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Review article

Nanoparticles as antimicrobial and antiviral agents: A literature-based perspective study

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ABSTRACT

The scientific explorations of nanoparticles for their inherent therapeutic potencies as antimicrobial and antiviral agents due to increasing incidences of antibiotic resistance have gained more attention in recent time. This factor amongst others necessitates the search for newer and more effective antimicrobial agents. Several investigations have demonstrated the prospects of nanoparticles in the treatment of various microbial infections. The therapeutic applications of nanoparticles as either delivery agent or broad spectrum inhibition agents in viral and microbial investigations can no longer be overlooked. Their large surface area to volume ratio made them an indispensable substance as delivery agents in many respect. Various materials have been used for the synthesis of nanoparticles with unique properties channelised to meet specific therapeutic requirement. This review focuses on the anti-bacterial, antifungal, and antiviral potential of nanoparticles with their probable mechanism of action.

1. Introduction

Nanoparticles (NPs), often referred to as invisible particulate substances with a diameter ranging from 1-100 nm (nm) are of paramount relevance in the modern science (Khan et al., 2017; Song et al., 2021; Vert et al., 2012). The large surface area to volume ratio of nanoparticles made them a unique delivery and antimicrobial agents in many respect (Ingle et al., 2013). Over the past few decades, nanoparticles have been used for human welfare in different fields (Sharma et al., 2019). In recent time an intense scientific exploration is ongoing on nanoparticles due to its potential applications in various fields including medical science (Singh and Nalwa, 2011), drug delivery (Medhi et al., 2020), electronics (Magdassi et al., 2010; Kim et al., 2010), optics (Li et al., 2010; Biju et al., 2008), agriculture (Ghasemnezhad et al., 2019; Scott and Chen, 2013), waste water treatment (El Nahrawy et al., 2019; Nahrawy et al., 2020), as sensor support (Abou-Hammad et al., 2019) among others (Guang et al., 2021; Han et al., 2021; Shen et al., 2021; Zhou et al., 2021). The prospective applications of NPs in various fields are premised on the nanoparticle's unique characteristics such as its shape, charge, size, high ratio of surface area to mass and, high reactivity. This has drawn the attention of many individual (Kim et al., 2007). Gold, silver, platinum, and other oxide nanoparticles have been extensively used in the field of nano-biomedicine for their distinctive properties (Daniel and Astruc, 2004; Jeyaraj et al., 2013; Hashimoto et al., 2016; Falcaro et al., 2016; Zhang et al., 2021).

Infectious diseases are a set of diseases or disorders caused by pathogenic microbes (bacteria, viruses, fungi, protozoa, parasites) that directly affect human health (Singh et al., 2014). In recent times, infectious diseases have become a great burden on the world economy as well as on public health. Various health issues including Chronic obstructive pulmonary disease (COPD), meningitis, human immunodeficiency virus (HIV), inflammatory bowel disease (IBD), severe acute respiratory syndrome (SARS), H5N1, trichomoniasis, pneumocystis pneumonia are generally caused by microbes which cause death to millions of people around the world annually (Sethi and Murphy, 2001; Durand et al., 1993; Lara et al., 2010; Singh et al., 2014). However, for the treatment of these infections, antibiotics are often the first choice. Antibiotics significantly inhibit the presence of different microbes and reduce the associated signs and symptoms (Ewald, 1980). But microbes' growing resistance against these antibiotics coupled with the abuse of drugs as well as the release of

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the antibiotics to the environment has impeded progress expected from the treatment option (Laxminarayan et al., 2013; Friedman et al., 2003; Atolani et al., 2020). Highly mutative capacity and rapid morphological changes may lead to microbial resistance. Recent research regarding this issue revealed that a new kind of β-lactamase has been developed by the bacteria that produce resistance against β-lactam antibiotics (Fishovitz et al., 2014). To overcome the resistance developed by microbes, nanoparticle-based treatment presents a very promising approach. Therefore, conjugated use of antibiotics with nanoparticles may enhance the inhibition capacity and show less chance of resistance by organisms (Sobhani et al., 2017). Rai et al. (2010) in his study showed the significant antibacterial activity of gold nanoparticles (52–22 nm) capped with cefaclor, a second-generation antibiotic. The antimicrobial activity was apparently due to the presence of β-lactam ring on the surface of the nanoparticles. Microbial biofilms, planktonic cells may also contribute to resistance and therapy failure. In the case of bacteria and fungi, the biofilm formation inhibition is frequently seen to achieve bactericidal and fungicidal activity. Biofilm is the complex structure of the pathogen that may often show resistance towards foreign chemicals. These microbial aggregates can be 10-10,000 times less sensitive towards antimicrobial agents than the organism itself in suspension (Harrison et al., 2005). Nanotherapy seems to have a significant effect on biofilms of bacteria and fungi imparting vague mechanisms. Cremonini et al. (2016), reported the antibiofilm activity of biogenic selenium nanoparticles that effectively retards the biofilm formation of gram-negative *Pseudomonas aeruginosa*. The same result was observed for TiO_2 nanoparticles against fungal biofilms (Haghighi et al., 2013). Planktonic microbes are also known to induce resistance although to a lesser extent compared to the biofilms. PVK–GO nanocomposites at a low concentrations exhibited antibacterial effects up to 30% and 57% for gram-positive and gram-negative planktonic cells and biofilms (Carpio et al., 2012).

Studies disclosed that nanoparticles carrying features like high surface area, charge, ability to deliver a large number of antibiotics or other substance, size and shape makes them ideal antimicrobial weapon (Bhosale et al., 2018; Fabiyi et al., 2020; Yien et al., 2012). These features saliently or latently may contribute to its antimicrobial efficacy. The size of nanoparticles are proven features that confers antimicrobial potency on the substance. Besides the innate antimicrobial potential of NPs, the vast varieties of analyses on NPs suggested that the large surface area of the NPs are imperative for microbial attachment and rapid penetration into the cell (Gurunathan et al., 2014; Yien et al., 2012). Philip (2010), reported the presence of different shapes of metal NPs including nano-sized rods, tubes, spherical, triangles, tetragonal, pentagonal, and hexagonal. Shapes of NPs are directly important in determining the types and extent of interaction with the membrane or enzymes of microorganisms. For instance, ZnO nanoparticles of different shapes (plate, sphere, and pyramid) showed shape-dependent activity on a typical enzyme β-galactosidase (GAL) (Cha et al., 2015).

The inhibitory mechanism that is followed by the nanoparticles is not correctly assembled and fully explained. However, evidence shows that induced oxidative stress (Gurunathan et al., 2012; Liu et al., 2011; Quinteros et al., 2016; Joe et al., 2018), released metal ions (Nagy et al., 2011; Bagchi et al., 2013; Liu et al., 2010; Panicker et al., 2020), other non-oxidative mechanisms (Leung et al., 2014; Aničić et al., 2018; Setyawati et al., 2013) are thoroughly followed, models. Moreover, microbial cell wall penetration, the generation of reactive oxygen species (ROS), damaged DNA and proteins, loss of cellular integrity are the underlying mechanisms that cause inhibition for bacteria, fungi, and likewise viruses. Cell penetration is often the initial step in the stages involved in some microbial cell inhibition process before other mechanisms are adopted. Adsorption or diffusion of NPs at the cell surface is the main penetration mechanism. Adsorption can be attained through the binding of NPs with the negative charged functional groups of proteins resulting in protein destruction and cell death (Padmavathy and Vijayaraghavan, 2011). While evidence has reported ROS formation into pathogenic cells through the diffusion process (Zhang et al., 2013). Besides, microbial destruction and inactivation due to an interaction between various surface-exposed groups of microbes and nanoparticles may seem to be a possible mechanism (Ray et al., 2007; Rogers et al., 2008).

From the overall discussion, some characteristics of nanoparticles are explored which can be very beneficial to future researchers. The antimicrobial activity of nanoparticles has been studied against a wide range of microorganisms including bacteria, fungi, viruses from time to time. This study aims to summarize the effects of different nanoparticles

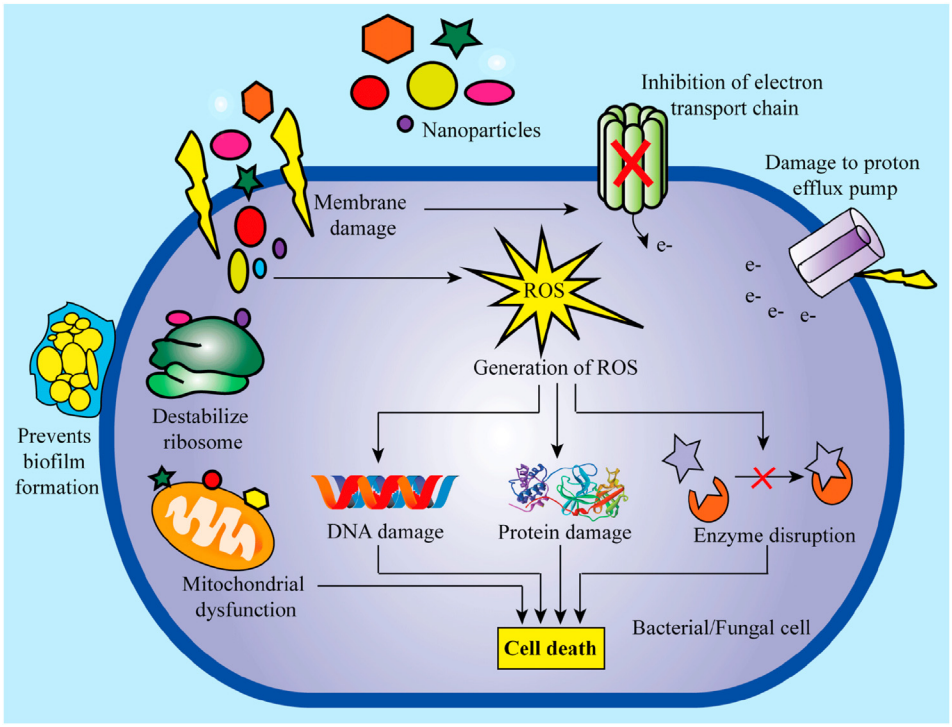

Figure 1. Schematic represents antimicrobial (bacteria and/or fungi) mechanisms of various nanoparticles. The antimicrobial (bacteria and/or fungi) activity of NPs has been attributed to their direct interaction with the bacterial and fungal cell wall/membrane and prevention of biofilm formation. In addition, NPs display potent anti-bacterial/anti-fungal effects through the generation of innate along with adaptive host immune responses, production of toxic reactive oxygen species (ROS), and stimulation of intracellular effects (e.g., enzyme disruption, DNA damage, and protein damage).

Table 1. Bactericidal potencies of some nanoparticles.

Nanoparticles (Diameter)	Test bacteria (strains)	Concentration	Mechanism of action	Reference
Chitosan nanoparticles (40 nm)	*S. choleraesuis* (Gram-negative)	0.25 μg/mL	Chelation with trace elements that inhibit growth. Formation of an impermeable layer around the cell that prevents the transportation of essential solution	Qi et al. (2004)
Silver nanoparticles (7 nm)	*E. coli* (Gram-negative) *S. aureus*(Gram-positive)	3.38 and 6.75 μg/mL	Damage DNA and disturb the synthesis of protein	Martinez castanon et al., 2008
Copper nanoparticles (10 nm)	*E. coli* (Gram-negative) *B. subtilis* (Gram-positive) *S. aureus* (Gram-positive)	20–300 mg/mL	Mechanism unclear	Jayesh et al. (2008)
Cephalor reduced gold nanoparticles (52-22 nm)	*Staphylococcus aureus* (Gram-positive) *Escherichia coli* (gram-negative)	10 μg/mL for *S. aureus* and 100 μg/mL for. *E. coli*	Inhibited synthesis of peptidoglycan layer, gold NPs generated holes in the bacterial cell wall leading towards increased permeability, leakage of cellular contents.	Rai et al. (2010)
Zinc oxide nanoparticles (30 nm)	*Camphylobacter jejuni* (Gram-negative)	0.05–0.025 mg/mL	Disruption of the cell membrane and oxidative stress in *C. jejuni*.	Xie et al. (2011)
Zero-valent Iron (Fe°) nanoparticles, spherical (31.1 nm)	*Staphylococcus aureus* (Gram-positive) *E. coli* (Gram-negative)	MIC for both strains at 30 μg/mL and complete growth inhibition at 60 μg/mL	Oxidative stress generation via ROS and visible damage to bacterial protein and DNA.	Mahdy et al. (2012)
Copper oxide nanoparticles (20 nm)	*S. aureus* (Gram positive) *B. subtilis* (Gram positive) *Psedomonas aeruginosa* (Gram negative) *E. coli* (Gram negative)	100 μg/mL	Rupture bacterial cell and leading to protein denaturation	Azam et al. (2012)
CaO nanoparticles (16 nm)	*Staphylococcus epidermidis* MTCC 435 (Gram-positive) *Pseudomonas aeruginosa* ATCC 27853 (Gram-negative)	MIC for strains are 2, 4mM MBC 4, 8 mM respectively.	Loss of cellular integrity, change in the cell morphology including disruption of cellular membrane	Roy et al. (2013)
Fluorescent Ag nanoparticles (nAg-Fs), 1.5 nm	*Staphylococcus epidermidis*NCIM2493, *Bacillus megaterium* (Gram-positive) *Pseudomonas aeruginosa* ATCC27853, *Escherichia coli* (Gram-negative)	No cell growth observed at conc. 2.0 μg/mL	Penetration of nAg-NPS into cell cytoplasm, leakage of cytoplasmic contents	Bera et al. (2014)
Magnetic Iron oxide nanoparticles (50–110 nm)	*S. aureus* (Gram-positive)	DMF solution with 40 and 60 mJ laser fluencies showed the highest antibacterial activity	Could be due to stress generated by ROS disrupting bacterial cell membrane.	Ismail et al. (2015)
Biogenic Selenium nanoparticles: Sm-SeNPs(-) (*Stenotrophomonas maltophilia*) (170.6 ± 35.12nm), Bm-SeNPs (+) (*Bacillus mycoides*) (160.6 ± 52.24 nm)	*Pseudomonas aeruginosa* (Gram negative) (INT, CFC20, CFC21, CFCB, CFCA strains)	*P. aeruginosa* INT 256 μg/mL [Sm-SeNPs(-)], 512 μg/mL [Bm-SeNPs(+)] *P.aeruginosa* (CFC21, CFC20, CFCA, CFCB) 8–16 μg/mL [Sm-SeNPs(-)], 32–64 μg/mL [Bm-SeNPs(+)]	Bacterial biofilm formation inhibition, disaggregation of the mature exopolysaccharide matrix produced by microbes.	Cremonini et al. (2016)
Ciprofloxacin loaded chitosan nanoparticles (72 nm)	*Escherichia coli* ATCC 25922 (Gram-negative) *Staphylococcus aureus* ATCC 25923 (Gram-positive)	40 ng/mL for *E. coli* 250 ng/mL for *S. aureus*	Increased penetration of the drug into the bacterial cells, growth inhibition.	Sobhani et al. (2017)
Silver oxide nanoparticles (42.7 nm)	*Streptococcus mutans* (Gram-positive) *Lactobacillus acidophilus* (Gram-positive)	***Streptococcus mutans*:** At conc 250 μg zone of inhibition (ZI) was 6 ± 0.8 mm, MBC was 22 ± 0.2% ***L. acidophilus*:** zone of inhibition 8 ± 0.4 mm, MBC 25 ± 0.5%	Mechanism unclear	Manikandan et al. (2017)
ZrO_2 nanoparticles (15–21 nm)	*Bacillus subtilis* MTCC 1305, *Staphylococcus aureus* MTCC 3160 (Gram-positive) *Escherichia coli, Pseudomonas aeruginosa* MTCC 2453 (Gram-negative)	Zone of inhibition 20 mm was observed for 100 μg/mL ZrO_2 NPs	The electromagnetic attraction between positively charged NPs and negatively charged cell surface.	Fathima et al. (2017)
Nickel ferrite ($NiFe_2O_4$) nanoparticles (NFOTP)	*Staphylococcus aureus* NCIM 5021, *Streptococcus pyogenes* NCIM 5280 (Gram-positive) *Escherichia coli* NCIM 2345, *Salmonella typhimurium* NCIM 2501 (Gram-negative)	Zone of inhibition for *E. coli* was seen but no numeric value is mentioned.	Higher negatively charged surface of *E. coli*, thin surface and formation of reactive oxidative species (ROS) and oxidative stress lead to cell death.	Bhosale et al. (2018)
Magnesium oxide nanoparticles (10.28 nm)	*Escherichia coli, Enterobacter cloacae, Acinetobacter baumannii* (Gram negative)	Highest activity shown for *E. faecalis* at MIC 7.81 μg/mL, ZI	ROS liberation, the interaction of MgO NPs with bacterial cell (suggested).	El-Sayyad et al., (2018)

(*continued on next page*)

Table 1 (*continued*)

Nanoparticles (Diameter)	Test bacteria (strains)	Concentration	Mechanism of action	Reference
	Enterococcus faecalis, *Staphylococcus aureus,* *Staphylococcus epidermidis,* MRSA (Gram-positive)	22.mm, others ranged 125.0–15.625 μg/mL		
Nalidixic acid-vanadium (V-NA) nanoparticles (170–330 nm)	*E. coli* (Gram-negative) *B. cereus* (Gram-positive) *P. aeruginosa* (Gram-negative) *S. aureus* (Gram-positive)	*E. coli*: 10 μM (MIC), 5.3 μM (IC50), 50 μM (MBC) *B. cereus*: 10 μM (MIC), 3.1 μM (IC50), 25–50 μM (MBC) *P. aeruginosa*: 625 μM (MIC), 430 μM (IC50), 5000 μM (MBC) *S. aureus*: 125 μM (MIC), 40 μM (IC50), 250–500 μM (MBC)	Electrostatic interaction between hybrid NP and bacterial cell due to highly negative charged surface	Bueloni et al. (2020)
Gold-chitosan hybrid nanoparticles (16.9 nm)	*S. aureus* (Gram positive) *P. aeruginosa* (Gram-negative)	0.25 mg/mL	Mechanism still unclear	Hussein et al. (2020)

against microbial infections with the possible mechanism of action. It further aims to draw the attention of researchers to conduct advanced level exploration on the promising traits of nanoparticles in this specific affair.

2. Methodology

A search (till September 2020) was done in the following databases: PubMed, Science Direct, MedLine, and Google Scholar with the keyword 'Nanoparticle', paring with 'anti-bacterial. antifungal and anti-viral activity/effect'. No language restrictions were imposed. Articles were assessed for information about the nanoparticles, microbial strains, test results, and possible mechanisms of action.

Inclusion criteria

The following inclusion criteria were adopted:

1. Studies with nanoparticles and synthesized nanoparticles from various sources.
2. Studies carried out *in vivo*, *in vitro* or *ex vivo* with or without experimental animals including microbial strains.
3. Studies with or without activity's mechanism.

Table 2. Antifungal potential of some nanoparticles.

Nanoparticles (Diameter)	Test fungi (strains)	Concentration	Mechanism of action	Reference
Silicon nanoparticles (7 and 14 nm)	*Candida albican*	-	Inhibited the yeast to hyphal transition that is induced in the presence of serum.	Cousins et al. (2007)
SDS stabilized silver nanoparticles (AgNPs), 25 nm	*Candida albicans* (I, II) *Candida tropicalis,* *Candida parapsilosis*	0.052 mg/L (*C. albicans* I) 0.1 mg/L (*C. albicans* II) 0.42 mg/L (*C. tropicalis*) 0.84 mg/L (*C. parapsilosis*)	The surfactant activity of NPs disrupts the cell wall of yeast.	Panáček et al. (2009)
Zinc oxide nanoparticles (70 nm)	*Botrytis cinerea* *Penicillium expansum*	3–12 mol/Ll^{-1}	Inhibition of growth by affecting cellular functions	He et al. (2010)
Zinc oxide nanoparticles (ZnO NPs), 70 ± 15 nm	*Botrytis cinerea,* *Penicillium expansum*	3 mmol/L	Deformation in fungal hyphae by affecting cellular function	He et al. (2011)
Nanoparticles of low molecular weight (LMW) chitosan, high molecular weught (HMW) chitosan (170–435 nm)	*Candida albicans,* *Fusarium solani,* *Aspergillus niger*	*C. albicans*: MIC for LMW chitosan 0.25–0.86 mg/mL, MIC for HMW chitosan 0.6–1.0 mg/mL, *F. solani*: MIC for LMW chitosan 0.86–1.2 mg/mL, MIC for HMW chitosan 0.5–1.2 mg/mL	Disruption of fungal cell membrane integrity due to particle size and zeta potential of NPs.	Yien et al. (2012)
Gold nanoparticles (25 nm)	*Candida sp*	16–32 μg/mL	Inhibition of H + ATPase leading to intracellular acidification and cell death	Wani and Ahmad. (2012)
TiO_2 nanoparticles (70–100 nm)	*Candida albicans*	5.14 μg/mL	Inhibition of fungal biofilms	Haghighi et al. (2013)
Copper nanoparticles (3–10 nm)	*Phoma destructiva* (DBT 66) *Curvularia lunata* (MTCC, 2030) *Alternaria alternate* (MTCC 6572) *Fusarium oxysporum* (MTCC 1755)	Zone of inhibition (ZI) value for *Phoma destructive*: 22 ± 1 mm *Curvularia lunata*: 21 ± 0.5 mm *Alternaria alternate*: 18 ± 1 mm *Fusarium oxysporum*: 24 ± 0.5 mm	Not clearly mentioned	Kanhed et al. (2014)
Zinc oxide nanoparticles (12–32 nm)	*Alternaria alternata* (ITCC 6531), *Aspergillus niger* (ITCC 7122), *Botrytis cinerea* (ITCC 6192), *Fusarium oxysporum* (ITCC 55), *Penicillium expansum* (ITCC 6755)	64 μg/mL (*A. alternata*) 16 μg/mL (*A. niger*) 128 μg/mL (*B. cinerea*) 64 μg/mL (*F. oxysporum*) 128 μg/mL (*P. expansum*)	Disruption of membrane structure and change in permeability.	Jamdagni et al. (2018)
Iron oxide nanoparticles (10–30 nm)	*Trichothecium roseum,* *Cladosporium herbarum,* *Penicillium chrysogenum,* *Alternaria alternate,* *Aspergillus niger.*	Varies between 0.063-0.016 mg/mL	Formation of ROS, damage of protein, and DNA by oxidative stress.	Parveen et al. (2018)

Exclusion criteria

The following exclusion criteria were adopted:

1. Titles and/or abstract not meeting the inclusion criteria, duplication of data.
2. Nanoparticles with other studies obscuring the current subject of interest.

Findings

Among the vast pieces of evidence, some randomly selected published articles found in the databases that contains screening reports on nanoparticles against microbial infections is herein summarized.

2.1. Application of nanoparticles in bacterial infections

Nanoparticles often show high bactericidal activities when tested against pathogenic bacterial strains (Figure 1). Metal nanoparticles can be bactericidal, bacteriostatic depending on their particle size, capping method, and concentration (Slavin et al., 2017). Through vast analysis of shreds of evidence, it has been noticed that nanoparticles manifest antibacterial activity on both gram-positive and gram-negative strains. In the case of gram-negative strains, the cell wall composition shows a thin layer of peptidoglycan polymer (~7–8nm) with a surface carrying negative charges (Sirelkhatim et al., 2015; Halder et al., 2015). These features are directly linked to the antibacterial activity exhibited by the NPs, the thin cell-wall ensures better penetration into the bacterial cell and, the negatively charged surface provides high electrostatic interaction between cells and NPs leading to the formation of reactive oxygen species (ROS) and oxidative stress. This results in bacterial cell destruction and inhibition (Pramanik et al., 2012; Mai-Prochnow et al., 2016; Chen et al., 2013). Unlike the gram-negative bacteria, gram-positive contains only the outer peptidoglycan layer not the polysaccharide membrane with structural lipopolysaccharides. This ensures better permeability towards substances (Cabeen and Jacobs-Wagner, 2005). In the case of gram-positive strains, the presence of a smaller negative charge in the surface enhances NPs penetration allowing the entrance of negatively charged superoxide radical anions and peroxide ions to ensure cell destruction at a relatively low concentration (Padmavathy and Vijayaraghavan, 2008; Sonohara et al., 1995; Reddy et al., 2007). Mahdy et al. (2012) stated that zero-valent Iron (FeO) nanoparticles generate oxidative stress via ROS and damage bacterial protein and DNA of some tested gram-positive and gram-negative strains. Some nanoparticles (Cu) also seem to have an affinity towards carboxyl and amine groups present in the cell surface (Beveridge and Murray, 1980; Ren et al., 2009). They may interfere with DNA molecules after entering the cell and disarrange the helical structure by cross-linking within the nucleic acid strands.

Fluorescent Ag nanoparticles (nAg-Fs) of 1.5 nm shows antibacterial activity against gram-positive (*Staphylococcus epidermidis, Bacillus*

Table 3. Antiviral potentials of nanoparticles.

Nanoparticles (Diameter)	Test virus (strains)	Concentration	Mechanism of action	Reference
Acyclovir loaded into β-cyclodextrin-poly(4-acryloylmorpholine) conjugate nanoparticles (150 nm when unloaded, 200 nm when loaded)	HSV-1 BGM, HSV-1 MRC	IC_{50} 0.05 μg/mL, IC_{99} 0.15 μg/mL (HSV-1 BGM), IC_{50} 0.05 μg/mL, IC_{99} 0.59 μg/mL (HSV-1 MRC)	Increased drug accumulation and sustained drug delivery results in cell death	Cavalli et al. (2009)
Silver nanoparticles (30–50 nm)	HIV-1 isolates	0.44 to 0/91 mg/mL	Prevention of CD-4 dependent virion binding, fusion, infectivity, inhibition of post-entry stages of HIV-1 lifecycle.	Lara et al. (2010)
Gold nanoparticles (17 nm)	HIV-1	0.05–0.12 mg/mL	The mechanism of gold nanoparticles against HIV-1 is not clear but it inhibits the HIV-1 fusion	Vijayakumar and Ganesan (2012)
Copper Iodide nanoparticles (160 nm)	Feline Calicivirus	10 ng/mL to 10 μg/mL	ROS generation and subsequent capsid protein oxidation	Shionoiri et al. (2012)
Silver/chitosan nanoparticles (3.5, 6.5, 12.9 nm)	H1N1 influenza A	100 μg of Ag NPs was added to 1 mg of chitosan	Inhibiting viral penetration into the host cell	Mori et al. (2013)
Cuprous oxide nanoparticles (45.4 ± 68 nm)	Hepatitis C virus (HCV)	2 μg/mL	Attachment and entry inhibition of HCV infection	Hang et al. (2015)
Iron oxide nanoparticles (10–15 nm)	H1N1 Influenza A	4.25 ± 0.2 pg	Change in viral RNS transcripts within 24 h, 08 fold reduction when treated with Iron oxide	Kumar et al. (2019)
Silver nanoparticles of *Lampranthus coccineus* (10.12–27.89 nm), *Malephora lutea* (8.91–14.48 nm).	HAV-10, HSV-1, CoxB4	***L. coccineus*:** HAV-10- no activity, HSV-1- 520.6 μg/mL, COxB4- no activity (aqueous nano extract) 11.7 μg/mL, 36.36 μg/mL, 12.74 μg/mL (hexane nano extract) ***M. lutea*:** no activity for aqueous nano extract, HAV-10- 31.38 μg/mL, HSV-1-no activity, COxB4- 29.04 μg/mL (hexane nano extract)	Not determined	Haggag et al. (2019)
Iron oxide nanoparticles (10–15 nm)	A/Puerto Pico/8/1934H1N1 influenza virus strain (PR8-H1N1)	1.1 pg	Inactivation of cell protein through the interaction of nanoparticles and –SH group (Proposed, not investigated yet)	Kumar et al. (2019)
Zinc oxide nanoparticles (16–20 nm)	H1N1 Influenza	75 and 200 μg/mL	Suppress the proliferation of influenza virus at an inhibition rate of 52.2%	Ghaffari et al. (2019)

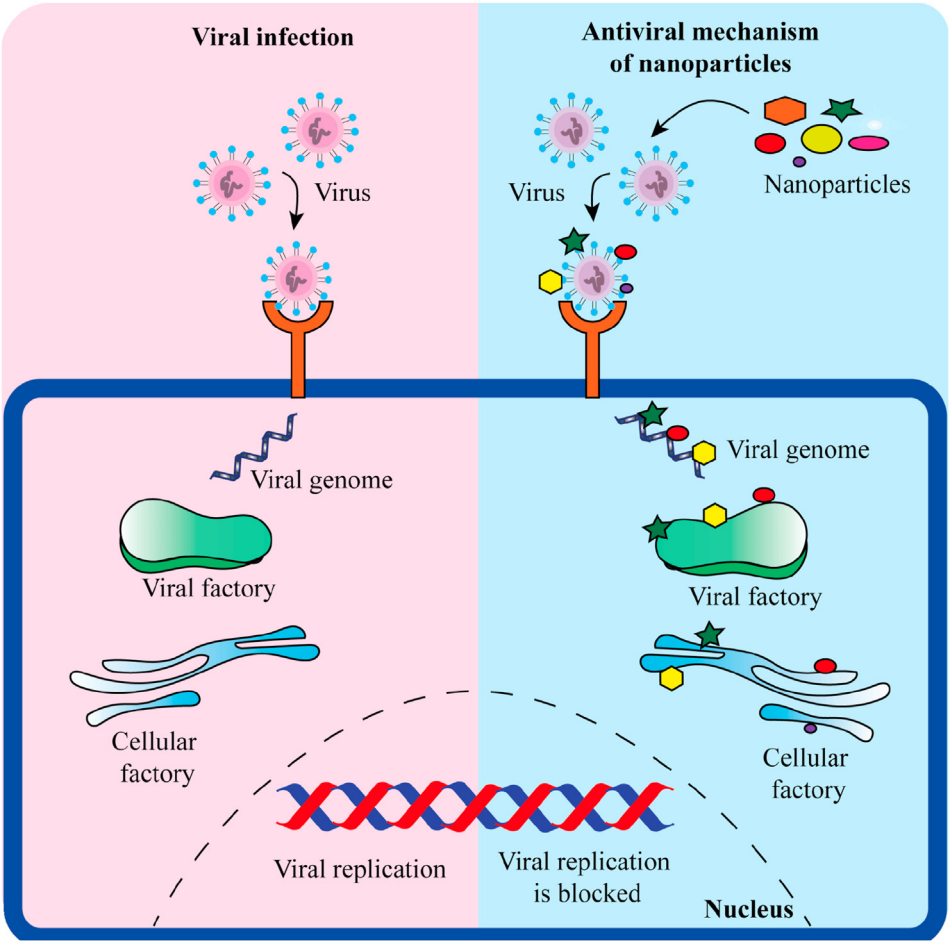

Figure 2. Schematic representations of the antiviral mechanism of some nanoparticles. NPs directly enter into the host cell besides the direct interaction with viral surface glycoproteins and exert their antiviral activity through binding to viral and host cellular factors thereby blocking the viral replication mechanism.

megaterium), gram-negative (*Pseudomonas aeruginosa, Escherichia coli*) strains with an IC_{50} value of 2 μg/mL. The antibacterial activity is observed due to the perforation of nAg-NPS into the bacterial cell cytoplasm and leakage of the cytoplasmic contents which causes cell death (Bera et al., 2014). Again silver nanoparticles synthesized from tulsi leaf extract inhibits *E. coli* and *S. aureus* with a MIC value of 0.314 μg/mL and 1.25 μg/mL respectively. The antibacterial mechanism behind it is yet to be explored (Singhal et al., 2011). Aljabali et al. (2018) reported that the antibacterial activity of gold nanoparticles against *E. coli* with a zone of inhibition of about 0.5mm.

Nanoparticles of various metallic oxides and other metallic compounds have also shown potent antibacterial efficacy. The metal oxide is proven to be a hopeful combating weapon towards a wide range of pathogenic microbes including MDR isolates (El-Sayyad et al., 2018). CaO nanoparticles exhibit antibacterial activity by interfering with bacterial cell integrity and disrupting the cell membrane of *S. epidermidis*, *P. aerugin* with a MIC value of 2 and 4 mM respectively (Roy et al., 2013). Magnesium oxide nanoparticles are effective against a set MDR resistant Gram-positive and Gram-negative strains and significantly inhibits the growth at a concentration of 7.81 μg/mL. Though the mechanism is still ill-defined it indicates the reactive oxygen species (ROS) liberation, and interaction with the cell wall (El-Sayyad et al., 2018). SiO_2 doped Fe_2O_3 NPs (5.89–19.89 nm) exhibited bactericidal activity against *B. subtilis* and *E. coli* and inhibits bacterial growth (Arshad et al., 2019). In addition to this, bacterial biofilm structures also seem to be effectively inhibited by nanoparticles. Biogenic Selenium nanoparticles retard the biofilm formation of gram-negative *Pseudomonas aeruginosa* (Cremonini et al., 2016). Some reported bactericidal potencies of nanoparticles are indicated in Table 1.

2.2. Application of nanoparticles in fungal infections

From ancient times, fungal infections have been significantly contributing to the ever-increasing morbidity and mortality rate (Ardi et al., 2020; Friedman et al., 2020; Khoury et al., 2020). The fungicidal and fungistatic activity of nanoparticles is being studied to control outbreaks caused by pathogenic fungi. Silver nanoparticles stabilized with surfactants of size 25nm are proven to have potent antifungal activity when tested against 4 *Candida* strains with a MIC value ranging from 0.21-1.69 mg/L. Surfactant activity of the AgNPs disrupted the cell wall of the tested yeasts (Panáček et al., 2009). Gold nanoparticles also seem to be effective on *Candida* strain at 16–32 μg/ml, surfactant, and acidification activity of nanoparticles are directly involved with the fungicidal activity in these two cases. The fungicidal activity observed was size and shape-dependent where small-sized nanodiscs showed inhibition of H + ATPase, leading to intracellular acidification and cell death (Wani and Ahmad, 2012). In some cases, nanoparticles cause deformation in fungal hyphae and inhibit hyphal transition that may often lead to fungicidal activity (He et al., 2011; Cousins et al., 2007).

Oxides of different nanoparticles are also seen to have potential effect on different fungi. Previous studies revealed that zinc oxide NPs (12–32 nm) disrupts membrane structure and alter the permeability of *Alternaria*

alternate, Aspergillus niger, and *Botrytis cinerea* at a concentrations ranging from 16-128 μg/ml (Jamdagni et al., 2018). Haghighi et al. (2013) claimed that titanium oxide (TiO2) at a conc. 5.14 μg/mL inhibits biofilm formation of *Candida albicans*. Oxidative stress on fungal cells by reactive oxygen species (ROS) formation may destroy the cell and exhibit antifungal activity. Iron oxide nanoparticles form ROS and damage the proteins and DNA of fungal cells by oxidative stress (Parveen et al., 2018). The antifungal potentials of some other nanoparticles are indicated in Table 2. The anti-fungal activity of various nanoparticles is as displayed in Figure 1.

2.3. Application of nanoparticles in viral infection

Viruses are particles that are generally smaller than living cells. They are generally smaller than bacteria and are the main cause of several minor illnesses (Singh et al., 2014). The main mechanism that is adopted by virucidal agents often shows direct interference with the first phase of viral replication (Cagno et al., 2018). Kumar et al. (2019) proposed that iron oxide nanoparticles change viral RNS transcripts of H1N1 Influenza A virus within 24h with a MIC value ranging from 4.25 ± 0.2 pg. Zinc oxide (16–20 nm) suppresses the cell proliferation of H1N1 influenza virus thus shows antiviral activity (Ghaffari et al., 2019). The small size of nanoparticles may also contribute to the effectivity due to the impact of zeta potential (Gaikwad et al., 2013). AgNPs of size 10–80 nm are reported to have antiviral activity when tested against Monkeypox virus where size 10 nm is more potent to be used as a therapeutic antiviral agent (Rogers et al., 2008). Elechiguerra et al. (2005) reported the potency of small-sized AgNPs that could easily append to viral cell inhibiting its further attachment to host cell and lastly attenuation of viral replication.

Silver nanoparticles of 30–50 nm size inhibit HIV-1 isolates by preventing CD-4 dependent virion binding, fusion, infectivity, inhibition of post-entry stages of the HIV-1 lifecycle thus prevents the attack of HIV (Lara et al., 2010). Silver nanoparticles also show the antiviral effect on HAV-10, HSV-1, CoxB4 strains via obscure mechanism (Haggag et al., 2019). Mori et al. (2013) also suggest that silver nanoparticles show activity on H1N1 influenza virus by inhibiting viral penetration into the host cell. Since precision drug delivery is one of the major setback in the development of potent anti-viral drug candidates, recent researches have suggested that polymeric nanoparticles are potential anti-viral drug delivery agents equipped with a sustained and controlled drug-delivery mechanisms, improved bioavailability with less toxicity and side effects (Haggag et al., 2019). Cavalli et al. (2009) reported the antiviral effects of acyclovir loaded β-cyclodextrin-poly (4-acryloylmorpholine) conjugate nanoparticles against HSV-1 virus. The virucidal activity is achieved due to increased drug accumulation and sustained drug delivery in viral cells. The antiviral potentials of some nanoparticles are as indicated in Table 3. The antiviral mechanism of various nanoparticles has been shown in Figure 2.

3. Conclusion

People all around the globe are faced with the challenge of various microbial infections alongside other deadly diseases caused directly or indirectly by pathogenic microbes including bacteria, fungi, viruses, protozoa, and parasites. Despite having promising therapies and medicines, it is seen to be difficult to successfully eradicate the problem. This study aims to focus on the possible scope of nanoparticles regarding this occurrence. Nanoparticles are used in different fields for human welfare and hold good promise in the pharmaceutical and biomedical industries properly harnessed. Nanoparticles show different activities according to their size, shape, charge, and surface area. These unique features are even being used against different infectious diseases that may be directly related to pathogenic microbes. From the recent studies considered, it is obvious that nanoparticles possess activity against different microbial infections. Small particle size and the charged surface has provided NPs an easy route to enter the pathogenic cells, interfere with cellular contents such as protein and DNA thereby inducing programmed cell death. Moreover, antibiotic therapy in conjugation with nanotherapy is now being considered a methodical approach to overcome microbial resistance. However, some drawbacks which include selectivity index, efficiency and toxicity are major factors to be further analyzed. The mechanism of action adopted by the nanoparticles is not fully understood thereby underscoring the need for more studies. A need for effective *in-vivo* analysis is also necessary to evaluate the effectiveness alongside the safety. Although, some nanoparticles are limited because they exhibit some measure of toxicity at elevated concentrations, they nonetheless have potential applications in biomedical sciences in the near future if well harnessed. It is therefore concluded that this concise review adds credence to the existing pool of knowledge on NPs and also encourages that more studies should be carried out to further establish the potential applications of NPs in the management of various microbial infections.

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Author contribution statement

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