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USE OF NANOTECHNOLOGY TO MITIGATE ANTIMICROBIAL RESISTANCE

Muhammad Ifham Naeem[1],*, Abdul Rehman[2], Rabia Zahid[3], Urva Tehseen[3], Zarneela Arbab[3], Shamreza Aziz[1], Tayyaba Akhtar[1], Hafiz Manzoor Ahmad [4], Muhammad Rafi Ullah[4], Qaiser Akram[5], Maria Asghar[1], Kinza Tanveer[1], Muhammad Omar Anjum[1] and Muhammad Aeraf[6]

[1]KBCMA College of Veterinary and Animal Sciences, Narowal, Sub-campus UVAS Lahore, Pakistan
[2]Allama Iqbal Medical College, Lahore, Pakistan
[3]Institute of Microbiology, University of Agriculture, Faisalabad, Pakistan
[4]Department of Clinical Sciences, KBCMA College of Veterinary and Animal Sciences, Narowal, Sub-campus UVAS Lahore, Pakistan
[5]Department of Pathobiology, KBCMA College of Veterinary and Animal Sciences, Narowal, Sub-campus UVAS Lahore, Pakistan
[6]Institute of Microbiology, University of Veterinary and Animal Sciences, Lahore, Pakistan

Corresponding author: afhamnaim4@gmail.com

ABSTRACT

During the wake of infectious diseases, they were the arch nemesis of physicians. People used to die even due to the slightest of diseases. Any infection even as small as a regular fever sometimes meant the loss of life. Soon, the researchers came forward with antibiotics as the ultimate weapon against bacterial diseases. Mankind triumphed over diseases. The happiness of this success soon turned into a premonition of fear. The ultimate weapon of mankind was going blunt against bacteria due to the development of resistance in the bacteria for countering antibiotics. The bacteria once again started causing incurable infections that were reminiscent of the dark past mankind was trying to overcome. Antimicrobial resistance (AMR) means bacteria's ability to survive despite the application of antibiotic drugs in the effective vicinity. This means that the drugs that previously killed the bacteria easily are now unable to affect them. All this happened due to antibiotic misuse, allowing the bacteria to develop resistance. But the days of fear because of antimicrobial resistance will soon be left behind because nanotechnology is here to rescue us from this dire situation. If researched enough nanotechnology has various applications that can easily help us solve the antimicrobial resistance issue in a short time. Nanotechnology can not only help mankind in battling diseases by attacking microbes directly, but it also has several applications in various other fields. The advancements achieved through nanotechnology in diagnosis, treatment, and improved nutrition can all help us synergistically to combat the prevalence of diseases in our society. This review will delve into the deeper aspects of combating antimicrobial resistance using nanotechnology. A better explanation of antimicrobial resistance concepts will explain how AMR developed in bacteria and which mechanisms the bacteria adapt to nullify the effect of antibiotic effects. A better comprehension of bacterial resistance action will ultimately assist in understanding how the nanoparticles can be used to exploit those mechanisms for killing these pathogens.

***Keywords*:** Antimicrobial Resistance, Nanotechnology, Nanoparticle Conjugated Antibiotics

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1. INTRODUCTION

During the late 19th century, death by infectious diseases was common. It was not until the first quarter of the 20th century around 1910 that antibiotics came to the rescue of dying mankind (Cohen et al. 2007; Huh and Kwon 2011; Katz and Baltz 2016; Hutchings et al. 2019; Sharma et al. 2022). The first antibiotic was Salvarsan in 1910 just before the discovery of penicillin in 1928 (Hutchings et al. 2019; Waktole and Chala 2023). But this happiness was soon cut short when the microbes rapidly started developing resistance and the weapons of antibiotics became blunt and once again around 700,000 people are losing their lives annually because of AMR (Cohen et al. 2007; Huh and Kwon 2011; Abushaheen et al. 2020; Lahiri et al. 2022; Pasha et al. 2022; Zhang et al. 2022). Antibiotics were hailed as saviors when they were first discovered but soon the development of antimicrobial resistance in bacteria faded this happiness. The main culprit of this unfortunate phenomenon was the abundant misuse of antibiotics that made many of the commonly curable infections into untreatable maladies (Cohen et al. 2007; Huh

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and Kwon 2011; Chen et al. 2020; Wu et al. 2023). The bacteria began to develop antibiotic resistance through several different mechanisms like biofilm formation, drug inactivation, etc. (Pang et al. 2019; Abushaheen et al. 2020). This problem was further aggravated by the slow development of new antibiotics to replace the ones that had resistance against them and the need for new strategies to combat antimicrobial resistance was felt, even WHO encouraged the researchers to look for antibiotic alternatives (Allahverdiyev et al. 2011; Mühlen and Dersch 2016; Årdal et al. 2020; Giráldez-Pérez et al. 2022). However, as we know necessity is the mother of invention, similarly rise of antimicrobial resistance demanded the discovery of an alternative to counter it and this time the alternative was to use nanoparticles (Gupta et al. 2019; Ajose et al. 2022). These nanoparticles made use of various mechanisms like cell membrane disruption, homeostasis disturbance, and reactive oxygen species formation, quorum sensing to counter antibiotic resistance and kill pathogenic bacteria (Mba and Nweze 2021; Farhadi et al. 2022; Sundaramoorthy and Nagarajan 2022). Nanomaterials in general and nanoparticles specifically have gained the immense interest of scientists due to their diverse range of applications, especially in the medical field. The use of nano polymers in slow drug-release vehicles and fluorescence imaging techniques is a perfect example of how widely useful nanoparticles are. This study will discuss how antimicrobial resistance emerged, its mechanism of countering antibiotics, its effects and the mechanism of action of nanoparticles that can counter it along with examples of some important nanoparticles.

2. Antimicrobial Resistance

The threat of antimicrobial resistance has bothered mankind since the start of the 21st century as it became a worldwide challenge due to the irrational use of antibiotics (Cohen et al. 2007; Huh and Kwon 2011; Akova 2016; Machowska and Stålsby Lundborg 2019). The situation of antimicrobial resistance was further aggravated by poor infection control practices that increased the dissemination of resistant bacteria to the environment and other diseased people (Akova 2016). This caused the issue of antimicrobial resistance internationally rapidly (Akova 2016; Machowska and Stålsby Lundborg 2019). The development has been so rapid in bacteria that now 70% of bacteria are resistant to the drugs that were previously being used against them effectively according to recent research (Allahverdiyev et al. 2011). So, what is this antimicrobial resistance? It is a phenomenon where bacteria avoided lethal selection pressure through evolution and produced such genetic mutation that will save them from being killed by antibiotics. As long as the use of antibiotics persists the bacteria will keep developing resistance against them. WHO (2017), which has dubbed antimicrobial resistance a high-priority issue, also reported in 2017 that only a few new anti-microbial agents are now under development (Schrader et al. 2020; Uddin et al. 2021; Saxena et al. 2022). The main medium of the spread of antibiotic resistance was the antibiotic resistance genes that were transferred from environmental bacteria to pathogenic ones through horizontal gene transfer making the pathogenic bacteria even more dangerous (von Wintersdorff et al. 2016). Simply, antimicrobial resistance means the ability of bacteria to survive despite the application of antibiotic drugs.

2.1. The Emergence of Antimicrobial Resistance

Antibiotic resistance can develop in bacteria either naturally or it can be acquired (Uddin et al. 2021). The two main forms of antibiotic resistance mechanism include the normal, innate resistance with its gene always expressed in the organism and the mediated resistance that expresses upon antibiotic exposure (Reygaert 2018; He et al. 2020). Bacteria can gain acquired resistance through genetic conjugation, transposition, translation of acquired DNA (Lerminiaux and Cameron 2019), or through mutation of already existing DNA within the bacterium (Culyba et al. 2015; Mancuso et al. 2021). Hence the bacteria went through genetic selection to gain antimicrobial resistance.

2.2. Mechanism of Resistance Development

Bacteria can resist the antibiotic from functioning through four main pathways, theses pathways include limiting the drug uptake by shielding it with a lipopolysaccharide layer which makes Gram-negative bacteria less permeable against some antibiotics e.g., Vancomycin in comparison to Gram-positive bacteria (Blair et al. 2015; Munita and Arias 2016; Pasala et al. 2021). Drug efflux by active transportation out of cells is also a major cause of resistance in Gram-negative bacteria. According to the structure and energy supply, the five prime families of efflux pumps include the ATP-binding cassette (ABC)family, small multidrug resistance (SMR) family, multidrug and toxic compound extrusion (MATE) family, resistance-nodulation-cell division (RND) family, and major facilitator superfamily (MFS). Resistance to macrolides and Tetracyclines is an example of efflux-mediated resistance (Munita and Arias 2016; Grossman 2016; Reygaert 2018). Bacteria also show resistance by modifying the drug's target and it is done by changing the amount or arrangement of penicillin-binding proteins. (Bush and Bradford 2016; Reygaert 2018; Douafer et al. 2019). Bacteria produce different enzymes which help in the transfer of phosphoryl, acetyl, and adenyl groups to the compound of the drug. This transfer of chemical groups inactivates the drug and results in resistance against that specific group of drugs for instance aminoglycosides, chloramphenicol,

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streptogramins, and fluoroquinolones (Lin 2015). Bacteria cause drug inactivation by either destroying it or by altering the chemical structure of the drug (Blair et al. 2015; Garima et al. 2018; Abushaheen et al. 2020). The chemical structure of beta-lactam medicines is formed of a four-sided beta-lactam loop which is destroyed by the beta-lactamase produced by bacterial cells (Page 2012; Bush and Bradford 2016). Similarly, another well-known method of antibiotic-resistant infections occurs through biofilm formation and helps bacteria colonize (Ribeiro et al. 2016; Pang et al. 2019). Most of them produced biofilm which help them to survive in the environment and made them resistant to antibiotics, disinfectants, and phagocytosis (Hoiby et al. 2011). Biofilm is a strong shield of bacteria against antibiotics that it forms by embedding itself in a structured consortium of self-produced polymer matrices. This matrix consists of extracellular DNA, proteins, and polysaccharides. Nearly all bacteria and fungi form biofilms as a part of their defense mechanism against immunity, disinfection, and phagocytosis. Additionally, biofilms are also used as a means of communication among bacteria by bio-sensing (Hoiby et al. 2011). This means that bacteria have developed several ways to persist by rendering the antibiotics ineffective.

3. Nanotechnology

The study of ultrafine particles that are within a size range of about 1 to 100nm, these materials are generally referred to as nanoparticles (Emerich and Thanos 2003; Jiang et al. 2008; Albanese et al. 2012; Mohajerani et al. 2019). Despite feeling innovative and trendy the nanoparticles are nothing new for mankind. Humans have used gold, silver, copper, and zinc for centuries to treat various maladies (Malarkodi et al. 2014). The nanoparticles have been a very appealing topic for researchers for millennia, as these porous materials have large surface areas despite covering less space increasing the ratio of surface atoms to the internal atoms, increasing the influence of chemical properties of these materials, and producing a change in their physical properties, for example, copper loses its malleability at the nanoscale (Albanese et al. 2012; Sharma and Sharma 2012; Astruc 2020; Dubadi et al. 2023). These nanoparticles have appeared as a strong contender in the battle against antibiotic resistance. The nanoparticles can counter antibiotic resistance through several mechanisms. Some common pathways adopted by nanoparticles to counter antibiotic resistance include prevention of biofilm formation, enhanced intracellular drug accumulation, and reactive oxygen species formation (Zhang et al. 2010; Huh and Kwon 2011; Hajipour et al 2012). Thus, it can be said that the study of minute particles at the nano level is called nanotechnology and it's our best hope against emerging antibiotic resistance.

3.1. Types of Nanoparticles

3.1.1. Metals: The powdery state of metals is simply termed metal nanoparticles. This form is obtained after the thorough grounding of metal pieces effectively altering the physical properties of the metal (Halperin 1986; Jamkhande et al. 2019), making suitable cell wall lysis and cell membrane disruption agents against bacteria (Ramasamy et al. 2016; Godoy-Gallardo et al. 2021). So, we can just use ground metals as nanoparticles without much hassle of processing. The function of metal nanoparticles as nutraceuticals is helpful in improving animal production by increasing the bioavailability of feed supplements and their absorption in the gut (Hill and Li 2017). When metal nanoparticles are used as biocides, they cause the lysis of negatively charged cell walls of both the Gram-positive and Gram-negative bacteria (Kim et al. 2007; Chauke and Siebrits 2012; Gahlawat et al. 2016; Ramasamy et al.2016). Magnetic metal nanoparticles are dispersed in the body and used for diagnostic purposes for example MRI (Soenen et al. 2010).

3.1.2. Polymers: These are nanoparticles of polymeric nature formed by fragments that are a few nanometers long and have the ability to be grafted, with their main types including the nano-capsule and nano-sphere (Travan et al. 2009; Zielińska et al. 2020) on other types of materials giving them high biocompatibility properties with little or no side effects making them especially useful for drug delivery (Choi et al. 2010; Shim et al. 2002; Ichikawa et al. 2005; Taylor and Davidson 2005; Calzoni et al. 2019). The fluorescence property of these particles makes them extremely useful in diagnostic imaging (You et al. 2007; Yang et al. 2020). The combining ability of polymers makes them very useful in the field of medicine. These nanoparticles are used for drug and nutrient delivery, loaded with traditional antibiotics, and released in the body when they are at a certain distance from a pathogen inside the body of an animal. They act as a shuttle in the body of an animal (Turos et al. 2007; Greenhalgh and Turos 2008; Ghosh et al. 2012). The action of polymer nanoparticles as a biocide result in the destabilization of the bacterial cell wall. This is done by disrupting the homeostasis of the cell at an extremely lethal level (Moreau et al. 2002; Rosilo et al. 2014; Xu et al. 2015). The mode of action of polymer nanoparticles as a molecular biology agent is also of great importance. They act as DNA transfection vehicles (Agarwal et al. 2012).

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3.1.3. Nanostructured Materials: Nanoparticles manufactured by the combination of nanoparticles from various sources including nanoparticles of natural origin such as protein-based or lipid-based nanoparticles are called nanostructured materials (Hill and Li 2017). Thus, an origin-based chemical classification of nanoparticles can be made for ease of study. The nanostructured materials are designed for drug and nutrient delivery, they carry the nutrient or pharmaceuticals to the targeted area through the gastrointestinal tract (Li and Yao 2009; Sun et al. 2014; Akbari and Wu 2016). Nano-structured materials also work as diagnostic tools, once in the body their fluorescence can be triggered by two-photo excitation or light activation (Croissant et al. 2014; Ajmal et al. 2015; Feng et al. 2016). The reproduction aids provided by nanostructured materials, help in the purification of sperms via surface markers which are recognized by the nano-particle bounded antibiotics or lectins. The purification of sperms is done by the removal of the dead or damaged spermatozoa (Odhiambo et al. 2014; Petruska et al. 2014). As a molecular biological agent gene transfer mediation is done by nanostructured materials through the interactions between nucleic acids, nanoparticles, and sperm (Barkalina et al. 2014). A classification chart of nanoparticles has been formed according to their chemical nature (Fig. 1).

3.2. Mechanism of Action

The proper mechanism of action of the nanoparticles like metal oxides has not been fully discovered until now, although various researchers have presented several hypotheses like cell membrane disruption, disturbance of bacterial cell homeostasis, etc. (Muzammil et al. 2018; Nisar et al. 2019). The nanoparticles may act by producing protein dysfunction, formation of reactive oxygen species, membrane impairment, disruption of cellular structures, depleting antioxidants, altering signal transduction, or interfering with nutrient assimilation mechanism (Fig. 2) (Stoimenov et al. 2002; Shrivastava et al. 2007; Lemire et al. 2013; Nisar et al. 2019; Kavitha et al. 2023). This signifies the diversity of mechanisms of action followed by different types of nanoparticles to fight bacteria. Such examples are seen in the mechanism of action in gold and silver nanoparticles. Silver nanoparticles accumulate on the cell wall and form pits in it disturbing integrity, leading to structural damage and ultimately death (Sondi and Salopek-Sondi 2004; Brayner et al. 2006; Cavalcanti-Adama et al. 2006; Zhang and Rock 2008; Prabhu and Poulose 2012). The diversity of nanoparticles has made it difficult for researchers to determine a thumb rule for their mode of action.

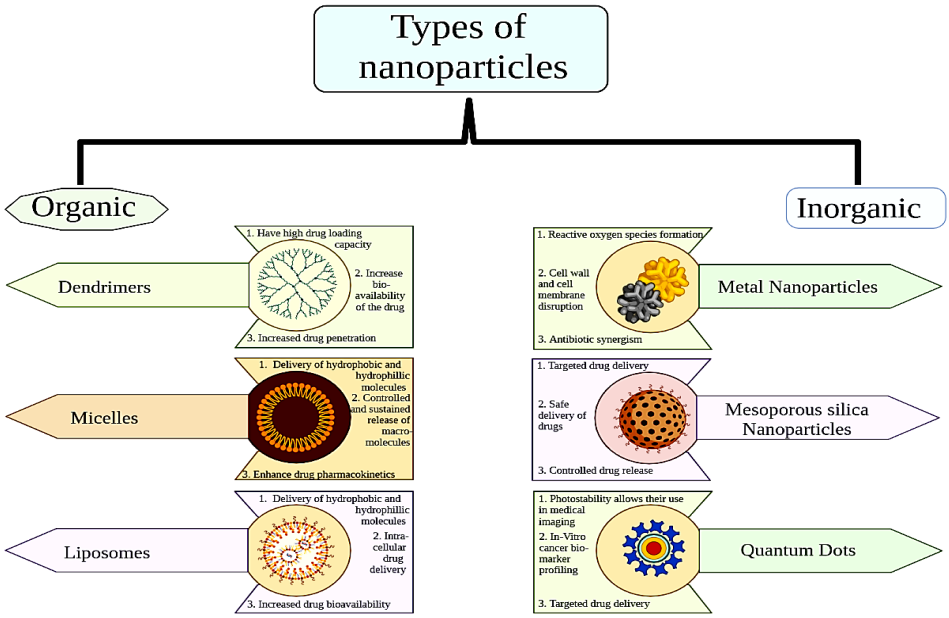

Fig. 1: Classification of nanoparticles according to their chemical nature. Chemically the nanoparticles are classified into organic and inorganic substances. Some important examples of these nanoparticles are also mentioned in the figure along with their major uses.

4. Nanoparticle Conjugated Antibiotics

4.1. Silver nanoparticles (AgNPs)

Researchers have long known silver nanoparticles for their antimicrobial properties, but their use was reduced after the discovery of antibiotics, however, the recent rise of antibiotic resistance has given new importance to the use of silver nanoparticles, especially as antibiotic agents extracted from plants, against several multidrug-resistant strains of bacteria (Klasen 2000; Atiyeh et al. 2007; Mikhailova 2020; Parashar et al. 2022; Ramzan et al. 2022;

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Alavi and Hamblin 2023). Besides being an antibiotic itself the ability of silver to bind with various polymeric chains of antibiotics has led to a rapid increase in its combinations with antibiotics, which enhances the effect of these antibiotics (Choi et al. 2003; Shi et al. 2006; Franci et al. 2015; Vazquez-Muñoz et al. 2019). This has made the silver nanoparticles, especially the plant-extracted ones extremely useful against common diseases like mastitis (Akhtar et al. 2023a; Akhtar et al. 2023b). Several examples in the research literature prove the synergistic effect of silver nanoparticles and antibiotics to act against resistant bacteria (Table 1).

Table 1: Effect of combination of some important antibiotics with silver nanoparticles.

Compatible antibiotics	Pathogen	MIC(μgml^{-1}) of AgNPs	Size of nanoparticles (nm)	MIC of AgNPs used alone (μgml^{-1})	References
Doxycycline	*K. pneumonia*	6.25–50	20- 45	2- 4	(Rai et al. 2012; Kumar et al. 2016; Khosravi et al. 2020)
Vancomycin	*P. aeruginosa*	0.5	20- 45	2- 4	(Ghosh et al. 2012; Rai et al. 2012; Hwang et al. 2012)
Chloramphenicol	*P. aeruginosa*	0.5	20- 45	2- 4	(Ghosh et al. 2012; Rai et al. 2012; Hwang et al. 2012)
Streptomycin	*E. coli*	0.5	20- 45	2- 4	(Ghosh et al. 2012; Rai et al. 2012; Hwang et al. 2012)
Ampicillin	*S. aureus*	0.625	5- 10	2- 4	(Fayaz et al. 2010; Rai et al. 2012; Parvekar et al. 2020)
Chloramphenicol	*S. typhi*	29.37	20- 45	2- 4	(Fayaz et al. 2010; Rai et al. 2012; Al- Aarajy et al. 2022)

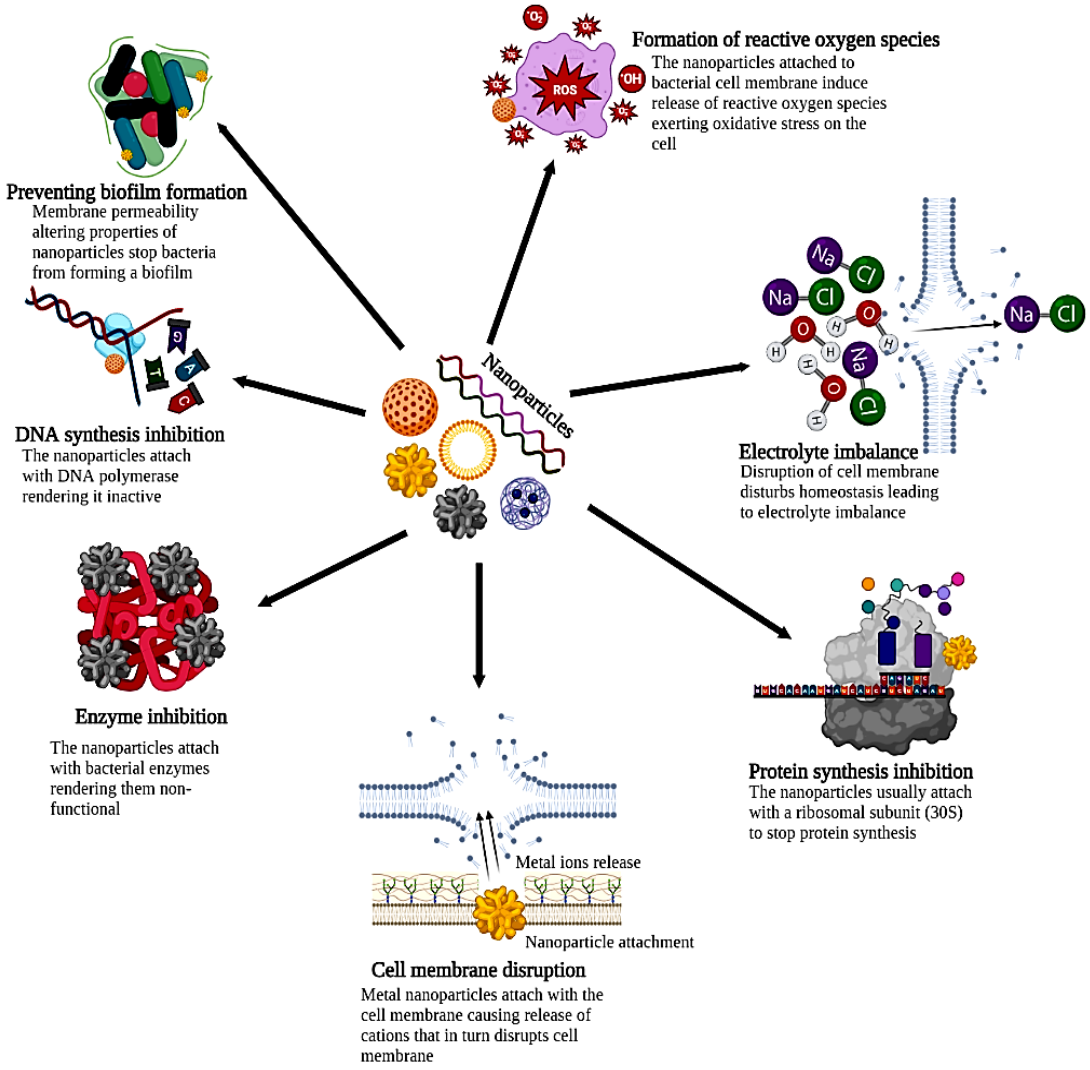

Fig. 2: Antibacterial mode of action of some important nanoparticles according to their major uses. There are several methods by which a nanoparticle can kill bacteria or stop their growth.

4.2. Gold nanoparticles (AuNPs)

Gold particles have been used for medicinal purposes in ancient China and India for a long time serving both as an antibiotic and anticancer agent (Mahdihassan 1985; Ahmad et al. 2003; Almeida et al. 2014). Gold nanoparticles have strong antibacterial activity, and their efficacy increases if antibiotics are added into the action, the

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nanoparticles also act as carriers for antibiotics improving their bactericidal effect too, especially with amoxicillin (Burygin et al. 2009; Zhang et al. 2010; Zhao et al. 2010; Lima et al. 2013; Bindhu and Umadevi 2014; Li et al. 2014; Kalita et al. 2016; Soliman et al. 2023). Gold nanoparticles found their application as antibiotics long ago and even in the modern day, they have proven efficient enough for their effective use as synergistic agents for antibiotics. Some examples of synergistic effects of gold nanoparticles and antibiotics have been enlisted (Table 2).

4.3. Bismuth nanoparticles (BiNPs)

Bismuth is a highly magnetic metal with a delicate crystalline structure that is generally used as bismuth carbonate, bismuthinite, and bismuth oxide which also has a potent antibacterial action with good biocompatibility as a drug carrier and a water treatment agent (Drummond 2006; Luo et al. 2012; Zhao et al. 2015; Samaniego et al. 2023). The antibacterial activity of Bismuth nanoparticles has been reported in the literature, but its synergistic effect was described in a few reports only, with low toxic activity as compared to other heavy metals (Hernandez-Delgadillo et al. 2013; Tarjoman et al. 2015; Mehrabiyan and Roghaye 2016). The good biocompatibility of bismuth nanoparticles makes it an effective weapon against antimicrobial resistance if used synergistically with antibiotics.

Table 2: Combination of some important antibiotics with gold nanoparticles (11- 22nm) and prone pathogens

Compatible antibiotics	Pathogen	Zone of inhibition (mm) (Combination of antibiotic and AuNPs)	Amount of AuNPs in solution (µg)	Amount of 0.5nM AuNPs suspension used for disks (µL)	Zone of inhibition for ciprofloxacin (5µg/mL)/fluconazole (5mg/mL) alone at 5µg/mL (mm)	References
Ciprofloxacin	*S. aureus*	21	2.7	40	11	(Grace and Pandian 2007; Zawrah and Al- Moez 2011; Shamaila et al. 2016)
Ciprofloxacin	*S. typhimurium*	27	1.35	20	26	(Grace and Pandian 2007; Zawrah and Al- Moez 2011; Shamaila et al. 2016)
Ciprofloxacin	*P. aeruginosa*	23	2.7	40	20	(Grace and Pandian 2007; Zawrah and Al- Moez 2011; Shamaila et al. 2016)
Ciprofloxacin	*L. monocytogenes*	23	2.7	40	20	(Grace and Pandian 2007; Zawrah and Al- Moez 2011; Shamaila et al. 2016)
Ciprofloxacin	*E. coli*	22	1.35	20	20	(Grace and Pandian 2007; Zawrah and Al- Moez 2011; Shamaila et al. 2016)
Fluconazole	*A. flavus*	12	2.7	40	14	(Grace and Pandian 2007; Jabir et al. 2011; Zawrah and Al- Moez 2011; Shamaila et al. 2016)
Fluconazole	*A. niger*	14	2.7	40	0	(Grace and Pandian 2007; Jabir et al. 2011; Zawrah and Al- Moez 2011; Shamaila et al. 2016)
Fluconazole	*C. albicans*	13	2.7	40	20	(Grace and Pandian 2007; Jabir et al. 2011; Zawrah and Al- Moez 2011; Shamaila et al. 2016)

4.4. Copper/ Copper Oxide Nanoparticles (CuNPs/CuONPs)

Copper has been reported as a fantastic fungicidal and antibacterial agent and is a recommended material for the disinfection of wastewater from hospitals (Lin et al. 1998; Ahamed et al. 2014). Copper nanoparticles show greater bactericidal activity (Table 3) as compared to the copper ions and have been reported to be active against biofilm but tend to have increased chances of toxicity due to the formation of reactive oxygen species (Esteban-Cubillo et al. 2006; Theivasanthi and Alagar 2011; Ramyadevi et al. 2012; Ingle et al. 2013; Subhankari and Nayak 2013; Chatterjee et al. 2014; Lewis-Oscar et al. 2015; Singaravelu et al. 2022). The synergistic effect of copper nanoparticles with antibiotics has little supportive evidence in the literature (Khurana et al. 2016; Singaravelu et al. 2022). Despite being effective bactericidal agents, the increased chance of toxicity with copper particles has hindered its widespread application.

4.5. Zinc Oxide Nanoparticles (ZnONPs)

Zinc oxide is generally regarded as a safe food additive with antimicrobial efficacy that increases if used in nanoparticle form (Reddy et al. 2007; Sharma et al. 2012; Ramani et al. 2013). The antibacterial effect of Zinc oxide nanoparticles gained attention as they were reported to be effective against several bacteria to counter

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antimicrobial resistance, as shown in Table 3, especially it can be used to counter β-lactamase resistance as it acts through the creation of reactive oxygen species mechanically destroying cell walls by releasing Zn^{+2} ions that become attached with the cell membrane (Ansari and Husain 2012; Salmon et al. 2012; Sirelkhatim et al. 2015; Yi-Huang et al. 2015; Lallo da Silva et al. 2019; Kavitha et al. 2023). Zinc is a common food additive and an agent of choice against the most annoying type of resistant bacteria viz, beta-lactam-resistant bacteria.

Table 3: Antimicrobial effects of some important nanoparticles

Nanoparticle	Pathogen tested	Zone of Inhibition (mm)	Reference
Zinc and its derivatives	*B. subtilis*	10	(Namasivayam et al. 2015; Datta et al. 2017)
	S. aureus	11	(Namasivayam et al. 2015; Datta et al. 2017)
	E. coli	20	(Namasivayam et al. 2015; Datta et al. 2017)
	E. aerogenes	36	(Datta et al. 2017)
	S. agalactiae	27	(Abdul-Hamza and Mohammed 2021)
Titanium	*S. aureus*	25	(Shopsin et al. 1999; Yang-Hwei et al. 2008; Hamal et al. 2009; He et al. 2014; Santhoshkumar et al. 2014; Vincent et al. 2014; Jesline et al. 2015; Natarajan et al. 2015; Abdul-Hamza and Mohammed 2021)
	E. coli	23	
	P. aeruginosa	16	
	S. agalactiae	20	
Iron Oxide	Methicillin-resistant *S. aurues*	14	
	E. coli	12	
	P. aeruginosa	19	(Behera et al. 2012; Agarwala et al. 2014; Ismail et al. 2015; Masadeh et al. 2015; Patra et al. 2016; Yadav et al. 2016; Manikandan and Ramasubbu 2021)
	S. aureus	16	
	C. glabrata	20	
	K. pneumoniae	17	
	B. cereus	17	
	M. mucilaginosus	20	
Copper and its derivatives	*C. albicans*	14	(Esteban-Cubillo et al. 2006; Theivasanthi and Alagar 2011; Ramyadevi et al. 2012; Padil and Černík 2013; Subhankari and Nayak 2013; Agarwala et al. 2014;Lewis- Oscar et al. 2015; Khurana et al. 2016; Bhavyasree and Xavier 2020; Abdul-Hamza and Mohammed 2021)
	E. coli	18	
	S. aureus	16.2	
	K. pneumoniae	14	
	A. niger	*13*	
	P. aeruginosa	12	
	Methicillin- resistant *S. aurues*	22	
	S. agalactiae	35	
Magnesium Oxide	MDR *S. aureus*	40	(Jeong et al. 2007; Kadhem et al. 2019)
	MDR *E. coli*	30	

4.6. Iron Oxide Nanoparticles (Fe_2O_3NPs)

Iron oxide nanoparticles are the ones that have gained the most attention for their diverse application in various fields, they are being used against biofilm formation in bacteria, magnetic resonance imaging and nanoparticle-loaded liposome systems (Chan et al. 1993; Babes et al. 1999; Berry and Curtis 2003; Kong et al. 2004; Kawai et al. 2006; Ehrenberg et al. 2009; Shkodenko et al. 2020). Iron oxide nanoparticles show great synergistic effects with various antibiotics, as shown in Table 3, and great biocompatibility with the least toxicity when used before irradiation with light, light irradiation may render it toxic (Kooti et al. 2015; Patra et al. 2016; Muzammil et al. 2018). Iron nanoparticles have various uses to combat diseases although they are a bit sensitive to light and radiation making them a little difficult to handle.

4.7. Magnesium Oxide/ Calcium Oxide Nanoparticles (MgONPs/CaONPs)

Magnesium oxide and calcium oxide nanoparticles in aqueous ethanol solutions show strong antibacterial action against both gram-negative and gram-positive bacteria because of their alkaline nature granting them the ability to create reactive oxygen species, as shown in Table 3 (Jeong et al. 2007; Yamamoto et al. 2010; Vidic et al. 2013; Bhattacharya et al. 2021). These nanoparticles show great synergistic activity when combined with enterococcal drugs (Iram et al. 2016). Magnesium and calcium oxide nanoparticles are effective against a wide range of bacterial agents and their effectiveness increases with synergism.

4.8. Titanium Oxide Nanoparticles (TiO_2NPs)

Titanium oxide is a metal oxide with antibacterial activity through biofilm inhibition, the creation of Reactive Oxygen Species that damage the DNA, cell membrane, and other macromolecules, making it effective against numerous types of bacteria, such as shown in Table 3, including methicillin-resistant *S. aureus* (MRSA), *E. coli*, etc. (Wei et al. 1994; Shopsin et al. 1999; Yang-Hwei et al. 2008; Hamal et al. 2009; Blecher et al. 2011; He et al. 2014; Jesline et al. 2015; Natarajan et al. 2015; Zubair et al. 2021). The reactive oxygen species formation characteristic of titanium oxide nanoparticles makes them an especially useful tool to bypass the antimicrobial resistance mechanisms.

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4.9. Toxicity

Nanoparticles entering body by injection, inhalation, contact and ingestion may lead to toxicity depending on the dose and route of intake, majorly causing toxicity by dissolution (Pernodet et al. 2006; Liu et al. 2009; Buchman et al. 2019). Although nanoparticles can induce toxicity in humans, further studies are needed to confirm the exact mechanism and establish the relationship between *in vitro* and *in vivo* conditions (Cuiyue and Yuling 2016; Tanna et al. 2016; Wenchao et al. 2016). The improper dose of nanoparticles can produce undesirable side effects.

5. Future of Nanotechnology against Diseases

Nanotechnology is considered a potent agent that can transform our obsolete practices of diagnosis and treatment of infectious diseases if used correctly and safely (Anselmo and Mitragori 2016; Xu et al. 2019). Nanoparticles can not only enhance drug delivery, but they can also be used to overcome drug resistance initiated by infectious disease-causing agents (Kirtane et al. 2016; Munita and Arias 2016; Malaekeh-Nikouei et al. 2020). In recent years scientists have started working on alternatives to control infectious diseases along with treating them (Kandeel et al. 2022; Rashid et al. 2023). Nanoparticles have various applications that can transform our traditional practices and enhance the results of our activities by many folds.

5.1. Drug Delivery Agents

Some chronic infectious diseases like HIV infection and TB, as reported by the WHO TB guideline of 2010, require longer treatment with a complicated dosing regimen, which is sometimes difficult to follow and hence reduces optimum drug levels, additionally the resistance gained by their pathogens as in case of TB makes it even more difficult to treat (Kirtane et al. 2016; Ali et al. 2019). Sustained or bulk release of drug can be controlled through a polyester-based drug release system, whose properties can be altered by changing the length of the polymer chain, hydrophobicity of the monomer and size of the particle, simultaneously nanoparticles can be used to counter drug resistance too (Langer 1998; Makadia and Siegel 2011; Tăbăran et al. 2020). Hence, the controlled and sustained drug release by nanoparticles in the body can help us overcome the hassle of hectic treatment regimens and battle antimicrobial resistance at the same time. This phenomenon is exceptionally observed in the futuristic application of nanoparticles as smart drug delivery agents (Fig. 3). These nanoparticles show different behaviors depending upon the types of cells or surfaces they are interacting with.

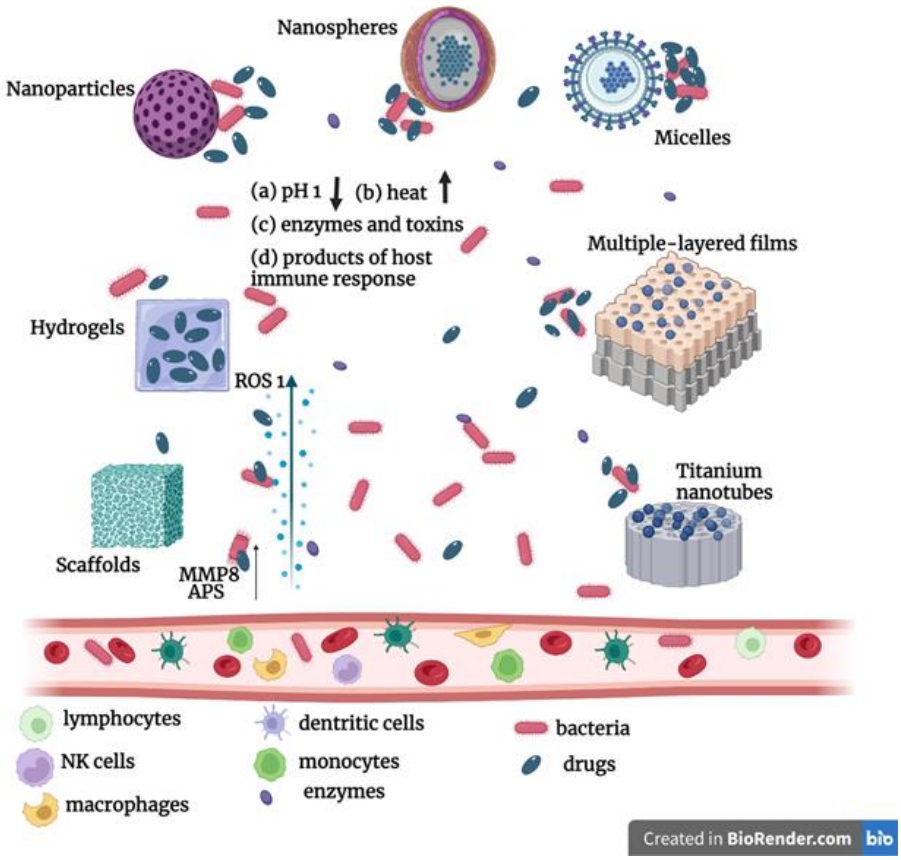

Fig. 3: The interaction of various nanoparticles-based drug delivery systems with target bodies

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5.2. Biocidal Agents

Metal and polymer nanoparticles can be used as biocidal agents, as recently they have been put to use against mastitis because they can lyse the negatively charged cell membrane of gram-positive and negative bacteria, disrupting the homeostasis up to a lethal extent (Moreau et al. 2002; Kim et al. 2007; Chauke and Siebrits 2012; Rosilo et al. 2014; Xu et al. 2015; Gahlawat et al. 2016; Ramasamy et al. 2016; Kalińska et al. 2023). The abilities of nanoparticles like disrupting bacterial homeostasis give them bactericidal effects.

6. Conclusion

Antibiotics were the biggest invention of the medical industry to battle diseases. However, the physicians and other members of medical society started ignoring the proper use of these jewels of medicine. The improper use soon led to the development of antimicrobial resistance in bacteria and the antibiotics became ineffective against them. The phenomenon of antimicrobial resistance is now jolting the base of health security of the whole of mankind and will soon be able to bring it to the ground. Researchers are now worried that in the near future, mankind will be pushed back to the era of diseases. It will be just like the dark past that humans had to face before the invention of antibiotics.

However, there is a ray of hope for now. The discovery of nanoparticles has given mankind the same hope that once antibiotics gave it. The antimicrobial effect of nanoparticles and the synergistic effects obtained by the use of nanoparticles are the only options available for people to combat the horrendous future where no antibiotic will be able to cure diseases.

Researchers are now hopeful that if work is started on the nanoparticles soon for their proper application in the medical industry the upcoming danger of total drug resistance will be easily averted. More effort should be placed on the research and development of new antibiotics while increasing the application of nanoparticles. More emphasis is needed by researchers to tell the world that nanotechnology holds the bright disease-free future everyone is hoping for. Additionally, besides combating antimicrobial resistance directly, nanotechnology will also open various paths in the future that will help us combat diseases as a general issue.

Scientists from various sectors of technology have contributed to the development of nanotechnology. Besides medical fields, various other sectors like engineering are working on the refinement of nanotechnology for improvement in its desirable characteristics. Asian countries are especially playing a major role in research on nanotechnology as 40% of all technical articles come from Asian countries.

Authors' Contribution

TA and RZA conceptualized the idea. SA and MIN developed the layout and wrote the manuscript. SR, RZ, UT, and ZA developed the figures and tables. QA, MA, KT, MOA, HMA, MRU, and AR made final alterations. All authors finally approved the review article.

ORCID

Muhammad Ifham Naeem https://orcid.org/0009-0005-4317-8444
Abdul Rehman https://orcid.org/0009-0002-1653-1116
Rabia Zahid https://orcid.org/0009-0008-2436-8906
Urva Tehseen https://orcid.org/0009-0007-7831-8376
Zarneela Arbab https://orcid.org/0009-0000-4413-9432
Shamreza Aziz https://orcid.org/0000-0001-6213-3632
Tayyaba Akhtar https://orcid.org/0000-0001-7054-8213
Hafiz Manzoor Ahmad https://orcid.org/0000-0003-4704-090X
Muhammad Rafi Ullah https://orcid.org/0000-0001-9681-5359
Qaiser Akram https://orcid.org/0000-0002-1084-9098
Maria Asghar https://orcid.org/0009-0002-8083-1252
Kinza Tanveer https://orcid.org/0009-0000-7160-466X
Muhammad Omar Anjum https://orcid.org/0009-0006-3988-7501
Muhammad Aeraf https://orcid.org/0009-0001-3855-9550

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