med; 7:180-98.

Logeswari, P., Silambarasan, J., Abraham, J. (2015). Synthesis of silver nanoparticles using plants extract and analysis of their antimicrobial property. *J Saudi Chem Soc* 19:311–317. https ://doi.org/10.1016/j.jscs.2012.04.007

Lu, Z., Rong, K., Li, J., Yang, H., Chen R. (2013). Size-dependent antibacterial activities of silver nanoparticles against oral anaerobic pathogenic bacteria. *J Mater Sci Mater Med* **24**:1465-71

Mahdihasan, S. (1985). Cinnabar-gold as the best alchemical drug of longevity, called Makaradhwaja in India. *Am. J. Chin. Med.* **13**, 93-108.

Makarov, V., Love, A., Sinitsyna, O., Yaminsky, S. M. I., Taliansky, M., Kalinina, N. (2014) Green nanotechnologies: synthesis of metalnanoparticles using plants. *Acta Nat* **6**:35–44

Malarkodi, C. and Annadurai, G. (2013). "A novel biological approach on extracellular synthesis and characterization of semiconductor zinc sulfide nanoparticles," *Applied Nanoscience*, **3**(5): 389–395.

Malarkodi, C. Chitra, K. Rajeshkumar, S. (2013). "Novel eco-friendly synthesis of titanium oxide nanoparticles by using *Planomicrobium*sp. and its antimicrobial evaluation," *Der Pharmacia Sinica*, **4**(3): 59–66.

Marsh, P. D. and Martin, M. V. (2009). *Oral Microbiology*, Churchill- Livingstone, London, UK, 5th edition.

Mashwani, Z. R., Khan, M. A., Khan, T., Nadhman, A. (2016). Applications of plant terpenoids in the synthesis of colloidal silver nanoparticles. *Adv. Colloid Interface Sci.* **234**:132–141. https ://doi.org/10.1016/j.cis.2016.04.008

Mittal, A. K., Chisti, Y., Banerjee, U. C. (2013). Synthesis of metallic nanoparticles using plant extracts. *Biotechnol Adv* **31**:346–356. https://doi.org/10.1016/j.biote chadv .2013.01.003

Monteiro, D. R., Gorup, L. F., Takamiya, A. S., Ruvollo-Filho, A. C., Camargo, E. R. D. and Barbosa, D. B. (2009). "The growing importance of materials that prevent microbial adhesion: antimicrobial effect of medical devices containing silver," *International Journal of Antimicrobial Agents*, **34**(2): 103–110.

Muniyandi, J., Sangiliyandi, G., Muhammad, Q., Min-Hee, K. and Jin-Hoi, K. (2019). A Comprehensive Review on the Synthesis, Characterization, and Biomedical Application of Platinum Nanoparticles 102- 152 www.mdpi.com/journal/nanomaterials DOI: http://dx.doi.org/10.1016/B978-0-323-42864-4.00004-X

Murray, C. J., Vos, T., Lozano, R. (2012). Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. **380**(9859):2197–2223. doi:10.1016/S0140-6736(12)61689-4 (PubMed) (CrossRef) (Google Scholar)

Narayanan, K. B. and Sakthivel, N. (2010). Biological synthesis of metal nanoparticles by microbes. *Adv. Colloid Interf. Sci.* **156** (1-2): 1-13.

Ojo, S. A., Lateef, A., Azeez, M. A., Oladejo, S. M., Akinwale, A. S., Asafa, T. B., Yekeen, T. A., Akinboro, A., Oladipo, I. C., Gueguim-Kana, E. B. and Beukes, L. S. (2016). Biomedical and catalytic applications of gold and silver-gold alloy nanoparticles biosynthesized using cell-free extract of *Bacillus safensis* LAU 13: antifungal, dye degradation, anti-coagulant and thrombolytic activities. *IEEE Trans. Nanobiosci.* **15**(5): 433-42.

Peters, L., Wesselink, P., Moorer, W. (2000). Penetration of bacteria in bovine root dentine *in vitro. Int Endodon J*. 2000, **33**(1):28–36. doi:10.1046/j.1365-2591. 00268.x (PubMed) (CrossRef) (Google Scholar)

Petersen, P. E. (2008). World Health Organization global policy for improvement of oral health – World Health Assembly 2007. *Int Dent J*. 58(3):115–121.(PubMed) (Google Scholar).

Philip, D. (2011). *Mangifera indica* leaf-assisted biosynthesis of well-dispersed silver nanoparticles. *Spectrochim. Acta. A.* **78**(1) 327-331.

Rahimi-Nasrabadi, M., Pourmortazavi, S. M., Shandiz, S. A. S., Ahmadi, F., Batooli, H. (2014). Green synthesis of silver nanoparticles using *Eucalyptus leucoxylon* leaves extract and evaluating the antioxidant activities of the extract. Nat Prod Res **28**:1964–1969. https://doi.org/10.1080/14786 419.2014.91812 4

Rai, M. K., Deshmukh, S. D., Ingle, A. P., Gade, A. K. (2012). Silver nanoparticles: The powerful nanoweapon against multidrug-resistant bacteria. *J Appl Microbiol*;**112**:841 -52.

Rajeshkumar, S. Malarkodi, C. Paulkumar, K. Vanaja, M. Gnanajobitha, G. and Annadurai, G. (2013).“Intracellular and extracellular biosynthesis of silver nanoparticles by usingmarine bacteria *Vibrio alginolyticus*,” *Nanoscience and Nanotechnology*, **3**(1): 21–25.

Rautaray, D., Ahmad, A. and Sastry, M. (2003). Biosynthesis of CaCO3 crystals of complex morphology using fungus and an actinomycete. *J. Am. Chem. Soc.* **125**(48): 14656-14657.

Roco, M.C., (2011). The long view of nanotechnology development: the national nanotechnology initiative at 10 years. *J. Nanopart. Res*. **13:** 427-445.

Roopan, S. M., Madhumitha, G., Rahuman, A. A., Kamaraj, C., Bharathi, A., Surendra, T. (2013). Low-cost and eco-friendly phyto-synthesis of silver nanoparticles using Cocos nucifera coir extract and its larvicidal activity. *Ind Crops Prod* **43**:631–635. https ://doi. org/10.1016/j.indcr op.2012.08.013

Sadeghi, B., Gholamhoseinpoor, F. (2015). A study on stability and green synthesis of silver nanoparticles using *Ziziphora tenuior* (Zt) extract at room temperature. Spectrochim Acta Part A Mol Biomol Spectrosc **134**:310–315. https ://doi.org/10.1016/j. saa.2014.06.046

Sadhu, S., Saha - Chowdhury, P. and Patra, A. (2008). “Synthesis and time-resolved photoluminescence spectroscopy of capped CdS nanocrystals,” *Journal of Luminescence*, **128**(7): 1235– 1240.

Samiei, M., Aghazadeh, M., Lotfi, M., Shakoei, S., Aghazadeh, Z., Vahid Pakdel, S. M. (2013). Antimicrobial efficacy of mineral trioxide aggregate with and without silver nanoparticles. *Iran Endod J.* **8**:166-70.

Shaik, M. R., Khan, M., Kuniyil, M., Al-Warthan, A., Alkhathlan, H. Z., Siddiqui, M. R. H., Shaik, J. P., Ahamed, A, Mahmood, A., Khan, M., Adil, S. F. (2018). Plant-extract-assisted green synthesis of silver nanoparticles using *Origanum vulgare* L. extract and their microbicidalactivities. *Sustainability* **10**:913. https ://doi.org/10.3390/su100 40913

Shankar, S. S., Rai, A., Ahmad, A. and Sastry, M. (2004). Rapid of Au, Ag and bimetallic Au core – Ag shell nanoparticles using Neem (*Azadirachta indica*) leaf broth. *J. Colloid Interf. Sci.* **275**(2): 496-502.

Shantiaee, Y., Maziar, F., Dianat, O., Mahjour, F. (2011). Comparing microleakage in root canals obturated with nanosilver coated gutta-percha to standard gutta-percha by two different methods. *Iran Endod J* **6**:140-5.

Speiser, D. M. Ortiz, D. F. Kreppel, L. Scheel, G. McDonald, G. and Ow, D. W. (2008). "Purine biosynthetic genes are required for cadmium tolerance in Schizosaccharomyces pombe," *Molecular and Cellular Biology*, **12**(12): 5301–5310.

Steigerwald, M. L. and Brus, L. E. (1990). "Semiconductor crystallites: a class of large molecules," *Accounts of Chemical Research*, **23**(6): 183–188,

Trindade, T., O'Brien, P., Pickett, N. L. (2001). Nanocrystalline semiconductors: synthesis, properties and perspectives. *Chem. Rev.* **13:** 3843-3858

Vanaja, M., Rajeshkumar, S., Paulkumar, K., Gnanajobitha, G., Malarkodi, C. and Annadurai, G. (2013). "Phytosynthesis and characterization of silver nanoparticles using stem extract of *Coleus aromaticus*," *International Journal ofMaterials and Biomaterials Applications*, **3**(1): 1–4.

Van der Ouderaa, F. J. G. (1991). "Anti-plaque agents: Rationale and prospects for prevention of gingivitis and periodontal disease," *Journal of Clinical Periodontology*, 1**8**(6): 447–454

Velayutham, K., Rahuman, A. A., Rajakumar, G., Roopan, S. M., Elango, G., Kamaraj, C., Marimuthu, S., Santhoshkumar, T., Iyappan, M., Siva, C. (2013). Larvicidal activity of green synthesized silver nanoparticles using bark aqueous extract of *Ficus racemosa* against *Culex quinquefasciatus* and *Culex gelidus*. *Asian Pac J Trop Med* **6**:95–101. https ://doi.org/10.1016/S1995 -7645(13)60002 -4

World Health Assembly (20007)

Zhao, L., Wang, H., Huo, K., Cui, L., Zhang, W. and Ni, H. (2011). Antibacterial nano-structured titania coating incorporated with silver nanoparticles. *Biomaterials* **32**:5706-16.