

## Review Article

# A review of applications and mechanisms nanoparticles on inhibiting the growth of pathogens

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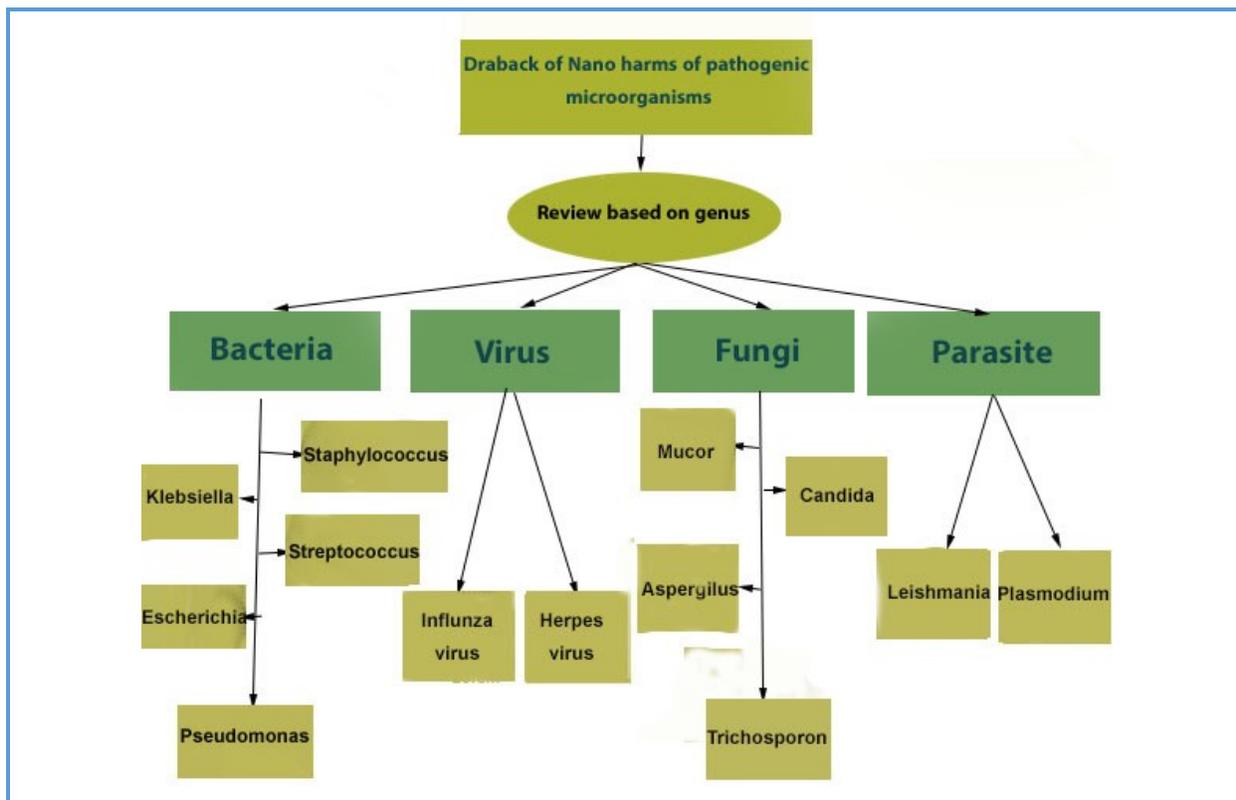
Synergistic effect

### ABSTRACT

The purpose of this research study was to assess the use of nanoparticles in combat pathogenic microorganisms and also to investigate the synergistic effect of nanoparticles with antibiotics in eliminating these factors. In this work, the influence of different nanoparticles on microorganisms was evaluated in 89 studies. It was found that nanoparticles can be used against microorganisms, either independently or by their synergistic effect with antibiotics. The study found that metal nanoparticles have a more anti-microbial effect, among metal nanoparticles, silver nanoparticles exert the most specific among all microorganisms. Meanwhile, metal nanoparticles can be a good alternative to the use of antibiotics and inhibitors of pathogens.

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## Graphical Abstract



## Introduction

Nanoparticles are materials with general dimensions at the nanoscale (below 100 nm). In recent years, these substances have had a significant impact on medical science examples of its various applications in the medical sciences include its effect on medical imaging and the use of nanoparticles as gene transfer carriers [1]. Therefore as a promising tool for drug and gene advancement delivery, medical imaging and diagnostic biosensors [2]. Recently, resistance to drugs against the microorganisms has increased [3]. This resistance has been observed among bacteria [4], in particular. It was reported that one patient died of resistance to *Klebsiella pneumonia* [5]. This drug resistance is transmitted indirectly between bacteria and increases the risk of death from bacterial

infection [6]. Resistance to antiviral drugs is also increasing [7]. Therefore, there is an urgent need for an alternative or complementary treatment to treat antibiotic-resistant bacteria and other pathogenic microorganisms [8]. The need for new antibiotics stems from the relatively high prevalence of bacterial infections and the increased resistance of bacteria to conventional antibiotics. Nanotechnology, the use of materials with atomic or molecular scale dimensions, has been increasingly used in medical applications and is being considered as an approach to eliminate or reduce the activity of numerous microorganisms [9] Overall, the results revealed that, the NPs synthesis method seems to be efficient and can be used to remove the toxic and hazardous substances. [10] In this article, we study different nanoparticles on microorganisms and also their synergistic effect with other drugs.

## Bacteria

### *Staphylococcus*

**Ag NPs:** The antibacterial effect of silver nanoparticles is induced by the induction of oxidative stress and the release of metal ions. In principle, these particles penetrate the wall and enter the cell, causing damage to DNA and eventually cell death during a series of activities (Figure 1) [11]. Also, by combining metal nanoparticles, its effect against bacterial killing can be increased. The mixture of silver nanoparticles and copper-containing NPs (PTMs) increase the bactericidal effect compared to silver nanoparticles alone. [12], are also more effective in inhibiting the formation of *S. aureus* biofilm [13].

**CuO NPs:** CuO nanoparticles are used as antibacterial agents against the *S. aureus* and MRSA. Their action is such that  $\text{Cu}^{2+}$  ions released from the nanoparticles enter the bacterial cell and create reactive oxygen species, causing the oxidative stress (Figure 1) [14]. CuO NPs caused the regulation of proteins involved in nitrogen metabolism, electron transfer, and substance transport [15].

**Fe<sub>2</sub>O<sub>3</sub> NPs:** Magnetic iron oxide nanoparticles as a multifunctional substrate can prevent biofilm formation. It has also been shown to prevent colony assembly, That is why this substance can be used to prevent the risk of infection in surgical implants used against *S. aureus* [16]. It was reported that, iron oxide nanoparticles derived from *Ramalina sinensis* revealed good antibacterial properties by producing reactive oxygen species and oxidative stress [17].

**ZnO NPs:** Antibacterial activity of zinc oxide nanoparticles has been recorded against many species of *Staphylococcus*. It was reported that there is a direct relationship between the concentration of ZnO nanoparticles and its

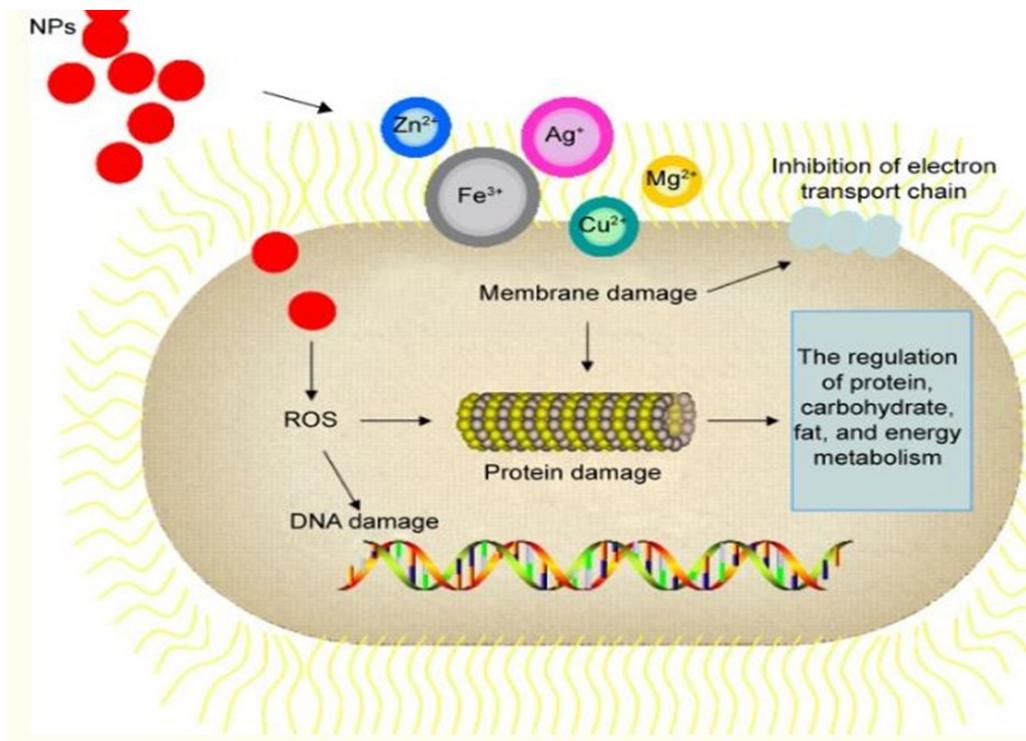
bactericidal effect [18]. These nanoparticles produce reactive oxygen species (ROS) which thus exert their bactericidal effect [19]. It has also been observed that zinc oxide nanoparticles have a synergistic effect on some antibiotics such as ciprofloxacin and increase the inhibitory effect of bacteria [20].

**Pt NPs:** Nano-Pt separates the cytoplasmic membrane and cell wall, releases the material from the bacteria, and thus exerts its antibacterial effect [21]. It is also specified that among noble metals, platinum nanoparticles (PtNPs) are less important due to their catalytic properties and toxicity. Simple one-step synthesis of PtNP using aqueous extract of Indian brown seaweed *Padina gymnospora* and their catalytic activity with a polyvinyl pyrrolidone (PVP) polymer as PVP/PtNPs nanocomposites in specific concentrations have antimicrobial properties. In principle, the catalytic properties of PtNPs as polymer/metal nanocomposites (PVP/PtNPs) are preparations for an antibacterial activity [22].

**MgO and CaO NPs:** Metal oxides such as MgO and CaO also have antimicrobial properties against the *S. aureus* [23]. These nanoparticles produce reactive oxygen species (ROS), which is associated with the bactericidal properties of these nanoparticles [24]. Also, the combination of NPs and MgOs with the help of light radiation can enhance the production of ROS and kill bacteria. (Figure 1) [25].

**CoFe<sub>2</sub>O<sub>4</sub>, CrO NPs:** CoFe<sub>2</sub>O<sub>4</sub>, CrO can be useful for the treatment of *S. aureus* infections, Of course, it is known that CrO nanoparticles, it has a stronger antibacterial effect than CoFe<sub>2</sub>O<sub>4</sub> [26].

**TiO<sub>2</sub> NPs:** TiO<sub>2</sub> produces reactive oxygen species (ROS) that damage microbial cell walls. The TiO<sub>2</sub> NP compound has also been synthesized and demonstrated excellent antibacterial (antibiotic) properties against the *S. aureus* [27].



**Figure 1.** NPs can through multiple mechanisms inhibiting the growth of pathogens

**Se NPs:** Inorganic mineral nanoparticles (such as selenium) have the ability to kill the microbes by various mechanisms. These nanoparticles can produce ROS which can damage the various cellular components. Se nanoparticles can lysis the cell by Induce damage to MRSA and MRSE bacterial membranes [28].

**CdO NPs:** The antibacterial properties of cadmium oxide nanoparticles are effective on the activity and growth of the *S. aureus* [29]. It was also proved that there is a direct relationship between increasing the concentration of cadmium nanoparticles and the antibacterial effect [30].

### *Streptococcus*

**Ag NPs:** Silver nanoparticles are effective in killing *Streptococcus mutans*, and this nanosilver has a greater antibacterial effect on *S. mutans* (which is an oral bacterium) at low

concentrations [31]. The antibacterial activity of nanoparticles is related to their size; smaller particles have more antibacterial activity [32].

**PEGylated Nano-BA12:** Nano-bacitracin with PEGylated coating have good antimicrobial properties against *Streptococcus pneumoniae*. PEGylated Nano-BA12K is much more stressful than bacitracin and exerts its bactericidal properties by depolarizing the membrane potential [33].

**MgO NPs:** The antibacterial effect of magnesium oxide on streptococci has been confirmed. The nanoparticles had a favorable anti-biofilm property which leads to a significant reduction in cell adhesion and biofilm formation was induced [34]. One of the advantages of magnesium nanoparticles over other nanoparticles is that they can be effectively degraded and metabolized in the body, and the degraded products release  $Mg^{2+}$  and OH ions and are effectively removed from

the body, so there is no concern about the aggregation of heavy metals in the body [35].

**CaO NPs:** CaO nanoparticles have antimicrobial activity. It is effective against the *S. mutans*, it was found that CaO has a significant inhibitory property on *S. mutans* [36]. CaO nanoparticles can increase their potency in killing bacteria by changing and improving conditions in size [37].

**TiO<sub>2</sub> NPs:** The photocatalytic activity of TiO<sub>2</sub> is associated with a wide range of antimicrobial activities. These nanoparticles are associated with the production of highly oxidizing reactive oxygen species and react with molecules such as lipids, proteins, and nucleic acids, which damage cell membranes and affect the population of *S. mutans* [38].

**ZnO, CuO NPs:** ZnO and CuO free nanoparticles inhibit the formation of *S. mutans* biofilm, and these substances cause cell damage by producing oxygen radicals (ROS), hydroxyl radicals [39]. ZnO antibacterial activity is primarily attributed to the production of reactive oxygen species (ROS) on the surface of these oxides. Oxide Zinc causes an increase oxidation occurs in prokaryotic and eukaryotic cell membranes and is effective on resistant microorganisms [40].

### *Escherichia*

**Ag NPs:** Silver nanoparticles affect the membrane and cause membrane abnormalities. Interactions lead to potential surface changes and lead to membrane depolarization at the nanoparticle shrinkage point [41]. Use of elemental nanoparticles Active and fluoroquinolone antibiotics for the treatment of multidrug-resistant bacterial strains of *Escherichia coli* show a synergistic effect [42].

**Chitosan Nanoparticles:** Chitosan is a natural antimicrobial agent found in the shells of crustaceans, such as crab, shrimp. One of the applications of chitosan nanoparticles is its

antibacterial properties [43]. However, its antimicrobial activity is dependent on many factors such as its molecular size, source, components, pH, concentration, and type of microorganism, which should be considered before being applied [44].

**ZnO NPs:** This nanoparticle causes damage to membranes, proteins and DNA by forming ROS [45]. In essence, ZnO nanoparticles cause the loss of membrane integrity by producing free radicals. The attachment and inclusion of nanoparticles alter the cell membrane resting potential, inhibit the membrane, and reduces membrane permeability and cell death [46]. combination of ZnO-Al<sub>2</sub>O<sub>3</sub> nanoparticles also has a good inhibitory effect on *E. coli* [47].

**Au NPs:** The effect of gold nanoparticles on bacteria is such that it disrupts the bacterial cell membrane and forms reactive oxygen species (ROS) and It causes cell death by creating pores in the bacterial membrane [48]. Having a mixture of gentamicin and colloidal gold particles may increase the antibacterial effect [49]. As well the combination of antibiotics and Au nanoparticles may potentiate the antimicrobial effects of several antibiotics, including polymyxin B, ciprofloxacin, ceftazidime, ampicillin, clindamycin, vancomycin, or erythromycin [50].

**Fe<sub>3</sub>O<sub>4</sub> NPs:** Iron oxide nanoparticles increase ROS in bacteria, Iron oxide nanoparticles condense inside the cytoplasm and the inner nanoparticles form intracellular vacuoles that form clusters on the surface of bacteria and rupture the outer cell membrane to break up the cytoplasm [51].

**TiO<sub>2</sub> NPs:** The outer membrane of the bacterium first decomposes against these nanoparticles, and the With a series of reactions, begins the partial decomposition of the outer membrane, followed by irregularity of the cytoplasmic membrane resulting in cell death [52]. It has also been confirmed that the

antimicrobial properties of hollow  $\text{CSTiO}_2$  nanowires developed against various bacteria, including *E. coli-resistant* strains, showed superior performance compared to  $\text{TiO}_2$  nanoparticles. Ultraviolet radiation is evident in the antimicrobial activity of this nanoparticle [53].

**MgO NPs:** MgO NPs can damage cell membranes and kill bacteria [54]. In essence, these nanoparticles show shrinkage, membrane mixing, as well as chromatin density, and morphological changes can be attributed to cellular uptake of MgONPs by macro-pinocytosis or endocytosis, increasing ROS production, which activates the apoptosis pathway. And leads to cell death [55].

**CdO NPs:** Nano CdO can be useful in the treatment of infectious diseases caused by *E. coli*. CdO nanoparticles show effective antibacterial activity against Gram-negative [56]. The bactericidal effect of this nanoparticle is greater than that of Gram-positive bacteria because this nanoparticle damages the structure of the bacterial membrane [57].

**$\text{Al}_2\text{O}_3$  NPs:** LPS can be attached to  $\text{Al}_2\text{O}_3$  nanoparticles by hydrogen bonding and ligand exchange. Structural changes induced by  $\text{Al}_2\text{O}_3$  NPs in phospholipids may lead to loss of amphiphilic properties, membrane degradation, and cell leakage [58].

**CuO NPs:** These nanoparticles produce reactive oxide (ROS). In other words, the occurrence of a redox cycle (oxidation and reduction) as a result of the loss of glutathione and the effect on sulfhydryl protein groups, destroys DNA and oxidizes and destroys lipids [59]. The combined effect of copper oxide nanoparticles and Nisin also reduces the growth of bacteria [60].

**$\text{TiO}_2$  NPs:** These substances inactivate cellular enzymes and DNA, causing small pores in bacterial cell walls and increasing

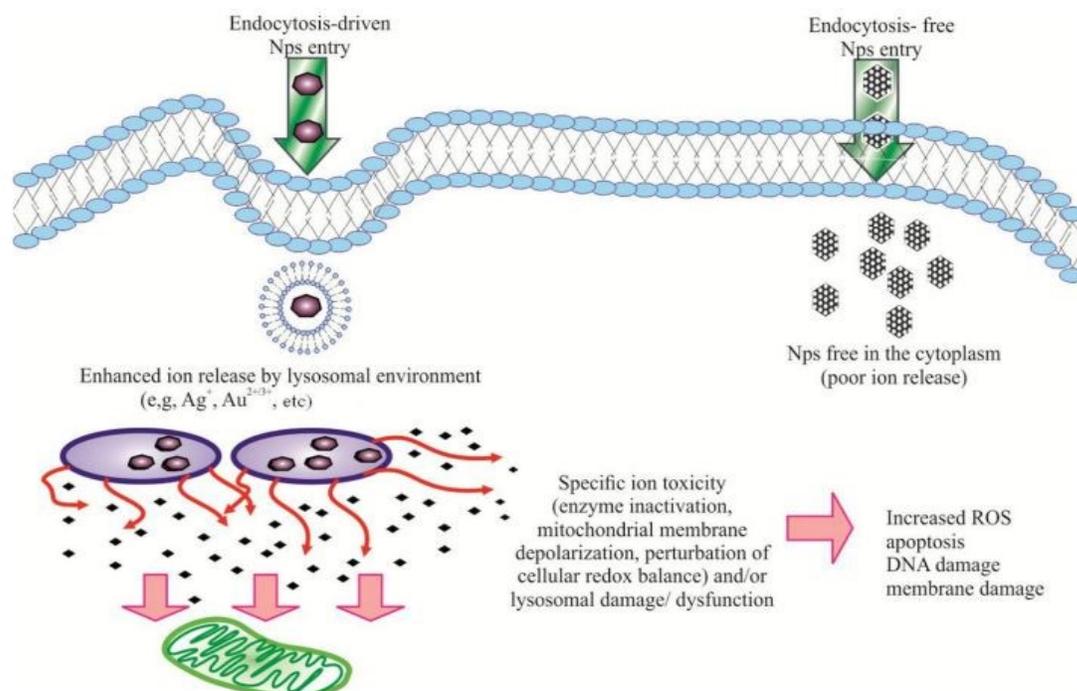
permeability and cell death [61]. These particles also produce free radicals, such as radicals. Hydroxyl anion and superoxide, and reduce the growth of *E. coli* [62]. And alumina NPs show good inhibitory effect on *E. coli* growth only in high and certain concentrations [63].

### *Pseudomonas*

**Ag NPs:** These nanoparticles have an antibacterial effect against *Pseudomonas aeruginosa* drug-resistant bacteria. AgNPs can enter drug-resistant bacteria and disrupt their morphology and structure. This antibacterial activity is concentration dependent [64]. The combination of tetracycline-silver nanoparticles has also been confirmed to increase the inhibitory effect of the drug on bacteria [65].

**Au NPs:**  $\text{Au}_3$  can oxidize Produce free radicals that may cause DNA damage and mutations [66]. The ability of phospholipid-coated gold nanoparticles to destroy *P. aeruginosa* biofilms has been confirmed [67]. The cationic ligands of gold NPs have also been shown to contribute to their antimicrobial activity. This effect has been attributed to the strong ionic interaction with bacteria, which shows that positively charged ligand molecules increase the membrane permeability of bacteria: such as gold magnetite NPs and functional gold  $\text{AuO}/\text{Au}^+$  used for possible inactivation of synthesized multidrug-resistant bacteria [68] Entry through endocytosis increases the bactericidal properties of nanoparticles (Figure 2).

**CaO NPs:** CaO-NPs exhibits good antimicrobial activity against *P. aeruginosa*. These nanoparticles also inhibit biofilm formation [69]. Cell membrane abnormality has been confirmed. This nanoparticle produces ROS species [70].



**Figure 2.** Schematic comparison of NPs-induced general toxicity via active internalization mechanisms, and endocytosis-free

**TiO<sub>2</sub> NPs:** This nanoparticle causes damage to the bacterial membrane and complete destruction of bacterial cells. In addition, key factors in bacteria such as biofilm, lipase and protease expression are inhibited by TiO<sub>2</sub>/UVAIs [71].

**Fe<sub>2</sub>O<sub>3</sub> NPs:** Iron Oxide Nanoparticles Option It is good for inhibiting the growth of *P. aeruginosa* [72]. The effect of Fe<sub>2</sub>O<sub>3</sub> nanoparticles with the action of imipenem antibiotic on Metallo-β-Lactamase (MBL) *P. aeruginosa* with a predefined concentration of nanoparticles increases the effects of imipenem against resistant bacteria [73].

**MgO NPs:** The exact antibacterial mechanism of MgO nanoparticles is still unknown. A number of mechanisms, such as the formation of reactive oxygen species (ROS), the interaction of nanoparticles with bacteria, the subsequent damage to the bacterial cell, and the alkaline effect, have been proposed to explain

the antibacterial mechanism of MgO nanoparticles [74].

#### *Klebsiella*

**Ag NPs:** These nanoparticles enter the cell through energy-dependent processes and are rapidly confined to vesicular structures, endosomes, and lysosomes. NP releases relatively toxic ions (Ag ions) through processes and causes significant amounts of ions to leak into the cell. Specific ion poisoning (e.g., depletion/inactivation of the enzyme, protein denaturation, etc.) and/or damage/dysfunction becomes lysosomal. Eventually, it leads to increased levels of ROS, apoptosis, DNA and membrane damage [75]. Prepared AgNPs by various plant extracts increases the antibacterial effect of tetracycline against *Klebsiella* bacteria [76]. This nanoparticle also has a synergistic effect on *Klebsiella pneumoniae* with the antibiotic imipenem [77].

**ZnO NPs:** ZnO NPs can be useful in killing *Klebsiella* by having a direct interaction in the destruction of the LPS membrane against *Klebsiella pneumoniae* [78]. This nanoparticle produces oxygen species (ROS), of which ROS is a major factor for several mechanisms, including cell wall damage. Due to the local interaction of ZnO, membrane permeability increases with the internalization of NPs due to loss of proton moment and the uptake of ions in these cases leads to mitochondrial weakness, intracellular excretion, and release in the expression of oxidative stress genes, which inhibits cell growth and cell death [79].

**Cu-AgNPs:** A combination of copper and silver nanoparticles, Cu-Ag NPs have antibacterial on *K. pneumoniae* via activity synergies between toxicity mechanisms [80].

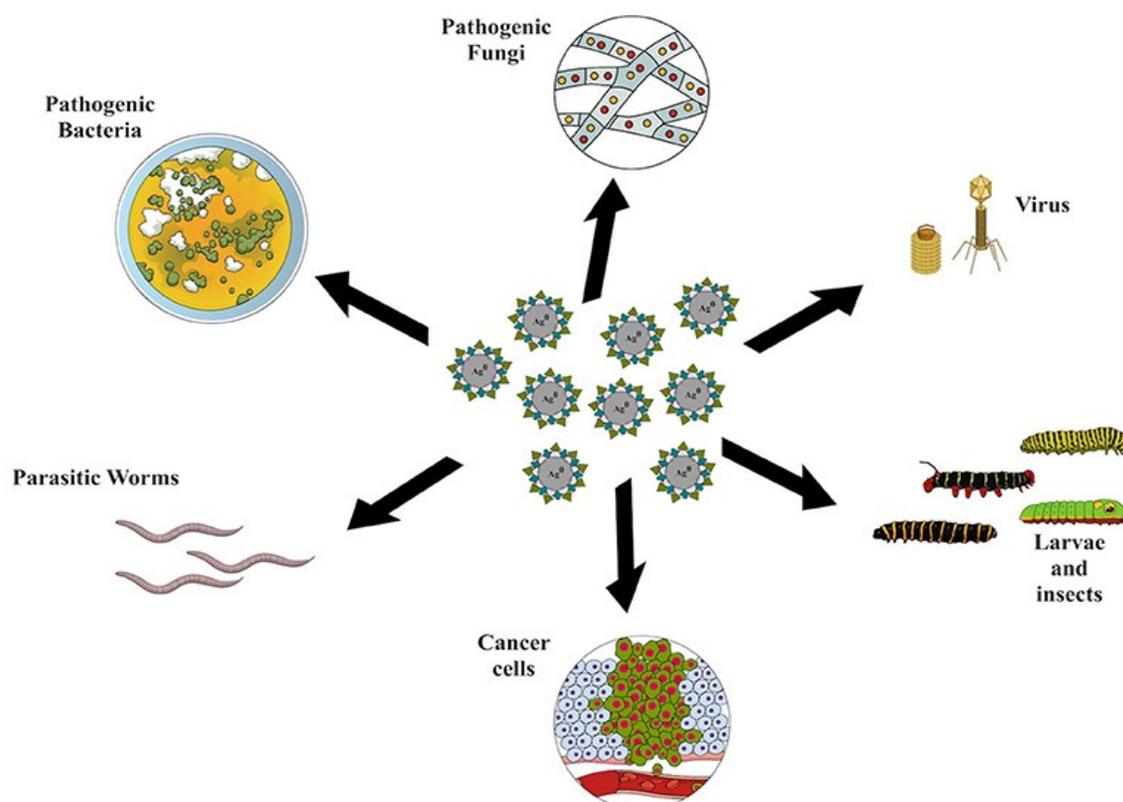
**Au NPs:** Zhang *et al.* (2013) showed that ROS production and metal ion emission are

significantly increased by uncoated and UV-irradiated AuNPs (365 nm) [81]. AuNPs partially affect the expression of *mrkA*, *wzm* and *acrB* genes in *Klebsiella* bacteria. the potential use of AuNPs in the development of new therapies for the prevention of biofilm-associated *K. pneumoniae* infections can be investigated [82].

## Fungi

### *Aspergillus*

**Ag NPs:** Nano-Ag can perform an antifungal activity by disrupting the structure of cell membranes and inhibiting the natural germination process due to the destruction of membrane integrity [83], and reduces the gradual growth in two species of *Aspergillus* sp. *Aspergillus niger* and *A. terreus* (Figure 3) [84].



**Figure 3.** Applications of silver nanoparticles synthesized using fungi [85]

**TiO<sub>2</sub> NPs:** TiO<sub>2</sub> catalysts are loaded with nanoparticle-Ag and–nanoparticle-Co. They can reduce the survival of *A. niger* spores [86]. A study demonstrated that the TiO<sub>2</sub>-NP synthesized using green plant extracts have good antifungal activity in certain concentrations against the fungal agent and inhibited mycelial growth [87].

**Nano-chitosan:** CNPs and CAgNCs can cause membrane damage and disruption of mycelial levels, resulting in cell death [88]. Three mechanisms as Chitosan inhibition mode is suggested. In the first mechanism, the plasma membrane of fungi is the main target of chitosan. A positive charge of chitosan during the process increases the permeability of the membrane and causes leakage of cell contents, which in turn leads to cell death. For the second mechanism, chitosan in a process makes the nutrients necessary for the normal growth of fungi are not available. Finally, the third mechanism suggested that chitosan could penetrate the cell wall of fungi and attach it to its DNA. This inhibits mRNA synthesis and thus affects the production of essential proteins and enzymes [89].

**ZnO NPs:** Nano-ZnO is very powerful in killing *Aspergillus* and loading nano-ZnO with 5% nano-Pd (Palladium nanoparticle) increases the antifungal activity of Nano-ZnO in our collection [90]. ZnO NPs also have an excellent ability to inhibit the growth of *Aflatoxins* in *flavus*, so this nanoparticle may be a step towards its possible use [91].

#### *Trichosporon*

**Ag NPs:** Silver nanoparticles on other fungal species, such as *Trichosporon* and *T. asahii* have an inhibitory effect, this nanoparticle does not affect the fungal wall but damages the surface of the mycelium, which leads to the removal of intracellular components and shrinkage of the mycelium, and at higher concentrations of

nanoparticles this damage becomes more severe [92].

#### *Mucor*

**ZnO, MgO NPs:** The effect of MgO nanoparticles on the germination spores of *Mucor plumbeus*. MgO inhibits spores, increases the concentration of nanoparticles, increases inhibition of spore germination. Also in a study on the effectiveness of nanoparticles MgO nanoparticles, and ZnO in Showed different concentrations in the germination of *Mucor* spores [93].

#### *Erythricium Salmonicolor*

**ZnO NPs:** ZnO nanoparticles (ZnO NPs) with antifungal activity in the function of *Erythricium salmonicolor* and it has been confirmed that this nanoparticle changes the growth pattern of this fungus and causes significant thinning of hyphae fibers and in certain concentrations significantly inhibits the growth of this fungus. ZnO NP nanoparticles cause the cytoplasm to shrink from the electron and cause significant detachment from the fungal cell wall. These effects need to be studied more carefully [94].

#### *Candida*

**CuO NPs:** CuO nanoparticles show the ability to inhibit fungi of *Candida albicans*, *Candida crocus*, and *Candida glabrata* cells with CuO NPs at specific concentrations [95]. Polycaprolactone fibers were prepared with copper oxide nanoparticles. Polycaprolactone-copper fibers (PCL-CuONPs) showed significant antifungal effect applications in all composite antibiotics to determine antifungal activity in *Candida* [96].

**Fe<sub>3</sub>O<sub>4</sub> NPs:** Fe<sub>3</sub>O<sub>4</sub>-NP has antifungal properties against *Fusarium oxysporum* *Aspergillus flavus* [97]. It has been determined in research that the colloidal antifungal activity

of Fe<sub>3</sub>O<sub>4</sub> NP, which can be useful for medical devices such as catheters, implants, and dentures, is inhibited by the growth of *C. albicans* [98].

## Virus

*Alpha-Beta-Delta-Gamma influenza virus, Herpes virus*

**Ag NPs:** Silver nanoparticles inhibit the virus by interacting with the sulfhydryl group in membrane glycoproteins. Internal nanoparticles interact with virus levels and nucleus proteins to disrupt virus replication and entry [99].

**ZnO NPs:** PEGylated ZnO-NPs have been shown to be a new, effective, and promising antiviral agent against H<sub>1</sub>N<sub>1</sub> influenza virus infection [100]. It has been proven to prevent various surface properties with cellular receptors and viral particles and their effect in reducing HSV-1 infection. Surface-modified ZNPs can potentiate the potential of HSV-1 infection by neutralizing the virus instead of interfering with cellular targets [101].

**TiO<sub>2</sub> NPs:** TiO<sub>2</sub> nanoparticles inactivate influenza virus [102]. TiO<sub>2</sub> nanoparticles with photocatalytic properties have a disinfectant effect. Also, TiO<sub>2</sub>/UV process can be an effective tool to reduce the spread of SARS virus, a spiral virus of ssRNA (+) group [103].

**Au NPs:** Nanoparticles may interact with the viral genome (DNA or RNA) to reach the cell and perform its antiviral activity. But they may also have another process for dysfunction [104]. AuNP with sialic acids has the ability to control infection by influenza A virus it is believed that AuNPs functionalized with sialic acid. It is able to prevent the interaction of hemagglutinin with sugar, therefore, the virus cannot enter the cell. existing glycoproteins gp120. AuNPs covered with glucose binds to the drugs

abacavir and lamivudine be able to prevent virus replication in cell assays [105].

## Parasite

### *Plasmodium*

**Ag NPs:** The effects of Ag-NP on the *Leishmania tropica* parasites, the causative agent of leishmaniasis, are not available in the literature. The metabolic activity and infection of the promastigotes revealed antisense effects by preventing the survival of amastigotes within host cells [106].

**GO NPs:** Graphene oxide nanoparticles may exhibit antiparasitic properties by blocking the mechanisms of the *Plasmodium falciparum* parasites and the nutrient depletion [107]. Several researchers reported the synthesis of Ag NPs/GO and Ag NPs/RGO compounds. Ag NPs/GO with different Ag loads, effects that Ag NPs/GO nanocomposite has antimicrobial activity against bacteria and microorganisms [108].

### *Lishmania*

**AS-NPs:** AS-NPs growth, oxygen consumption, infection, and proliferation inside collective parasite of *L. donovani* in certain concentrations It inhibits nanoparticles. As-NPs can significantly inhibit the oxygen uptake and intracellular proliferation of the parasitic pathogens [109].

**ZNO NPs:** ZNO NPs causes oxidative stress due to the production of ROS in parasites. As a result, it is associated with the increased activity of the antioxidant enzymes, SOD, and GST [110].

## Conclusions

Due to the increased drug resistance worldwide, it requires new technology. Nanoparticles have been selected as an effective

material and a suitable alternative to antibiotics and antimicrobial drugs (fungi, viruses, and parasites). It is clear that the use of nanoparticles can be a good alternative for the treatment of infections caused by pathogenic microorganisms, and the combination of nanoparticles with antibiotics and drugs can increase their effectiveness, which requires further research. A comparison of different nanoparticles also showed that the effect of silver nanoparticles on microorganisms is wider than other nanoparticles. Also, due to the poor diagnosis and overuse of drugs and the inability of drugs, microorganisms are usually able to develop resistance to antibiotics. Infections caused by the MDR microorganisms are a serious global health issue. To solve these problems, metal nanoparticles are highly effective against various MDR pathogens, alone or in combination with antibiotics. However, for the use of these nanoparticles for therapeutic applications, different bacteria are present. Therefore, due to its high anti-bismuth efficiency, research on the lethal effect of these nanoparticles on microorganisms is ongoing.

### Disclosure Statement

No potential conflict of interest was reported by the authors.

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