International Journal of Pharmacy and Pharmaceutical Sciences

Print ISSN: 2656-0097 | Online ISSN: 0975-1491 Vol 13, Issue 8, 2021

Review Article

INORGANIC NANOPARTICLES: AN ALTERNATIVE THERAPY TO COMBAT DRUG RESISTANT INFECTIONS

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Received: 07 Mar 2021, Revised and Accepted: 09 Jun 2021

ABSTRACT

One of the most urgent challenges that medical sciences face today is overcoming the problem of drug resistance. This review paper encompasses research studies that provide a solution towards this major concern. It aims to highlight the therapeutic effects of various metal-based nanoparticles over conventional antibiotics. Severe infections caused by bacteria, viruses, fungi and parasites are transmitted easily and spread across millions of people round the globe. Resistance developed by these organisms and their various strains against regular antibiotics has posed great threat to save the lives of humans. Nanoparticles are tiny in nature and thus capable of generating Reactive Oxygen Species (ROS). These ROS bursts to create severe oxidative stresses causing damage to DNA, lipids peroxidation and protein changes resulting in cell death. This mechanism is quite different from traditional antibiotics and hence gives better results towards microbial resistance. The study demonstrates the use of metal nanoparticles such as silver, zinc oxide, aluminium oxide, gold, copper oxide, titanium dioxide, magnesium oxide, iron oxide in combination with various antibiotics to efficiently kill infectious microbes.

Keywords: Bacterial infection, Fungal infection, Viral infection, Parasite infection

DOI: https://dx.doi.org/10.22159/ijpps.2021v13i8.42643. Journal homepage: https://innovareacademics.in/journals/index.php/ijpps.

INTRODUCTION

These infectious diseases spread through fungi, viruses, bacteria and parasites, which have become the cause of many deaths throughout the world [1]. Infectious diseases were classified 2 groups: emerging and re-emerging. New diseases were being referred as emerging infectious diseases whereas re-emerging diseases are not new but suffer from drug resistance and thus they again appear, due to which there is difficulty in treating and controlling them [2]. However, the ability to prevent infection of the human body is only possible by the immune system. Although some infections are direct, whereas others are very transmissible and dangerous [3]. Transmission of infections occurs when some microorganism enters the host cell, resulting in their replication inside the host cell, causing the tissue to be damaged. However, it is necessary to mention that some microbes can replicate the body's externally, which results in tissue damage [4].

Drug resistance largely interferes with the treatment of infectious diseases, which makes it necessary to develop a novel therapy which could overcome this resistance. The therapeutic agents such as any metal nanoparticles were used for the treatment of infectious diseases. Metal nanoparticles show antimicrobial activity, which depends on size. Small size of nanoparticles easily penetrates the bacterial cell wall, resulting in cell death [5]. Hence, drug delivery capability as well as their therapeutic efficacy is aimed at improvement at the pathological site. Metal nanoparticles have good properties [physico-chemical] [6]. The unique Physico-chemical properties of metal nanoparticles make them a potent weapon against infectious diseases. Hence, these were designed for the majority of biomedical applications [7]. This review focuses on the biological activity of metal-based nanoparticles that are affordable and non-toxic and provide potential therapeutics against various fungal, parasitic, viral and bacterial diseases.

Search criteria

Exploring the latest knowledge over the subject through Research gate, Pubmed, EMBASE, Google scholar, Google web searches, SCOPUS and Web of Science greatly assisted in writing this review paper. Updated information has been incorporated on the basis of an extensive literature search on this subject.

Mechanism of nanoparticles to microbes

As a supplement to antibiotics, Nanomaterials as antimicrobials are highly promising and are receiving great interest as they can fill the gap where antibiotics are often unsuccessful. It includes combatting multidrug-resistant biofilm and mutants [8, 9]. An antibacterial nanoparticle is now in use [metal, metal oxide, and organic NPs] indicates the diversity of internal and modified chemical composition properties. Thus, it is unexpected that they have several ways [fig. 1]. Apart from this, there is considerable variation in the genetics of the target bacteria, as well as inhibiting them in cell wall structure, essential metabolic pathways and many components can prove to be very fatal for microorganisms. In addition, the physiological condition of bacteria, i.e., the planktonic, growth rate, biofilm, the sensitivity of the bacteria to stable or starved, can contribute significantly to the nanomaterials [10, 11]. In some cases, the ratio between bacteria and nanomaterials is important for subsequent toxicity. Furthermore, many environmental factors play a role and affect nanomaterials lethality, which contain bacteria, including pH, aeration and temperature [12]. With other nanoparticles, the physiological properties of particles including chemical modification, coating, size, shapes, and mixing in different ratios and the use of solvent affect all their antibacterial activity [13]. Thus, the Mode of Action and Level of hazard of Nanomaterials Antibacterial is still unclear and literature can find in other reports [14, 15]. However, as usually, nanomaterials works with two major routes, Which are related to each other and occur in many cases simultaneously: 1. reactive oxygen The production of species [ROS], also known as oxygen-free radicals, acts as nanomaterials nanocatalysts and with different chemical structures to generate ROS associated with their hazardous and toxic effects has been well-characterized in previous studies [16, 17]. Compared with microparticles or their bulk of origin, NPs possess unique physicochemical properties [size, surface area, shape, solubility, and aggregation status] that correlate with their potential to generate ROS [18-24]. 2. Disruption of membrane potential and integrity [25, 26].

Membrane damage occurs when the nm tie electrostatic bacteria goes to the cell wall and membrane, causing loss of membrane potential, membrane depolarization, and integrity, which in turn,

imbalance of transport, impaired respiration, obstruction of energy transit And/or cell analysis, and ultimately cell death [27].

The most effective determinant for both *in vitro* and *in vivo* cytotoxicity of ROS, Nanomaterials is believed to be, by the disruption of the respiratory chain itself or directly induced by the Nanomaterials [28]. A burst of ROS occurs through severe oxidative stress, causing damage to all the brain cells, thereby prohibiting lipid peroxidation, protein changes, enzymes and RNA and DNA damage. In high doses, ROS leads to cell death and low dose, causing severe DNA damage and mutations [29, 30]. In some cases, where ROS production is visible or induced by UV light [31] NM poisoning is photocatalytic, for example as show in table 1, TiO_2 nm was induced under almost-UV light, lipid peroxidation, which was *E. coli* leads to respiratory disease and death of cells [32]. Several other effects of nanomaterials include direct inhibition of specific essential enzymes, induction of nitrogen reactive species [NRS] [30, 12, 15, 16] and induction of programmed cell death [31].

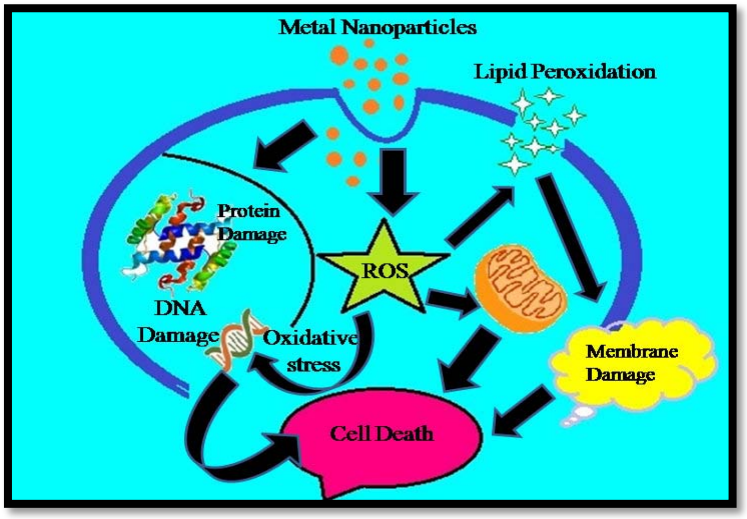

Fig. 1: Mode of action of nanoparticles on bacteria (Adapted and modified)

Table 1: Various nanomaterials kill to various bacterial cell wall

Nanoparticles	Size [nm]	Microbes	Time	Concentration	Target site	Reference
Ag	9.3	*E. coli*	10 min	-	Cell wall	[33]
Au	25	*C. pseudotuberculosis*	20 min	50, 100 and 200 µg/ml	Cell wall	[34]
Fe3O4 Ag	60	*E. coli, S. epidermidis, Bacillus subtilis*	24 h	60-70 µg/ml	Cell wall	[35]
MgO	4	*E. coli, B. megaterium*	20-60 min	-	Cell wall	[36]
ZnO	30	*Salmonella enteric, Escherichia coli*	16 h	0.5 mg/ml	Cell wall	[37]
Cu	100	*B. subtilis, E. coli*	24 h	60 µg/ml	-	[38]
TiO_2	8	*Staphylococcus aureus*	30 min	-	Cell wall	[39]
Al_2O_3	60	*E. coli, B. subtilis, Pseudomonas*	-	20 µg/ml	Flocculation	[40]

Classification of infections

Infectious disease is a clinically clear disorder that is caused by the presence of a pathogenic agent that can be either a bacteria, fungus, virus or parasite, from these diseases to one person [tuberculosis, malaria,] and due to the ability to move from one species to another [influenza, flu] sometimes called these communicable diseases. Infectious diseases can be highly classified: 1] known diseases which are insistent [e. g., tuberculosis, dengue, malaria,]; 2] New, previously unknown diseases [e. g., severe acute respiratory syndrome]; And 3] threatening to progress in the near future [e. g., avian influenza] is a major threat to these diseases because more than half of the world's deaths occur in these diseases, especially in developing countries [41]. Parasitism causes the benefits and infections received by pathogenic bacteria attacking the host [42]. These infections are described in below.

[i] Bacterial infections treated with metal-based nanoparticles

Treatment of bacterial infection is being interrupted by drug resistance due to which the danger is increasing on all over the world. Several molecular strategies have also been developed which increase their adhesion for host cells and their ability also gives the result of their colonies [43]. One such molecular strategy is hair-like organelles which are known as pili on the surface of bacteria. Bacteria are bound with host cells through these pili. Only Gram-positive and Gram-negative bacteria possess hair-like organelles structure [43-45]. Another probable molecular strategy is through forming biofilms that would protect bacteria in adverse conditions [43, 46]. Biofilm formation consists of protein, exopolysaccharides, EDNA etc. and has three main steps, i.e. the attachment to the surface of the host cell, the formation and separation of biofilm structure [47]. These components resists antibiotics and antibacterial agents. Biofilm creates adhesion between bacterial cells, from which multi-layered biofilms are formed. This segment will focus on the antibacterial activity of metal-based antibacterial compounds.

Silver nanoparticles

Several papers have been reported on silver nanoparticles penetrated to the bacterial cell wall. Subsequently, damage the structure of cell wall then cell death as shown in [fig. 1]. Some researchers have proposed that the silver nanoparticles produce free radicals and interact with bacteria and release silver ion, which causes cellular enzyme deactivation and inhibits several functions in cell and causing cell death. Another study reported that silver nanoparticles interact with DNA, inhibit to bacterial DNA replication, resulting cell death [70-77]. *Tuberculosis* is an infectious disease that affects the lungs and bacterium are caused by *Mycobacterium tuberculosis* [48-50]. Silver nanoparticles inhibited the growth of *Mycobacterium tuberculosis in vitro* and showed low cytotoxic effects. Silver nanoparticles were selected for the treatments and their therapeutic outcome as shown in (table 2).

Table 2: Various metal-based nanoparticles with antimicrobial activity their therapeutic outcome

Metal nanoparticles	Therapeutic effect	References
AgNPs	Hampers growth of *Mycobacterium tuberculosis*	[48-50]
AgNPs in urinary catheter	Potent against urinary tract infections causing bacteria	[51-56]
AgNPs combined with blue light and either of the *Clarithromycin, Azithromycin, Amoxicillin, Linezolid Or Vancomycin*	Very efficient against *Staphylococcus aureus.*	[57]
AgNPs synthesised by plants extracts	Stable and antibacterial nanoparticles.	[58-69]
AgNPs isolated from industrialized area	Molecular identification *Bacillus strain* CS 11	[70]
AgNPs	Effective against *Staphylococcus aureus* and *Escherichia coli*	[71-77]
AgNPs generated using biological Methods [virus, fungi etc.]	Efficient antibacterial activity.	[78-84]
AgNPs+*rifampicin* and *polymixin B*	Very Effectively treat *Acinetobacter baumannii* infection.	[85]
AgNPs+*amoxicillin*	Effectively treat *Escherichia coli*	[86]
AgNPs	prevention of gastrointestinal	[87]
Al_2O_3NPs	Good Antimicrobial sensitivity against *Escherichia coli*	[88]
Al_2O_3NPs	Nanoparticles entered Candida cells to disrupt their physiological activity.	[89-90]
Al_2O_3NPs prepare using plant extract	Effectively treat *P. aeruginosa*	[91]
Al_2O_3NPs	Potent against gram-negative and gram-positive bacteria	[92, 93]
AuNPs combined with ofloxacin	Superior bactericidal property	[94]
AuNPs combined with gentamicin	Effective against *Escherichia coli*	[95, 96]
AuNPs combined with kanamycin, ampicillin, streptomycin and levofloxacin	High potency against *Micrococcus luteus, E. coli, and Staphylococcus aureus*	[97, 98]
AuNPs	Highly active against pathogens and multi-drug resistant, Gram-negative and Gram-positive pathogens	[99]
AuNPs prepare using Mulberry leaf extract	Effective against human pathogen *Vibrio cholera* [gram-negative] and *Staphylococcus aureus* [gram-positive]	[100]
Cu_2O NPs	Good antibacterial activity against *Bacillus sp.* FU4	[101]
Cu_2O NPs prepare using plant extract	Good antibacterial activity against *S. dysenteriae, Vibrio cholerae non.0139 [L4], Vibrio cholerae non.0139 [CSK6669], S. pneumoniae, S. aureus and E. coli*	[102-104]
Cu_2O NPs	Highly active	[105]
Cu_2O NPs	Antibacterial against *Pseudomonas fluorescens, Aeromonas Hydrophila and Flavobacterium branchiophilum,*	[106]
FeNPs prepare using plant extract	Antibacterial properties *Escherichia Coli, Pseudomonas Aeruginosa, and Staphylococcus Aureus*	[107, 108]
Fe_2O_3NPs+erythromycin	Effective against *S. pneumonia*	[109]
Fe_2O_3NPs combined with ciprofloxacin	Poor antibacterial activity	[110]
Ga NPs	Hampered *mycobacteria*	[111]
Ga NPs	Effective against *Pseudomonas aeruginosa*	[112]
Ga NPs	Strongly inhibited *Mycobacterium tuberculosis*	[113]
Ga NPs	Destroyed metabolism of *F. Tularensis* Fe	[114]
MgONPs using plant extract of *Swertia chirayaita*	Gram+ve bacteria *S. epidermidis, S. aureus, B. cereus* and Gram-ve bacteria, *P. vulgaris, E. coli, K. pneumonia*	[115]
Tio2 NPs	Effective against *Streptococcus mutans* and *E. coli*	[116-121]
Tio2 NPs	Potent against *S. aureus*	[122]
ZnONPs nanoparticles coated wit gentamicin	Significant antibacterial activity *against Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, Listeria monocytogenes*, *Bacillus cereus*	[123]
ZnONPs prepare using *Azadirachta indica*	Good antimicrobial activity against Gram-positive and Gram-negative bacteria: *S. aureus, S. pyogenes and Escherichia coli*	[124]
ZnONPs	Concentration of the nanoparticles determined inhibition of *B. subtilis*	[125, 126]

Furthermore, silver nanoparticles also treat urinary tract infections which are caused by *P. aeruginosa and Enterobacter.*

These were also used in synergy with antibiotic to treat bacterial infection thereby enhancing the therapeutic outcome. *Li et al.* suggested the combination of *amoxicillin* and silver nanoparticles against *Escherichia coli* [85] to check for selected functionalities [hydroxyl and amido-groups] on amoxicillin with silver nanoparticles, which resulted in the formulation of powerful antibacterial activity. Apart from this, *Wan et al.* reported that the synergistic effect aginst *Acinetobacter baumannii* to combine the antibiotics polymixin B and rifampicin with the silver nanoparticles, which are treated with hospital-acquired infections [86]. The possible mechanism for this synergistic effect was due to the disruption of the bacterial cell wall by Ag+ion thereby producing cytotoxic ROS by the visible blue light.

Silver nanoparticles have been prepared using plant extract which contains secondary metabolites such as vincristine, tannin, flavanoids and polyphenols which helps to form Ag nanoparticles. Examples include *Catharanthus roseus [C. roseus] [L.] G. Don,* [13], *neem leaves* [12], *aloe vera* [14], *Parkia speciosa Hassk* pods [11]. These plant extracts were used as reducing and stabilizing agents and show antibacterial potency [58-69].

Aluminium oxide nanoparticles

Aluminium Oxide nanoparticles exhibit antimicrobial activity against pathogenic microbes. An Aluminium Oxide nanoparticle penetrates to bacterial cell wall, resulting damage to all respiratory function and cell death [fig. 1]. *Ansari et al.* reported the green synthesis of Aluminium Oxide nanoparticles using leaf extract of *lemon grass* and their antimicrobial activity against extended-spectrum metallobeta-lactamases and beta-lactamases of clinical isolates of *P. aeruginosa* was found greater [91], *Jalal et al.* reported that Aluminium Oxide nanoparticles generation using leaf extract of *Cymbopogon citratus*. These nanoparticles get attached to the surface of bacterial cell wall, disrupting physiological activity and causing cell death [89, 90]. *Sadiq et al.* Reported that Aluminium Oxide nanoparticles are demonstrated antimicrobial activity against *Escherichia coli* [87, 88, 92, 93].

Gold nanoparticles

Ahamad et al. reported that gold nanoparticles combine with antibiotic ofloxacin, resulting exhibit superior antimicrobial activity [94]. Other researches have also reported that the gold nanoparticles when combined with antibiotics gentamicin are efficient against both Gram-positive and Gram-negative bacteria [95, 96]. The combine antibiotic with gold nanoparticles to enhanced the antimicrobial activity. In

addition, *Saha et al.* reported that the combines kanamycin, ampicillin, streptomycin and levofloxacin [97, 98]. With the gold nanoparticles, which are treated with *E. coli, Micrococcus luteus and Staphylococcus aureus* infections [95-98]. Conjugating the antibiotic to the nanoparticles resulted enhanced antimicrobial efficiency when compare to antibiotic alone suggesting that the gold nanoparticles enhance interaction with the bacterial cell wall, resulting in cell death. Furthermore, *Advallane et al.* was reported that biosynthesis of gold nanoparticles using leaf extract of *mulberry* against human pathogen Vibrio cholera [gram-negative] and Staphylococcus aureus [gram-positive].

Copper oxide nanoparticles

Taran *et al.*, showed that Copper oxide nanoparticles demonstrated antimicrobial activity against bacterial strains and are highly active against *Bacillus sp.* FU4 [101]. *Chatterjee et al.* have reported similar finding in which the antibacterial activity of copper oxide is due to generation of ROS nand DNA degradation in bacterial cells as show in fig. 1 [105]. The copper oxide nanoparticles are attributed to attach to surface of the bacterial cell, disrupted cell wall and causing cell death. The antimicrobial activity is depends on the particles size. The small size of nanoparticles shows high antibacterial activity. The spherical shapes of copper oxide nanoparticles show the highly antimicrobial activity against *Aeromonas hydrophila, Pseudomonas fluorescens and Flavobacterium branchiophilum* [106].

Iron oxide nanoparticles

Massadeh et al., investigated that iron oxide nanoparticles combine with ciprofiloxin, exhibited the poor antibacterial activity which may be due to interaction with ciprofiloxin inhibiting the absorbance of nanoparticles on the surface of bacterial cell [110]. But *Aparicio-Caamaño et al.* suggested that the combination that could inhibit *S. pneumonia* growth: Fe nanoparticles with erythromycin. This was due to enhanced entry of erythromycin into the bacterial cell wall due to the FeO nanoparticles [100]. *Rafi et al.* reported that plant extract could be used to produce iron oxide nanoparticles where concentration would determine the shape,size and antimicrobial activity of the nanoparticles [98, 99].

Gallium nanoparticles

Gallium nanoparticles also exhibited antibacterial activity [table 2]. *Narayanasamy et al.,* investigated that GaNPs hampered the growth of mycobacterium for 15 d after a single drug-loaded [111]. *Kurtjak et al.,* investigated that Gallium nanoparticles with the good antimicrobial activity against *p. aeruginosa* [112]. *Choi et al.,* suggested that the prepare of gallium nanoparticles for enhanced the antimicrobial activity against *Mycobacterium tuberculosis* infection [113]. The nanoparticles enhanced the maturation of phagosome, which indicates their potential as anti-tuberculosis drugs [114].

Magnesium oxide nanoparticles

Magnesium oxide nanoparticles are attributed to the attachment to the surface of the bacteria cell wall, distrusting the ATP, resulting the cell death. *Gaurav et al.,* Magnesium oxide nanoparticles using plant extract and show antimicrobial activity against Gram+ve bacteria [*S. aureus, S. epidermidis, B. cereus]* and Gram–ve bacteria [*E. coli, P. vulgaris, K. pneumonia].* There are few paper published [106].

Titanium dioxide nanoparticles

Titanium dioxide nanoparticles' antimicrobial activity is due to interaction with surface of bacterial cell where photo-catalytic action results in cell permeability and therefore cell death. *Lin et al.,* prepared the Titanium dioxide nanoparticles with smaller size which produces the high content of ROS. The smaller surface area resulted in greater penetration and thus more damage of membrane [116-121].

Zinc oxide nanoparticles

Raghupati et al., prepared smaller zinc oxide nanoparticles which resulted in nanoparticles with good antibacterial activity. *Hsueh et al.,* reported the inhibition effect of ZnO NPs on the growth of *B. subtilis* to depend solely on nanoparticles concentration. The accumulation of nanoparticles on the outer membrane of bacterial cell resulted cell death [125-126]. *Voicu et al.,* coated ZnO NPs with gentamicin and determined their antimicrobial activity against, *Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli, Listeria monocytogenes and Bacillus cereus* [123].

[ii] Fungal infections treated with metal-based Nanoparticles

Fungus is a ubiquitous and diverse group of micro-organisms. Some groups of fungi are plant pathogens which can cause serious infections in human beings [127, 128]. Skin disorders are due to a fungal group known as dermatophytes [129, 130]. Dermatophytoses may lead to major problems in immune-compromised hosts, and growing expansion of fungal skin infections in patients with HIV [131, 132]. In addition, prophylaxis with Antifungal may be due to the emergence of resistant strains [133]. Therefore, there is a need to search for a new generation of antifungal agents [134, 135].

Silver nanoparticles

Only few studies have reported the effects of silver nanoparticles on dermatophytes as most of them focused on the effect on *Candida* species [136-143]. The antifungal activity of AgNPs in biostabilized footwear materials was evaluated against dermatophytes and other fungi [144]. Noorbakhsh *et al.* [145, 146] investigated the effects of biologically synthesized silver nanoparticles by *Klebsiella pneumoniae* against *Trichophyton rubrum.*

Copper oxide nanoparticles

Sengal et al. found the efficacy of Copper oxide nanoparticles combined with fluconazole against *Candida albicans* infection [147]. Gold nanoparticles are potential anti-fungal agents which are developed by plasmonic clinical sample synthesis. The gold nanoparticles were negatively charged and inhibited the cell, replication and good antifungal effect [148].

Magnetic nanoparticles have also been found to be effective against the antifungal effect. Niemirowicz *et al.*, suggested antifungal activity demonstrated against *C. glabrata, C. tropicalis, and* C. *albicans* [149, 150].

Titanium dioxide nanoparticles

The antifungal activity of titanium dioxide nanoparticles attributes to interaction with cell surface of fungi where photo-catalytic action results in cell permeability and cell death. *Haghighi et al.,* prepared the Titanium dioxide nanoparticles with smaller size which produces the high content of ROS. The smaller surface area resulted in greater damage of the membrane [151].

Zinc oxide nanoparticles

Sardella et al., prepared zinc oxide nanoparticles which demonstrated good antifungal activity against *Penicillium expansum and Botrytis cinerea* [152, 153]. *Xue et al.,* reported that zinc oxide nanoparticles inhibit growth of fungal by the accumulation of nanoparticles on the outer membrane of the fungal cell causing cell death [154]. In addition, it also showed its antifungal activity against *A. flavus* and *A. fumigates* [155, 156]. *Grijaba et al.* reported that the zinc oxide nanoparticles with antifungal activity against *Erythricium salmonicolor* [157].

Viral infections treated with metal-based nanoparticles

Some viral infections are persistent and cannot be removed from the body through the immune system alone such as Herpes, Hepatitis, HIV, etc. which may occur for many years. There are reports that metal-based therapeutics are effective to treat viral infections as explained below.

HIV

HIV is a viral infection with 36.7 million people suffering from HIV/AIDS worldwide [158-162].

Lara *et al.*, reported the use of silver nanoparticles as an anti-HIV activity in both the initial phase of viral multiplication and entry-level of the HIV-1 life cycle [158-162]. In the initial phase, the silver nanoparticles got bind to gp120, as it inhibits the CD4-dependent virion binding, its fusion and also its infectivity. With the use of gp120 glycoprotein, silver nanoparticles prevent the virus from binding on host cells [162].

Kesarkar *et al.* reported that coated gold nanoparticles with polyethylene glycol exhibited greater antiviral activity. Kesarkar *et al.* further reported that the most effective concentration of gold nanoparticles at 2 µg/g and 4 µg/g were used for inhibiting virus entry [174].

Table 3: Various metal-based nanoparticles with antifungal potency and their therapeutic effect

Metal nanoparticles	Therapeutic effect	References
Silver nanoparticles prepare using *Erythrina suberosa*	Antifungal Activity against *C. albicans, C. kruseii, T. mentagrophytes, and C. viswanathii.*	[136]
silver nanoparticles biofilms	Antifungal Activity against *Candida albicans*	[137]
Silver nanoparticles	Antifungal Activity against *Candida species*	[138-142]
Amphotericin B-conjugated biogenic silver nanoparticles	Antifungal activity against *Candida albicans* and *Candida tropicalis*	[143]
Silver nanoparticles	Antifungal Activity against Foot mycosis prophylaxis	[144]
Silver nanoparticles	Antifungal Activity against *Trichophyton rubrum*	[145, 146]
Copper oxide nanoparticles combine with fluconazole	Antifungal activity against *Candida albicans*	[147]
Gold nanoparticles	Human Cutaneous Preventing From fungal infection	[148]
Magnetic nanoparticles	Candidacidal activity against *C. albicans, C. glabrata and C. tropicalis*	[149]
Iron-oxide nanoparticles	Antifungal effect against different *Candida species*	[150]
TiO2 nanoparticles	Prevention of fungal biofilms especially biofilms formed on the surface of medical devices.	[151]
Zinc oxide nanoparticles	Antifungal activity against *Penicillium expansum and Botrytis cinerea*	[152, 153]
ZnO nanoparticles	Inhibit the fungal growth and benefit to public health and environment	[154]
ZnO-NPs	Antifungal Activity against *A. flavus* and *A. fumigates*	[155, 156]
ZnO-NPs	Antifungal activity against *Erythricium salmonicolor*	[157]

Table 4: Various metal-based nanoparticles and their antiviral efficacy with therapeutic results

Metal nanoparticles	Type of infection	Therapeutic result	References
Ag nanoparticles	HIV	Inhibits CD4-dependent viral binding.	[158-162]
Ag nanoparticles	Herpes	Prevention virus infection	[163, 164]
Ag nanoparticles	Hepatitis	Inhibits the production of HBV RNA and extracellular virions by interacting with HBV viral particles	[165-167]
Ag nanoparticles	Influenza	Damages morphological structure of influenza virus. Prevents binding sites of the virus.	[168-173]
Au [Gold] nanoparticles	HIV	Inhibits entry of virus	[174]
Au nanoparticles	Herpes	Inhibited attachment of virus and stops penetration into the cell.	[175, 176]
Au nanoparticle combined with interferon-alpha	Hepatitis	Targets interferon alpha	[177, 178]
Au nanoparticles	Influenza	Very reliable against influenza A virus	[179, 180]
FeO nanoparticles	Hepatitis	Hampered hepatitis C virus gene, protease and helicase, NS3. HCV NS3 gene encodes.	[181]
Cuprous nanoparticle	Hepatitis	Prevented virus entry that involved genotypes [1a, 1b, and 2a] thus restricting viral replication	[182]
ZnO nanoparticle	Herpes	Prevented viral entry and infection	[183, 184]

Herpes

Herpes simplex virus HSV-1 and HSV-2 causes Herpes.

When Silver nanoparticles and HSV-2 interacts, it results in the reduction of offspring of the virus with weak cytotoxicity *in vitro* [163]. The High concentrations of silver nanoparticles are toxic to Vero cells. 100 µg/ml concentration of silver nanoparticles was used for inhibit the viral replication.

Baram-Pinto *et al.*, reported the inhibition of HSV-1 virus by coating gold nanoparticles with mercarptoethene sulfonate. When the gold nanoparticles get attached to the surface of cell membrane, it inhibits viral entry and prevents from infection. These gold nanoparticles are non-toxic and very much useful for the treatment of viral infection [175, 176].

Mishra *et al.*, developed micro nanoparticles of zinc oxide nanoparticles coated with various nanoscopic spikes that mimicks cell induced filopodia, which bind to their cell surface and inhibit viral entry and prevent infection [183, 184].

Hepatitis

Hepatitis is a viral infection which are of various types namely A, B, C, D, E and G type Hepatitis. Hepatitis A is caused by RNA virus that spreads through oral route and sexual contact [174]. Hepatitis B is caused by DNA virus that pass on genetically and sexually. Hepatitis C is caused by RNA virus and passes on by infected blood or sexually. In addition, Hepatitis D is caused by RNA virus. It can be found only in those who are infected with Hepatitis B virus [HBV]. The dual infection of Hepatitis B virus [HBV] and Hepatitis D virus [HDV] can result in more serious disease and worse outcome. Hepatitis E virus is transmitted through contaminated water or food.

Hepatitis G virus is recently discovered and belongs to *Flaviviridae* family. Silver, gold, iron oxide and cuprous oxide nanoparticles were used for the treatment of hepatitis infections [table 4].

Lu *et al.*, investigated the nanosize [10 nm and 50 nm] of silver nanoparticles were studied *in vitro* as anti-HBV on the HepAD38 cell line. It has been observed that nanoparticles reduced the external HBV DNA formation of hepAD38 cells by 50%. These silver nanoparticles inhibits the production of hepatitis B virus RNA and virions [165-167].

Yarshi *et al.*, developed *In vitro* evaluation on a blood sample infected with hepatitis C virus for hepatitis C virus viral loaded in a 1:1 ratio and gold nanoparticles didn't show any activity on the virus [177, 178]. But they act as drug delivery systems such as Hyaluronic acid-gold nanoparticles combination was used to treat hepatitis C infection to the delivery of interferon-alpha in liver. Ryoo *et al.*, investigated that iron oxide nanoparticles were inhibited to hepatitis C virus gene, NS3 and encoded helicase and protease which are responsible for viral replication.

Similarly, 2µg/ml concentration of cuprous oxide nanoparticles was used for inhibition of viral replication. These cuprous oxide nanoparticles are attached to the surface of cell membrane to inhibit viral entry, to prevent from infection of hepatitis C [182].

Influenza

Influenza is a viral infection that spreads through the respiratory system which is spread all over the world, especially among people suffering from chronic diseases. Xiang *et al.*, reported the treatment of H3N2 influenza viruses by silver nanoparticles as they damage the morphological structure of the virus [168-173]. The damage was time-dependent. Li *et al.*, investigated the delivery of silver nanoparticles in combination with amantadine to inhibit the H1N1 infection by ROS

accumulation [168-173]. Other reports on silver nanoparticles also suggest about to inhibit the influenza virus and show anti-influenza activity, respectively [168-173]. Thus the antiviral activity was due to preventing virus attachment to the cell surface.

Parasitic infections

There are many examples of parasitic infections such as malaria, leishmaniasis, helminths etc. which suffer from drug resistance due to poor treatment compliance.

Malaria

Malaria is a mosquito-borne infection with 210 million people suffering from Malaria. In 2015, it was estimated that there were 438,000 people died in all over world [185-186]. It is spread by mosquitoes and caused by a parasite protozoan belonging to the Plasmodium type. The major challenge to treat malaria infections is drug resistance, which is due to bad treatment, mutation rates of parasites, efficacy of selected medicines and various strains of malaria parasites, which are responsible for co-infection.

Silver nanoparticles

There are few reports on silver nanoparticles against the antiplasmodial activity. Mishra *et al.*, reported that growth of *P. falciparum* in human R. B. C culture was inhibited by silver nanoparticles synthesized using leaf extract. These biosynthesized silver nanoparticles were used against antiplasmodial activity at concentration IC50 [g/ml] of 3.75 for Amylase [185]. Murugan *et al.*, reported the silver nanoparticles to have shown antiplasmodial activity against chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum* at [IC50] 72.45 and 76.08 µg/ml, respectively when using *C. tomentosum* as a reducing, capping and stabilizing agent [187].

Selvam *et al.*, developed biosynthesized silver nanoparticles using *Catharanthus roseus* leaf extract as a reducing and stabilizing agents, which showed antiplasmodial activity against *P. falciparum* at 25, 50, 75, and 100 µg/ml, respectively [189].

Gold nanoparticles

Dutta *et al.*, reported that gold nanoparticles synthesized using bark extract of *Syzygium jambos*, demonstrated antiplasmodial activity against chloroquine-resistant strains of *P. falciparum* at 51.63 and 49.38 µgm/l while activity against chloroquine-sensitive strains of *P. falciparum* at IC50 values of 49.54 and 45.49 µg/ml [202, 203].

Leishmaniasis

Leishmaniasis is caused by *Leishmania* parasites. It is caused by the bite of infected female phlebotomine sandflies. Over 90 sandfly are known to transmit *Leishmania* parasites. Some of the anti-leishmanial drugs suffer from drug resistance [197, 198] Some researches have revealed treatment of leishmanial infection by metal-based nanoparticles [table 5].

Silver nanoparticles

Lima *et al.*, found out an antileishmanial activity against promastigote forms of *Leishmania amazonensis* by synthesizing chitosan-based silver nanoparticles which demonstrated antileishmanial activity at MIC ranging from 1.69 to 3.38 µg Ag/ml [190-196]. Ahmad *et al.*, developed silver nanoparticles using *Sargentodoxa cuneata* extract and these nanoparticles thus acted as reducing, capping and stabilizing agents and showed antileishmanial activity at IC50 values of 4.37 and 5.29 µg/ml, respectively [190-196]. In another research, Zahir *et al.*, found out high antileishmanial efficacy of developed silver nanoparticles against *Leishmania* parasites at IC_{50} of 14.94 µg/ml and 3.89 µg/ml [190-196].

Gold Nanoparticles [GNPs]

Sazgarnia *et al.*, reported the increased exposure time of the microwave to the parasites in the presence of GNPs induced a significant decline in promastigotes survival rate in comparison to similar samples without GNPs. The least survival of amastigotes was also recorded in the groups containing GNPs [204].

Helminth

Helminth also commonly known as parasitic worms which are invertebrate, elongated, round or flat bodies. Helminth infection causes morbidity and mortality. Helminth infections are generally treated using anthelmintics agents but some of these infections offer resistance towards drug. Metal-based nanoparticles like silver, gold and zinc oxide were used for the treatment of Helminth infections.

Rashid *et al.*, reported that silver nanoparticles which were synthesized from *momordica charantia* plant extract and coated with polyaniline had a kill time of worms as 35.12±0.5 and 59.3±0.3 min [200-201].

Kar *et al.*, reported that Gold nanoparticles prepared with the help of gold chloride and mycelia-free fungus affected the parasite and cause paralysis resulting in death [205].

Iron oxide nanoparticles were more effective than zinc oxide nanoparticles when treated against T. *vitulorum* and evaluated for the antihelmintic activity. Treatment with low dose of 0.004%, results in an increase of SOD.

Table 5: Various metal-based nanoparticles with anti-parasitic efficacy with therapeutic results

Metal nanoparticles	Infection	Therapeutic outcome	References
Silver nanoparticles	Malaria	Inhibition of the growth of *P. falciparum in vivo* and *in vitro*	[185-188]
Silver nanoparticles	Malaria	The AgNPs showed antiplasmodial activity against P. falciparum	[189]
Silver nanoparticles	Leishmaniasis	Inhibition of proliferation and metabolic activity of promastigotes. Good antileishmanial activity *in vitro* and *in vivo*	[190-196]
Silver nanoparticles	Leishmaniasis	Ag-NPs demonstrated significant antileishmanial effects by inhibiting the proliferation and metabolic activity of promastigotes.	[197, 198]
Silver nanoparticles	Leishmaniasis	The IC50 for nanosilver solutions was high significantly [14.9 µg ml-1].	[199]
Silver nanoparticles	Helminth	Enhanced anthelmintic activity against worm	[200, 201]
Gold nanoparticles	Malaria	Moderate delayed parasitemia rise *in vivo*, moderate antiplasmodial activity against P. falciparum	[202, 203]
Gold nanoparticles	Leishmaniasis	The presence of GNPs during MW irradiation was more lethal for promastigotes and amastigotes in comparison to MW alone.	[204]
Gold nanoparticles	Helminth	Affected the physiological functioning of the parasite causing paralysis and subsequent death	[205]
Selenium nanoparticle	Leishmaniasis	Unlike selenium NPs, showed an anti-Leishmanial effect *in vivo*.	[206]
Copper [II] nanoparticle	Malaria	The two compounds showed significant antimalarial activities against the parasites	[207]
Zinc oxide nanoparticles and iron oxide nanoparticles	Helminth	The anthelmintic activity of the metal oxides nanoparticles was via induction of oxidative stress	[208]

Future prospects

Despite the above-mentioned clinical efficacy of inorganic metal nanoparticles, it is extremely necessary to develop cost-effective metal nanoparticles so that application of these inorganic nanoparticles can increase further to treat infections than other drugs Also, there is a more need to study the toxicological properties and pharmacological properties for the treatment of all infection. Metal-based nanoparticles have the ability to overcome drug resistance which makes it promising for the treatment of infectious diseases in the future of medical sciences.

CONCLUSION

Infection diseases were classified as bacteria, fungi, viral and parasitic as well as their treatments is affected by drug resistance. Nowadays, most of the medicines used for the treatment of infections are suffering from drug toxicity, which are non-selective, and these infections can be overcome by metal-based nanoparticles.

They can also be engineered by introducing selected biological moieties with specific binding activity to selected target cells thereby improving their therapeutic efficacy at the pathological site. Metal-based nanoparticles of antimicrobial activities is related to their ability to produce ROS that damage the bacterial cell wall and bind to DNA or RNA, due to disturbed the microbial replication process, mitochondrial function as well as bacterial enzyme activity. The combinations of antibiotics with nanoparticles are exhibits the good synergistic effects against the microbes.

ACKNOWLEDGEMENT

I wish to express my sincere acknowledgment to Dr. Ashok Kumar Chauhan, President, RBEF parent organization of Amity University Madhya Pradesh [AUMP], Dr. Aseem Chauhan, Additional President, RBEF and chairman of Amity University Gwalior Campus, Lt. Gen. V. K. Sharma, AVSM [Retd.], Vice-Chancellor of AUMP Gwalior Campus and Head of Biotechnology Department, Invertis University for their valuable support and encouragement throughout the work.

FUNDING

Nil

AUTHOR CONTRIBUTION

MG wrote the manuscript draft and design the concept and finalized the manuscript.

CONFLICT OF INTERESTS

The authors confirm they have no conflict of interests.

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