



# An Overview of Nanoparticle Properties and Their Bioactivity

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## Authors' contributions

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## ABSTRACT

The term "nanoparticles" being expressed in microbiology is coined from the Greek word "nano" meaning "dwarf". Nanoparticles range in size from 1-100nm. Nanoparticles vary in size, shape, and other properties and can exist with capping agents present after structure-controlled synthesis with starting materials like metals with or without organic agents. This systematic literature review article discusses current opinions on the properties of nanoparticles including the size and shape, surface area and surface charge, surface chemistry and reactivity and their magnetic properties. We also discuss the mechanisms of bioactivity of nanoparticles in reference to their interactions with microorganisms, penetration into microorganisms, disruption of cellular processes and their effects on microbial growth. We also discuss specifically, their antibacterial, antifungal and antiviral properties. This is followed by a review of their diagnostic and therapeutic applications, the factors affecting nanoparticle bioactivity (exposure time and other intrinsic physicochemical properties) and how the intrinsic properties of microorganisms such as strain selection and growth conditions are

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affected by the activity of nanoparticles. In this review, we also compare nanoparticle research in the new world with activities in third world countries. We conclude by discussing the toxicity and safety concerns in the use of nanoparticles including the environmental impact and regulatory guidelines in the use of nanoparticles followed by a recommendation on future guidelines for research.

**Keywords:** Nanoparticles; bioactive; antimicrobial; properties; bacteria; antibacterial.

## 1. INTRODUCTION

The term “nanoparticles” being expressed in microbiology is coined from the Greek word “nano” meaning “dwarf” [172]. With size of one-billionth of a meter in diameter, nanoparticles commonly are viewed using electron microscopy [11, 146]. They range in size from 1-100nm. Nanoparticles vary in size, shape, and other properties and can exist with capping agents present after structure-controlled synthesis with starting materials like metals with or without organic agents [173].

The size of a nanoparticle contributes to its versatility and enables it to be taken up more easily taken up by cells and other materials. This versatility aids in in-vitro research studies and in industry [161, 190]. Fields that employ the use of nanoparticles ranging from chemistry to physics to microbiology and to biomedicine and this attribute commonly leads to interdisciplinary studies [15, 203, 204].

Nanoparticles can be incorporated into antimicrobials to speed up reaction time and to increase efficacy of the resulting polymer molecule. This is however a task that will benefit from innovations in antimicrobial research showing the broad use and potential [187].

In antimicrobial research, the size of the nanoparticle also affects its ability to enter cells and its ability to be used as a carrier molecule in drug delivery and vaccine production [256]. This attribute of NPs with a range of uses have enabled them stand out and remain relevant in the future of Multi-Drug Resistance solution research [90, 254].

This article provides insight into the versatility, attributes and multidimensional applicability of nanoparticles as it relates to microbiology.

### 1.1 What they can be Synthesized from

The top-down method of nanoparticle synthesis involves deconstruction of larger metals and

molecules into smaller bits till the size becomes a nanoparticle [53]. The bottom-up approach involves the fusion of colloids till the nanoparticles are built up. The bottom-up approach reduces the loss of size and concentration of the final product [205, 241]. This approach offers a more cost effective method of nanoparticle synthesis than other approaches to nanoparticle synthesis. Green synthesis of nanoparticles is the use of natural substances such as plants, plant extract or cellulose as the substrate from which nanoparticles are made [8]. The involvement of microorganisms for nanoparticle creation is a phenomenon whereby the metabolic products and activities of microorganisms are harnessed in the creation of nanoparticles [166].

Types of nanoparticles include carbon-based nanoparticles, lipid-based nanoparticles, ceramic nanoparticles, metal nanoparticles, semiconductor nanoparticles and polymeric nanoparticles. As will be discussed, nanoparticles synthesised from gold are believed to have broad range of positive and negative effects on life forms [120, 267]. Small concentrations of nanoparticles synthesized from silver are highly useful in orthodontics [6]. They exhibit effects on the occurrence and prevalence of the microorganisms that form the biofilm matrix of the oral setting targeting microorganisms like *Lactobacillus* and *Streptococcus* [137]. Copper-chitosan nanoparticle complexes have proven to be effective in the prevention and control of biofilm forming cariogenic species of *Candida* and *Streptococcus* as demonstrated by Raile et al.,[185].

Nanoparticles, as stated by Zhang et al., [264] and Kushawa et al., [121] can be found naturally as part of food (cheese, milk, whey proteins and butter) and agricultural products since the development of modern agriculture [125]. Such nanoparticles include gold, silver, calcium carbonate, selenium and titanium oxide [232, 34, 81, 124].

## 1.2 Fields Nanoparticles can be Harnessed in

Despite the rapid evolution of the field of microbiology and the drift toward more standardised methods and tools in study of microbiological phenomena [143], articles originating from 3<sup>rd</sup> world countries on antimicrobial nanoparticles research still receive less citations from research carried out in 1<sup>st</sup> world countries as seen when searching scholarly databases with the keywords “Antimicrobial” “Nanoparticle” “Ibadan” [229, 138]. However, education in less developed countries still employ the tools of crude, antimicrobial research tools such as the Kirby-Bauer method along with Minimum Inhibition Control (MIC) in microbiological research purposes in 3<sup>rd</sup> world countries as seen in a study by Mustafa et al., [156]. The transfer of tools and technology is hence recommended for nanoparticle research in these countries [48].

Novel drug candidates also employ the use of nanoparticles in drug design [110]. In addition to that, the discovery of the capability of nanoparticles to permeate the brain-blood barrier took place in the late 20<sup>th</sup> century. This period ushered in more research on the creation of related drugs. It is hence recommended that malaria and syphilis’ drugs research apply NPs in the mitigation of the brain forms of these infectious diseases, including viral disease (e.g H1N1). Literature reviews show that the field of vaccine production, Cancer treatment [113, 104], gene delivery [68], and disease diagnostics [115] all in one way or another employ the use of nanoparticles with the need to undertake more studies. Nanoparticles have hence contributed hugely in experimental research and health informatics.

The invention of biodegradable, sterile products that range in applications from the food and agriculture industry, dye production to environmental sustainability have also harnessed the potentials of nanoparticles in order to preserve the natural ecosystem [126]. This justifies the need to provide less toxic food packaging materials with biodegradation potentials. Human existence has hence benefited from nanoparticles.

In medical sciences, medical devices are coated with nanoparticles to enhance antibacterial and therapeutic properties that are beneficial to convalescent individuals [218].

## 1.3 Promising Use in Microbiology Research

The need to use nanoparticles with immunocompatibility and soluble and metabolic-possibility qualities cannot be over emphasized [63, 64]. In the creation of antimicrobial agents, bioactive molecules are often shape-modified by nanoparticles. The shape of the resulting nanoparticle will determine its ability to penetrate the bacterial cell wall. The presence of surface coating on nanoparticles can enhance the efficiency of nanoparticles as antibacterial and antifungals. This is the basis of nanoparticle interaction with microorganisms [136, 99, 153].

Antimicrobial chemotherapy using nanoparticles involves the inoculation microorganisms with of petridishes containing nanoparticles or the use of bespoke systems which mimic the environment of the condition being studied [112]. This benefits studies involving pathogenic microorganisms like *Streptococcus* to detect the antimicrobial activity of the nanoparticle or the synergistic potential with the microorganism of interest [150]. The above represents the method applied in this therapy which is used in addition to recent methods including magnetic and photo/sonodynamic guided therapy in biological investigations [33]. Incubation in laboratory settings is hence being replaced with repeatable, optimized, biosensor-guided and photosensor-assisted antimicrobial nanoparticle research. Thanks to nanoparticle research, pathogenic bacterial effects which often required elaborate and time-consuming methods are now rapidly being isolated by guided nanoparticle therapies involving the infusion of isolation systems with specific nanoparticles that support the selection and inspection of the exact microorganism being investigated [127]. This shows the promise of the use of nanoparticles in antimicrobial research with high numbers of cited scholarly articles related to bioactive nanoparticle research [259, 80, 96].

## 2. PROPERTIES OF NANOPARTICLES

### 2.1 Classification of Nanoparticles

Nanoparticles can be broadly grouped based on their shape, surface area, surface charge, and surface chemistry. The size and shape of nanoparticles can affect their physicochemical properties and bioactivity. Nanoparticles can be synthesized to pass through cellular membranes, leading to a broad range of activities in the cell.

One of such activities of note in microbiology is oxidative stress, disrupting cellular membranes and activities and eventual lysis and destruction of such cells. Microbial cells and other biological cells can be impacted by the activities of nanoparticles. In the study of nanoparticles, it is expected to find variations in its properties in varying degrees, uniquely destroying potentially toxic microorganisms while also being solubilized by microbial metabolites [199, 40, 165].

## 2.2 Size and Shape of Nanoparticles

Whether they be synthesized in a laboratory or gotten from organic sources, nanoparticles vary in size and shape. These attributes contribute individually or together, in association with other properties discussed in this review to their consistency, stability and their ability to be mixed with other molecules. Most nanoparticles are observed to occur in spherical shapes are typically more stable than those with other shapes [3]. The size of nanoparticles can also affect their toxicity and cellular uptake. The aspect ratio of nanoparticles can affect their toxicity and cellular uptake as well [100]. The size and shape of nanoparticles can also influence their interactions with microbial cells. The size of the nanoparticle also affects its ability to enter cells and its ability to be used as a carrier molecule in drug delivery [263]. The shape and elasticity of a nanoparticle influences its ability to be taken up by cells [268].

Previously reported works on nanoparticle synthesis relied on the analysis of the characteristics of the formed nanoparticle. This was prior to the developments of in-vitro shape control strategies of nanoparticles. This development help in the synthesis of nanoparticles with unique and versatile characteristics, with scientists being able to make several fold increases in the beneficial characteristics [97]. Literature also shows characteristics-wide comparisons between nanoparticles synthesized and the ones synthesized recently, showing reliance on the morphology of the formed nanoparticle, designing experiments using the nanoparticles towards the already formed nanoparticle [59]. There was also no knowledge on the ability of the morphology of the nanoparticle to be known or controlled prior to or during synthesis but current tools like artificial intelligence are helping in this predictive research [75, 35]. Recent works have also shown the synthesis of nanoparticles with various shapes such as cubes, rods, disks

and flowers. There are also reports on variations of a known nanoparticle to exhibit toxicological effects at a time, yet having the potential to be a novel drug candidate at other times. Recent works however do outline the methods of control of the type and characteristics of the nanoparticle prior to or during synthesis [230].

## 2.3 Surface Area and Charge

Nanoparticles exhibit a high surface area-to-volume ratio while in solution, which can increase their distribution and aggregation, showing greater reactions with biological systems than larger molecules [31]. The surface charge of encapsulated and unencapsulated nanoparticles determine affinity to biological systems and molecules, influencing its overall bioactivity [111, 212]. The surface charge of a nanoparticle, being positive or negative, influences its affinity and attraction to other ions, and consequently on cells, and this property is closely related to the pH of the environment. Higher pH values are related to negative surface charges [93, 243]. This is especially useful in the selection of nanoparticles for pharmaceutical applications. The surface charge of nanoparticles can also influence its antibacterial activity, stability and toxicity as positively charged nanoparticles are more easily internalized by cells than negative and nanoparticles [49]. They are however more potentially toxic than negative nanoparticles as cells tend to be negatively charged [92].

## 2.4 Surface Chemistry and Reactivity

The surface chemistry of a nanoparticle can affect its dispersion and interaction with the ions and molecules in biological systems [202], influencing its total biochemical profile and bioactivity. The permeability of a nanoparticle through biological membranes can be enhanced by the modification of the surface chemistry of the nanoparticle. Such modification of its chemistry hence functionalization influences its attachment to membranes and its chemical reactivity by incorporation of stabilizing agents [204]. This phenomenon also improves their end-targeting and biocompatibility [184]. The reactivity of nanoparticles can be increased or decreased due to modifications or the state of the reactive surface area of the nanoparticle which also impacts the electro-mechanical profile of the environment [245]. This is also a basis in the classification of nanoparticles. Surface modification of nanoparticles can also affect their toxicity and safety. This chemical property is an

important factor which can be systematically altered when designing particles for specific applications in microbiology [149].

## 2.5 Optical and Magnetic Properties

Nanoparticles vary in their properties and can exhibit unique optical and magnetic properties due to their small size. The shape of a nanoparticle can be observed during evaluations [42]. Metal nanoparticles like gold, silver, titanium and iron can be studied this way. Generally, the more photosensitive a metal nanoparticle is, the better its antimicrobial and bacterial detection capability [214]. Silver nanoparticles have been shown to exhibit unique optical response and absorbance during colloidal observations [178]. The Magnetic property of a nanoparticle can influence its absorption and dispersal and its use and application [233,7]. The dispersion of nanoparticles in surrounding medium and living tissues sets it apart as an important molecule in drug delivery and in cancer research and other aspects of medicine [148, 101, 154]. The optical and magnetic properties of nanoparticles can be ultrasonically modified by controlling their size and shape, making them useful for a wide range of applications in microbiology. Incubation in laboratory settings is now being replaced with repeatable, optimized, biosensor-guided antimicrobial nanoparticles [116, 231].

The field of spectroscopy uses the idea of visualising nanoparticles in a laboratory using advanced, sophisticated tools and equipment paints a picture of what is worked on but may not do complete justice to the job of studying the antimicrobial attributes of nanoparticles [119]. Synthesis affects the exhibited properties and metallic nanoparticles may exert more heat in biological systems although this is a system that needs more research [175]. The green synthesis of nanoparticles presents a less toxic and cost-effective mode of synthesis, making them safer alternatives [57], but desirable properties may not be as potent as chemically synthesized nanoparticles or varying in other properties [252]. Deleterious effects observed in-vitro in the use of biosynthesized nanoparticles are mainly due to problems in study of nanoparticles properties and this is a drawback in the use of biosynthesized nanoparticles although this phenomenon presents an advantage in the harnessing of such nanoparticles in bacterial cell destruction [199].

Optical properties of nanoparticles include absorption, transmission, reflection and light

emission. These are dynamic attributes that are recognized in the synthesis of bioactive nanoparticles. The optical properties influence the decision on what needs to be added to enhance its bioactivity. For example, the oxygen atoms were added to surface of a nanoparticle after spectroscopic studies, in the synthesis of bioactive zinc oxide nanoparticles, improving its bactericidal properties [163].

## 3. MECHANISMS OF BIOACTIVITY

Bacterial infections derive from the presence and pathogenesis of the infectious agent. When pathogenic microorganisms gain entry to a host, they grow and multiply within the host, disrupting cellular activities, causing harm due to the release of toxins and destruction of host cells. Bacterial infections vary in severity and morbidity and mortality. The harmfulness of bacterial infections, as studied in microbiology, ranging from the lowest level, which is the level in which the bacterium is present but does not cause serious harm, to the level in which it may pose a public health risk. Bacteria are studied in-vitro in four safety levels, in biosafety levels (BSL 1-4). The most harmful and contagious ones are studied in biosafety level 4 laboratories. Prophylactic measures are engaged prior to or after first aid is done. In medical microbiology, samples are obtained and cultured. The microorganisms are then identified and treatment or control measures are then used to stop the infection and prevent further spread of the pathogen. Bioagents are classified based on their origin and composition in addition to their route of use and potential effects on or in living systems. Antibiotics and bioactive nanoparticles are examples of bioagents. Mechanisms of nanoparticle antibacterial actions are achieved by disruption of cell wall, protein denaturation, enzyme disruption, inhibition of DNA replication or DNA damage, and interruption of electron transport (Fig. 1). Nanoparticles can also act as efflux pump inhibitors to bacterial cells. This has been shown to help the bactericidal properties of antibiotics and to reduce biofilm-forming abilities of microbes [183, 37]. Oxidative stress is another method employed by nanoparticles in the destruction of bacterial cells [24]. Nanoparticles do this by the release of intracellular reactive oxygen species (ROS), causing oxidative damage to bio-compounds or inducing genomic instability and mutations [147]. The physicochemical properties of nanoparticles influencing cellular uptake make them useful in the elicitation of oxidative stress. When

nanoparticles are coupled with antibiotics, such antimicrobial properties can be enhanced (Fig. 2).

### 3.1 Interaction with Microorganisms

The bioactive interactions of nanoparticles could be genotypic and phenotypic. This is due to the unique genomic make-up of microorganisms. Bacteria, specifically, are known to undergo mutations which are passed down across generations. These mutations also, lead to observable effects as they are studied in the laboratory. One of such effects is antimicrobial resistance which is a serious global health problem [123, 30, 51]. Cellular processes impacted by the nanoparticle include gene expression and membrane permeability [189]. Activity occurs on microorganisms across several states of matter. There are physical and chemical interactions at the cellular level that guide such effects. As observed in studies, nanoparticles exert their effects on microorganisms either in non-complexed forms or in colloids. When the nanoparticle is docked, the new, altered quality

will determine the effect of the microbiological activity expressed [91, 180, 130, 174].

An antimicrobial agent is any substance that can prevent or hinder the growth of microorganisms. In the use of antimicrobial nanoparticles synthesized using green synthesis, the antagonistic or synergistic ability of microorganisms could influence the degree to which the nanoparticle works in such systems. As antimicrobial agents, nanoparticles could be antimicrobial, antifungal and render antiviral immunity [196]. Such nanoparticles include gold, biometabolites, chitosan-based nanoparticles and silver among others. Nanoparticles have proven to be bactericidal against even biofilm forms of the named pathogen, effective in anaerobic conditions and in micro aerated environments [70]. As antimicrobial agents, nanoparticles have been incorporated into matter to create environmentally friendly, sterile, packaging products [139]. The global burden of antimicrobial resistance can hence be lightened by the use of nanoparticles [88].

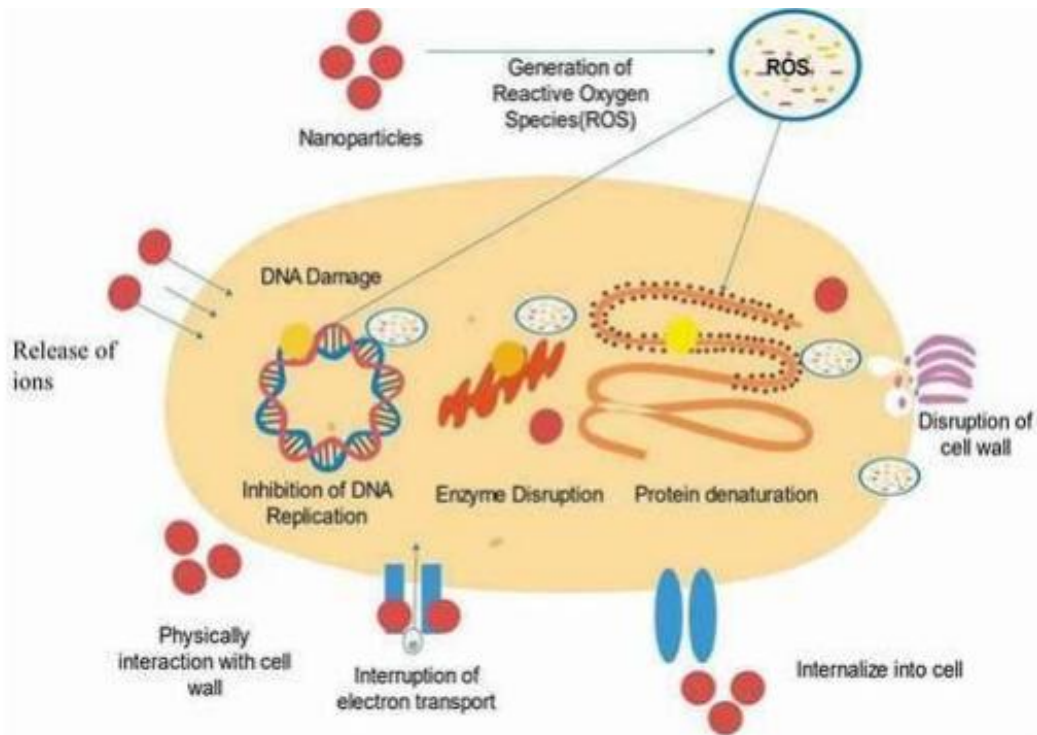
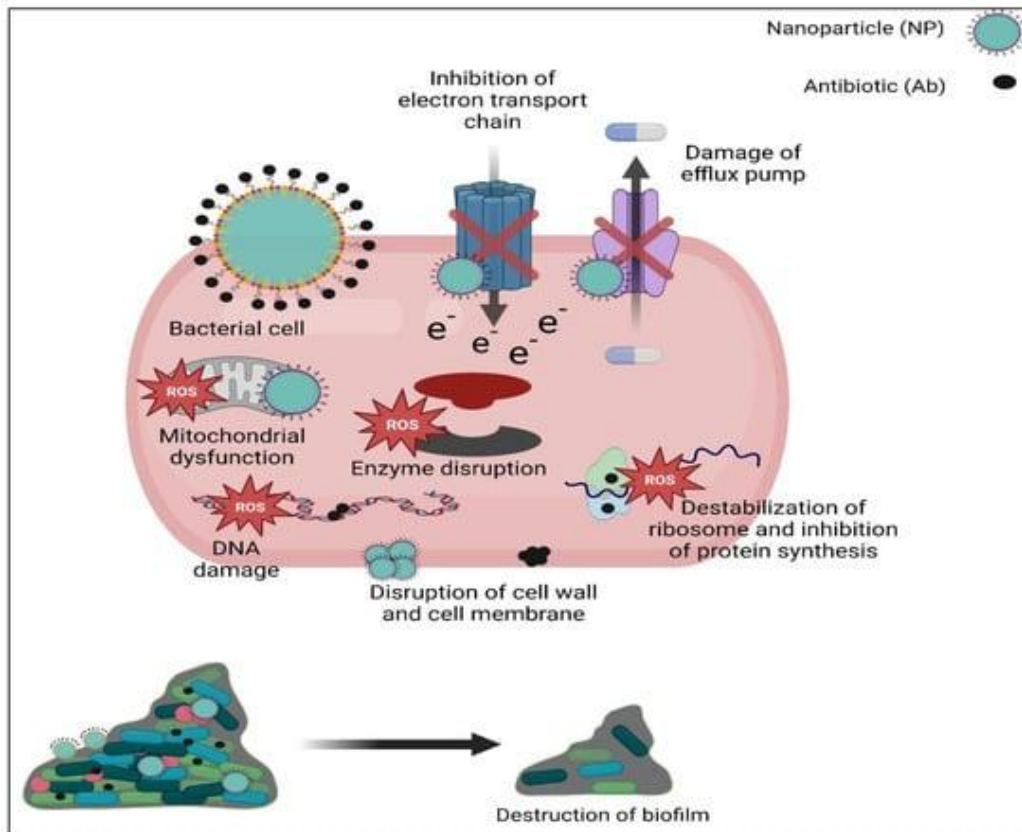


Fig. 1. Mechanisms of Nanoparticles Antibacterial Actions [44]



**Fig. 2. Synergistic activity of nanoparticles loaded with antibiotics [84]**

#### 4. APPLICATIONS OF NANOPARTICLES IN MICROBIOLOGY

Advances in the particle formation procedures of nanoparticles have led to varieties in the resulting nanoparticle, such that antimicrobial applications can be better applied and optimized [56]. Synthesised gold nanoparticles have a range of applications in Microbiology. They act as antimicrobials [73], as carrier molecules [207] and as biosensors in infection detection [246]. A common synthesis for the creation of gold nanoparticles is peptoid engineering. This method helps the structural control of the microbiological and bioactive properties of the gold nanoparticles [95]. In antimicrobial studies, nanoparticles shew great promise in the race to find novel antimicrobials in bioactive nanoparticle research [169]. There also abounds a high number of scholarly research articles on the antimicrobial effects of nanoparticles in the search of novel antimicrobials to combat the global burden of the multi-drug resistant infectious pathogens. Moreso, biochemical parameters of nanoparticles abound in experimental research. In Japan, there exists

several research showing the potential of nanoparticles as feed additives. Some experiments show the hypothetical postulations that nanoparticles may interfere with nutrient assimilation in living systems [69]. Hence, there is a duality of effects in nanoparticles bioactivity: antagonism [135] and enhancement.

In a search on Google Scholar, the interdisciplinary field of antimicrobial nanoparticle research has showed altogether more than 1000 citations in peer reviewed journals. This has created the collaboration of the microbiologist and the chemist in novel drug synthesis. It has however introduced the need for referencing of adequate journals in the field of nanoparticle research prior to the in-vitro creation of antimicrobial nanoparticles. Researchers also, give repeated reviews of nanoparticles that have proceeded in the highly scrutinized drug discovery pipelines, especially as molecules that have proceeded for clinical trials.

Antibiotics were discovered in a time when there was serious need to battle infections. The golden age of antibiotics was from 1950 to 1960. In this

time, more than half of the drugs in use today were discovered. However, there is a pressing need for novel antibiotics to combat Multi-Drug Resistant (MDR) pathogens [240]. The study of nanoparticles requires resources that may not be available in every antimicrobial research laboratory [39].

It is recommended that the presence and concentration of nanoparticles in products for use in antimicrobial research should be stated clearly. This will aid in further studies on the use of nanoparticles in microbiology research as presence of nanoparticles, which can permeate most biological membranes known, can have an impact on the integrity of such experiments [215, 176].

#### 4.1 Antibacterial Properties of Nanoparticles

Human existence is threatened due to MDR strains of pathogens. The blocking of common antimicrobials as the solution to this problem can hence be removed by the adoption and inclusion of antimicrobial nanoparticles in the environments of these pathogens [201]. MDR pathogens include *Escherichia coli*, *Streptococcus*, *Staphylococcus* and *Mycobacterium tuberculosis*.

*Lactobacilli* are microorganisms that make up the normal flora of the female vagina. They also are found in dairy food items like milk and yoghurt. They have antimicrobial potentials but can be pathogenic in the immunocompromised [118]. They also form biofilms in the mouth and are implicated in the formation of dental caries. They also exhibit antagonism against some other bacterial strains [192, 77, 26]. There are studies that suggest that nanoparticle conjugates of *Lactobacillus* and silver and iron are used in the production of antimicrobials against pathogens [213, 250]. Nanoparticles also have been noted to have the capability of acting against cariogenic forms of *Lactobacillus* e.g the Zinc Oxide (ZnO) nanoparticle [211]. Biofilms are poly-microbial aggregates that grow and attach on a variety of surfaces including living tissues, indwelling medical devices and other man-made objects in and on water and on any natural surface in the environment [108, 162]. Due to their polymer-induced aggregation, biofilms pose a public health threat by evading treatment with disinfectants and antibiotics. Biofilm-associated infections and diseases can occur in the blood, mouth, tissues and implants in the human body [17].

*Streptococcus* is a bacterium with multi drug resistant (MDR) strains. It is implicated in mouth and throat infections including caries and periodontal disease. Periodontal disease is an oral condition that leads to destruction of tooth-supporting tissues and leads to complications in children as well as in adults. This disease is induced by the dental biofilm leading to gingival inflammation [58, 122]. If left untreated, this condition can spread to the supporting bone tissues. All periodontal diseases are caused by periodontopathogenic biofilms in addition to the hosts' immune responses, behavioural, environmental and genetic susceptibility factors. Periodontal disease is hence, a notorious oral condition of concern [236, 67, 117]. Studies have shown the use of nanoparticles in the production of antimicrobials against *Streptococcus* and its associated biofilms [237, 102, 223]. Mechanisms include disruption of cell walls, efflux pumps and oxidative destruction of microbial cells [188, 151, 14].

#### 4.2 Antifungal Properties

Fungi are microorganisms that thrive in moist environments. Fungi include yeast and moulds. Along with spore production for reproduction and survival, they secrete primary and secondary metabolites as they grow and mature [249]. These compounds can be toxic to human cells in the case of *Aspergillus fumigatus* and are also capable of being toxic to microbial cells [247]. However, these metabolites are also harnessed in the production of antimicrobial drugs [195]. As a result of this, they can be tapped in the green synthesis of nanoparticles to produce bespoke antimicrobial nanoparticles and also be used as capping agents to synthesize nanoparticles docked with fungi to enhance certain beneficial features [159, 22]. Silver nanoparticles have antifungal effects against *Candida albicans* and *Aspergillus* [76, 160]. Other kinds of antifungal nanoparticles include zinc oxide and titanium [168, 246].

#### 4.3 Antiviral Properties

Viruses have been responsible for a lot of ailments and pandemics for centuries. The inability for viruses to replicate without a host cell proposes alternate systems for antiviral research [52]. This has made them difficult to be studied without the use of sophisticated equipment requiring specialized manpower. Many harmful viruses require biosafety cabinets from BSL 2 to BSL 4 [155]. However, viruses can be inactivated



and used as conjugants in the production of vaccines. These conjugants can be combined with nanoparticles in the production of vaccines [219].

Reports on vaccine production have shed light on the promise of antiviral nanoparticles [208, 256]. Nanoparticles also play a role in the diagnostics of certain infections and diseases caused by viruses. In this case, they are used as biomarkers due to their optical and magnetic properties [50, 86].

Antiviral nanoparticles inhibit viral attachment and entry into host cells. They also prevent replication of viral cells (as seen in the case of Sars-CoV-2). Antiviral nanoparticles include gold nanoparticles and carbon-based nanoparticles [83, 74, 19, 217].

#### **4.4 Diagnostic and Therapeutic Applications**

There is a wide range of potential applications of nanoparticles in diagnostics and therapeutics with need to study the propensity for in-vitro and industrial reproducibility of already tested nanoparticles [244, 78, 228]. Amenability of dispersal and transportability to standardisation gradient among others, depending on what product is being envisioned to be made [29, 65]. The type of product will determine the method employed and the attribute to accentuate. For instance, in the production of oral sanitary products, there is need to accentuate features of nanoparticles beneficial in prophylaxis and to reduce biotoxic features [10, 61]. In the formulation of stomach sickness medicines, it is required that the compound does not negatively affect to the acidic environment, but rather should provide remedy [200].

### **5. FACTORS AFFECTING NANOPARTICLE BIOACTIVITY**

For a nanoparticle to be bioactive, there are a number of qualities to be considered. These qualities serve as criteria for nanoparticles to be used for scientific and economic purposes. The bioactivity of nanoparticles has hence drawn attention to the application of nanoparticles in order to exploit their bioactive potentials [106, 41]. Qualities that drive nanoparticles and nanoparticle-containing final product to the market include reliable elicitation of bioactivity, versatility of abrasive/cojoining index and the

ability of the nanoparticle to ameliorate toxicity [6, 46]. The properties are discussed below.

#### **5.1 Nanoparticle Concentration**

The bioactivity of a nanoparticle depends on a number of factors which would be discussed shortly. One of such factors is the nanoparticle concentration. Inadequate nanoparticle concentration in a bioassay may lead to low bioactivity although low concentrations of nanoparticles have shown to lead to less biotoxicity [164]. Antimicrobial activity is present both in low concentrations and in high concentrations [255, 2]. This may be because the bioactivity of nanoparticles can be enhanced by combination with other molecules [193]. High nanoparticle concentration could lead to cytotoxicity. Because of these, there is the need to adjust concentrations of nanoparticles to suit the bioassay under consideration. However, elimination of size-associated diffusion constraints leads to optimal harnessing of the concentration of the nanoparticle [89]. This means that nanoparticles can be depleted in a bioassay without experiencing the full potentials of the nanoparticles. Nanoparticles can also be engineered to be continually released in living cells. Working in association with the cell's uptake ability, being constantly released after each uptake. This keeps the concentration constant in the cellular environment and beneficial features for which it was engineered stay present in the cell [32]. Bioassays, especially antibacterial investigations, can also benefit from continuous systems in long term exposure of such systems to bioactive nanoparticles in synthesis and application [145, 206]. The nanoparticle concentration also affects its thermal conductivity in bioassays and in its use as a drug in treatment of certain conditions. This directly or indirectly affects its efficacy as a drug in this instance [18].

The mass of a nanoparticle precursor is a quantitative parameter that can be modified in the synthesis of a bioactive nanoparticle. The mass concentration of a nanoparticle is a feature that is directly related to its solubility and toxicity [82].

Nanoparticles interact with bio-agents in a variety of ways, producing various effects observable invitro or in living systems. Coupling nanoparticles with bioagents may influence uptake of nanoparticles, reactivity, inflammation, accumulation, degradation, clearance of

nanoparticles in addition to the enhancement of various antimicrobial properties of the resultant molecules. When bioagents are applied as reducing agents with nanoparticles, they have also been observed to reduce the toxicity of nanoparticles, especially when added in lower concentrations [4]. The presence and concentration of bioagents coupled with nanoparticles can be controlled during.

## 5.2 Exposure Time

In this article, the exposure of a bioactive nanoparticle encompasses its bioavailability, biodistribution and its half-life in living systems. The exposure time of a bioactive nanoparticle is also related to its concentration and uptake by cells in a living system. Nanoparticles can be engineered to improve bioactivity by protecting encapsulated bioactive compounds from degradation [224]. When nanoparticles are used as carrier bioactive molecules, the rate of metabolism in the cell can be enhanced or reduced, making such reaction times longer [256]. Delayed-release bioactive nanoparticles can optimize the antibacterial or antiviral ability of the nanoparticle. The half-life of bioactive nanoparticle affects its bioactivity [62]. In human systems, nanoparticles vary in days required to be completely metabolized and eliminated from the human excretory system. The metabolism of the nanoparticle depends on such primary characteristics of the nanoparticle like size, shape surface characteristics and presence of other combining molecules in its synthesis [129, 177].

Organic nanoparticles are said to be more easily changed and metabolized by cells while the metallic ones have longer half-life and are said to be more toxic. The duration of exposure of metallic nanoparticles should hence be altered by concentration and surface area reducing strategies in order to be more easily eliminated from living tissues [260, 222].

## 5.3 Physicochemical Properties

From the information above, it can be said that the size, shape, and surface chemistry of nanoparticles influence their bioactivity. These parameters keep changing and can be altered to produce desirable bioactive effects. The physical properties are those parameters that can be measured physically and they exist as a result of the origin of the nanoparticle [36]. Chemical properties occur as a result of its intrinsic and

extrinsic molecular definition. The chemical properties of a nanoparticle and its physical properties related to form and morphology are sometimes collectively studied. The physicochemical properties of nanoparticles are unique to each nanoparticle and govern their bioactivity and govern their use in living systems [238].

The physical and chemical properties of nanoparticles, including the shape, size, roughness, zeta potential, doping modification, environmental conditions are often studied together. These factors influence the bioactivity of the nanoparticles. The properties of the nanoparticles influence the functionality as antimicrobial agents. The shape of the nanoparticles will determine its ability to penetrate the bacterial cell wall. The presence of surface coating (leading to roughness) can influence the efficiency of nanoparticles as antibacterial and antifungals. The zeta potential affects the ability of the NP to oxidatively stress a microorganism, leading to cell damage [242, 106].

Due to these factors, along with their versatility, nanoparticles make for ideal candidates in cellular and biologic in-vitro studies in antimicrobial research, a quality that set them apart from conventional antibiotics [14, 13]. nanoparticles can hence be incorporated into antimicrobials to speed up reaction time and increase efficacy of the resulting polymer molecule, as demonstrated in a study involving the combination of silver nanoparticles with wound dressings, improving efficacy [198]. This is an area that will benefit from innovations in antimicrobial and nanoparticle research as it shows the broader use and potential of nanoparticles.

## 5.4 Microbial Strain Growth Conditions

This is a property of microorganisms that affects its attraction to nanoparticles and consequently their effect on the microorganism in addition to the selection of the microorganism as a substrate in the production of nanoparticles [9, 182]. Microorganisms exhibit a wide variety of phenotypic properties which in some cases, change rapidly. The phenotypic properties are related, majorly to the genes present in the microorganism's genome. Bacteria are a group of microorganisms that grow under various conditions. The presence of nutrients, adequate pH, and temperature are features that bacteria

need for their growth and survival [60]. The ability of nanoparticles to affect these characteristics make them molecules of choice to influence the growth of microorganisms in-vitro and in living systems. Some strains of bacteria are susceptible to the effects of nanoparticles while others are resistant to the action of bioactive nanoparticles [210].

The activity of bioactive nanoparticles can also have an impact on the genetic composition of microorganisms, in cases where there are mutations to the cells. The mutations are also targeted for expression in studies of the impacts on nanoparticles on certain gene expression pathways. These mutations can then be passed down to future generations of the bacterium. These factors are also heavily influenced by the environment in which the microorganisms grow [181].

There are reports on the synthesis of nanoparticles that encountered a problem, not in the experimental design of nanoparticle synthesis but in the structure of final product from the synthesis and shed light on industrial production of nanoparticles and their multipurpose attributes and versatility [265, 234].

Nanoparticle selection error, insufficient product, change in layers of concentration gradient [170] and, more recently, biogenic delivery methodology inefficacy or uncertainty [38] are parameters that matter as methods and calibrations are switched in the study of nanoparticles. However, problems encountered in nanoparticle research may not reflect the fault being that of the scientist but as a result of the use of ineffective or un-standardized methods in the synthesis of nanoparticles [28].

The doping modification ability of NPs is the process by which an NP is mixed with another particle to create a colloid with pre-determined properties to improve its efficacy as an antimicrobial agent. The surface coating of an NP can hence be changed after addition or removal of metal ions on the surface of the NP or its colloid to increase its bioactive potential [27, 191]. The environmental conditions presents an extrinsic factor that may confer on the NP to render it active or inactive as an antimicrobial. The environmental condition is a feature that affects all the other factors discussed above. These properties can be manipulated in the synthesis procedures to create custom made molecules to suit the proposed purpose [134, 131].

Studies show the importance of the synthesis of nanoparticles particularly against microorganisms in creation of preservatives, packaging and other consumable food product from nanoparticles. The importance of the absence of other external mixture changing the product homogeneity in the production of such materials with nanoparticle in order to reduce toxicity and improve food safety. [179, 92, 167].

## 6. NANOPARTICLES AND TOXICITY

Toxicity is a phenomenon addressed in microbiology, medicine and biochemistry. Toxicity arises when a deviation from the normal leads to a dysbiosis in the system of a living organism. This can begin at the cellular level and may affect the organism at the organ level. It can also begin in the gut and in extreme situations can lead to death of the entire living organism. Toxicity can lead to failure of living systems including reproductive systems and excretory systems leading to reproductive disorder and metabolism disorders [132, 129, 128]. Toxicity can be caused by the host organism's microbiota, can be auto-induced and can be caused by external agents. The effects of toxicity range from asymptomatic to mild to life threatening situation as can be seen in toxic shock. Toxicity can therefore be caused by intrinsic and extrinsic factors. Toxicity in plants can also be caused by chemical agents or by microorganisms and their toxins. Chemical agents implicated in toxicity include toxic chemicals of various types including synthesized chemicals and nanoparticles in large enough quantities to cause this situation. Adverse effects of nanoparticles include necrosis, cell apoptosis, inflammation and shock [251, 144]. Properties that make nanoparticles useful in inducing toxicity include surface plasmon resonance and electrical resistance [66]. Microorganisms produce exotoxins and endotoxins and one rare but severe effect of toxicity caused by microorganisms is toxic shock caused by *Escherichia coli* toxins and shiga toxin to name a few [107]. Kinds of toxicity include cytotoxicity and nephrotoxicity. Toxicity can be ameliorated by the application of synthesized nanoparticles to address the situation. Toxicity can also be prevented by application of antibiotic functionalized nanoparticles. Nanoparticles synthesized for this purpose will possess properties that make them potent against toxic agents but not harmful to the host cell. One such example is the successful application of silver nanoparticles in the prevention of

microorganism-induced toxicity [94]. Other properties useful in the use of nanoparticles in ameliorating toxicity include bypassing drug resistance mechanisms in bacteria, inhibiting biofilm formation, penetrating cell walls and the disruption of important molecular mechanisms that lead to toxicity.

## 7. TOXICITY AND SAFETY PROFILE

Nanoparticle toxicity occurs in both prokaryotes and eukaryotes. Investigations on the cytotoxicity profile of antimicrobial nanoparticles need to be standardised to lower reaction time in the drug design pipeline [29]. In the age of advancement in science and research, procurement of nanoparticles for antimicrobial studies to yield potential new drugs will require proper identification of the exact and pure NP to be used for study and standardisation of methodology involving obtaining precursors of NPs for study [257, 221, 12]. This will assist in the attainment of global repeatability in experimental design and microbiological assays.

Internal use of nanoparticles (e.g in food) happens deliberately or without prior knowledge however its use as an antimicrobial, encourages its use and incorporation to more products. Hence, toxicology assays using mice, shrimps, or drosophila should be performed to determine its harmfulness in related environments [209, 226, 105, 264, 239].

Gold nanoparticles are shown to have antibacterial qualities against *Streptococcus* and other bacteria. However, they have the health drawback of being nephrotoxic. Silver nanoparticles also have antibacterial properties however, they may be cytotoxic to other cells [25, 21, 223, 47]. Copper NPs, which also have antimicrobial properties, have been shown to be toxic to the aquatic environment, in addition to carrying other harmful toxic and carcinogenic molecules that disrupt the natural ecosystem [98, 194]. The presence of antimicrobials in the natural environment can contribute to the antimicrobial resistance of deadly pathogens, contributing to the global burden of antimicrobial resistance. The toxicity of Zinc oxide nanoparticles to human lungs has been suspected and studied [1, 266], despite its use as an antiviral in H1N1 prophylaxis [253]. Cobalt nanoparticles have demonstrated the ability to prevent the growth of gram-negative enteric pathogens [186], however, cobalt nanoparticles have shown negative effects in the reproductive

system of mice, altering the organ and reducing testicular volume [109].

There are also reports on the propensity of the method and other extrinsic factors to affect the pharmacomicrobial profile assembly of bioactive nanoparticles. With removal of errors, there may be tiny changes and repetition of true negatives in results obtained from research involving the use of nanoparticles [79]. Reasons being the possibility, that the final equipment used being progressively newer respectively affected the levels of synthesis products, leading to small changes [225].

Showing the importance of accuracy and precision in nanoparticle synthesis and research, Hosseinzadeh et al., [85] reported the importance of calibrative manipulation in the synthesis of bioactive and potential drug complexes from nanoparticles.

Just as the beneficial properties of nanoparticles can be enhanced for better bioactivity, unfavourable properties including toxicity can be introduced in nanoparticle synthesis [158, 72]. Therefore the prevention of unfavourable physicochemical properties and also prophylaxis of negative health effects of nanoparticles should be taken into consideration. Activities like the toxicological screening of nanoparticles either in-vitro, in living systems like mice and rats and using artificial intelligence can help in the study of the potential harmfulness of nanoparticles [114, 103].

### 7.1 How the Release of Nanoparticles into Materials such as Bio-Application and Food can be Measured

Qualities that qualify nanoparticles for use in beneficial parlance are the same qualities, which if not controlled, may lead to negative effects on living systems and in the environment. It is not uncommon for nanoparticles (e.g Silver nanoparticles) to be found, albeit in trace amounts, along the food chain [55, 87]. Many substances containing nanoparticles are disposed into the environment. However, we cannot underestimate the usefulness of nanoparticles to humanity. Nanoparticles may be found in food, food packaging materials, drugs, and in other useful things to which nanoparticles are included or in which nanomaterials are indirectly employed [43]. It is important to measure the presence and quantity of nanoparticles to ensure safety for human use.

Methods used in investigating the presence of nanoparticles in materials such as foodstuff and drugs include electron microscopy, molecular assay, immunological assay, and electrochemical analysis [157]. Other innovative methods of assessing the presence of nanoparticles in a sample include nanobubblewaters (nbw) measurement [258] and the use of biosensors. These tools employ the investigation of the physicochemical properties of the nanoparticles present.

## 7.2 Environmental Impact

The environmental impact of nanoparticles have been extensively studied in the United States of America and the world alike. This is in part due to the presence of nanoparticles in waste products which end up in ground water, the environment and in water bodies. This could lead to the transfer of these nanoparticles up the food chain [171, 133, 197]. Nanoparticles in the environment can be reduced by the synthesis of nanoparticles with biodegradable properties for example in the production of plastics and other disposable products. Also, the disposal of toxicological nanoparticle samples should be directed to environments with containment strategies [5, 152, 141]. Regulatory guidelines should also stipulate how nanoparticle wastes should be properly disposed. These guidelines should be prepared, taking into consideration the origin of the nanoparticles and also by experts in the handling of these nanoparticles. Regulatory guidelines are also prepared based on the potential toxicity of the nanoparticles and the effects of its impact when it is exposed to the environment. Products containing nanoparticles should also be labelled appropriately, especially in products containing potentially toxic chemicals. These risk assessments are often periodically carried out in developed countries and differ in each region [220, 23, 248, 45].

## 7.3 Tools used in the Study of Nanoparticles

It has become necessary to employ the term “nanoscience” and the tools used in its study as it will be employed in microbiology in order to prevent the growth and spread of pathogenic microorganisms or support the growth of certain ones [16, 227]. The problem in nanoparticle research was further promoted as Marica et al. [140] mentioned a problem in the acceptance of the recognition of the efforts and methodology stating that non uniformity in synthesis yields

could lead to this problem, and some papers not being fully cited nor accepted for publication may be due to archaic methods, despite being hailed in industry and in the news for an innovative useful method to synthesize nanoparticles which became adopted in industry and in coastal research. Methods on the synthesis of nanoparticles, for the purpose of research are reported by [235], [71], [142]. More organic methods are reported by Dabhane et al. [54] and Alizadeh et al. [20].

Challenges in the study of antimicrobial nanoparticles include the cumbersome investigation into the abundant data on the advantages and toxicity of popular nanoparticles. However there is the need to conduct thorough investigations on the nephrotoxicity and cytotoxicity of newly synthesized nanoparticles to guide in further laboratory investigations on the promising nanoparticles. Another challenge lies in the study of the standardisation of antimicrobial nanoparticle research and nanoparticle-colloids utilisation including dose determination and calibration of doses in drug creation. The need to evaluate the interaction of nanoparticles with cells cannot be overemphasized. Challenges also include the investigation of the effects of nanoparticles on the normal flora of the host. Nanoparticles have often disrupted the microbiome in their utility as antimicrobial agents [262]. This will prevent solving a problem and creating another one simultaneously. Another challenge lies in the sorting out of the methods used in nanoparticle creation as there are various independent researches in nanoparticle research, with various experts presenting their own ideas in nanoparticle reports. Reports on duality need to be classified appropriately in order to distinguish the two-pronged attributes of nanoparticles that have both positive and negative properties within the same frame.

## 7.4 Summary of Key Points

Nanoparticles are particles with sizes ranging from 1 to 100 nanometers and possess unique properties such as high surface area, reactivity, and optical and magnetic properties. Nanoparticles have shown potential in various applications in microbiology, including antimicrobial activity, drug delivery, and diagnostic imaging. The mechanisms of bioactivity of nanoparticles involve interaction with microorganisms, penetration into microorganisms, disruption of cellular processes,

and effects on microbial growth. Factors affecting nanoparticle bioactivity include nanoparticle concentration, exposure time, physicochemical properties, and microbial strain and growth conditions.

Recent works on antimicrobial nanoparticle research have focused on the antimicrobial and diagnostic capabilities of Nanoparticles along with investigations on the effectiveness of nanoparticles. Future work will show the interdisciplinary research of nanoparticle engineering and reengineering, organic combination with nanoparticles and reimagining AMR drug design.

## 8. FUTURE DIRECTIONS FOR RESEARCH

Further research is needed to fully understand the potential applications and mechanisms of action of nanoparticles in microbiology. Future studies should aim to optimize nanoparticle design for specific applications, investigate the potential for nanoparticle-based combination therapies, and assess the safety and environmental impact of nanoparticle use. Additionally, the development of standardized protocols and guidelines for nanoparticle characterization and testing is necessary for accurate and reproducible research.

Future prospects will include more studies on nanoparticles and their toxicity before human use and the inclusion of data of safe, standardised nanoparticle drug-complexes into health informatics databases. Prospects also include more funding in the field of harnessing nanoparticles in diagnosis and treatment of diseases like cancer, diabetes, autoimmune diseases and antimicrobial resistant infections as more experiments are required. Finally, the spelling out of the safety guidelines in the use of nanoparticles for experimental research, including a thorough investigation of the toxicity and effects of bioactive nanoparticles on the host will help in nanoparticle research. Including this information in informatics databases will further embellish the field of antimicrobial nanoparticle research.

## 9. IMPLICATIONS FOR MICROBIOLOGICAL APPLICATIONS

The unique properties and mechanisms of bioactivity of nanoparticles have the potential to revolutionize the field of microbiology. The use of

nanoparticles in antimicrobial applications could provide alternative treatments for antibiotic-resistant infections, and nanoparticle-based diagnostic and therapeutic methods could improve the accuracy and effectiveness of microbial detection and treatment. However, the safety and environmental impact of nanoparticle use must be carefully considered and monitored to prevent adverse effects on human health and the environment.

## 10. CONCLUSION

This article provides an overview of nanoparticle properties and their microbiological uses in relation to their bioactivity. Current opinions on the properties of nanoparticles including the size and shape, surface area and surface charge, surface chemistry and reactivity and their magnetic properties are discussed. The mechanisms of bioactivity of nanoparticles in reference to their interactions with microorganisms, penetration into microorganisms, disruption of cellular processes and their effects on microbial growth are elucidated. Finally, insights are provided on the toxicity and safety concerns in the use of nanoparticles including the environmental impact and regulatory guidelines in the use of nanoparticles, and the importance of accuracy and precision in nanoparticle synthesis followed by a recommendation on future guidelines for research.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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