Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(3), 2951-2962 | ISSN:2251-6727

Hybrid Nanostructures of Bio-Actives and Metal Nanoparticles: A New Frontier in Combating Antimicrobial Resistance

Jaiganesh S[1], Akiladevi D[2*], Sanjay B M[3], Snehan D[4].

[1,3,4] Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Pallavaram, Chennai-600117.

[2*]Professor and Head, Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Pallavaram, Chennai-600117.

(Received: 25 March 2026 Revised: 30 April 2026 Accepted: 21 May 2026)

KEYWORDS

Metal nanoparticles, Bioactive compounds, Stability, Biocompatibility, Controlled release, Multitarget antimicrobial, Biofilms, Hybrid.

ABSTRACT:

The bioactive compound-capped metal nanoparticles (MNPs) synthesis has gained significance as a rationally designed approach to enhance antimicrobial activity against the multidrug-resistant pathogens. Though bioactive molecules have unique biological activity, MNPs such as silver, zinc oxide and copper possess physiochemical properties like high surface reactivity, ROS production, membrane permeability, etc. Together, these hybrid systems show an emergence of combined action mechanisms such as improved cell uptake, targeted membrane disruption, higher oxidative stress and blockage of crucial metabolic and genetic activities. Functionalization of the MNP surface with natural compounds, phytochemicals, peptides, or antibiotics also improves stability, biocompatibility, and controlled release, allowing the use of lower effective doses while reducing toxicity. Studies have shown that hybrid nanomedicines are superior to individual components and exhibit broad-spectrum activity against Gram-positive and Gram-negative bacteria, biofilms, and resistant strains. Hence, this review discusses about bioactive compounds and metal nanoparticles individually and its integrative formulations as an effective multitarget antimicrobial strategy with great potential for therapeutic, biomedical, and environmental applications.

1. INTRODUCTION

Microbial infections are a major cause of chronic infections and mortality. According to Shabnam Sharmin, infectious diseases are a group of illnesses or conditions that directly impact human health and are brought on by harmful microorganisms (bacteria, viruses, fungi, protozoa, and parasites) [1]. Because of their potent effects and affordability, antibiotics have long been preferred treatment for microbial infections. However, a number of studies have directly demonstrated that the widespread use of antibiotics has resulted in the formation of microbial strains that are resistant to many drug [2]. For example, the effectiveness of β-lactam antibiotics (such as penicillin, cephalosporins, and monobactams) against Gram-negative bacteria has decreased due to an increase in bacteria testing positive for extended-spectrum β-lactamase (ESBL). Bacterial penicillin-binding proteins (PBPs) usually are responsible for gram-positive bacteria's resistance to β-lactam antibiotics. All beta-lactam antibiotics are linked by PBPs [3]. In fact, some strains have developed resistance to almost every antimicrobial agent that is widely used. A notorious case is methicillin-resistant *Staphylococcus aureus* (MRSA), which is resistant not only to methicillin (developed to combat penicillinase-producing *S. aureus*) but also to aminoglycosides, macrolides, tetracyclines, chloramphenicol, and lincosamides [4]. Similarly, some fungal organisms, like *Aspergillus and Candida spp.*, show multi-drug resistance to the azole group of drugs like fluconazole, clotrimazole, itraconazole, and voriconazole. Chloroquine is a malaria drug that shows resistance by the Plasmodium falciparum parasites [5]. Therefore, development of novel antimicrobial compounds or modification of the available ones to

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(3), 2951-2962 | ISSN:2251-6727

combat resistant pathogens is urgently needed. So, to overcome this antimicrobial resistance, much research has focused on isolating certain bioactive molecules from plants such as Thymoquinone, Thymol, Berberine, Curcumin, Catechins, and Tannins, which are some of the bioactive compounds isolated from plants that are studied to have antimicrobial activity. These bioactive molecules are nowadays used as an important drug to overcome microbial infection. In general, administering these bioactive antimicrobial agents in their free form has a number of drawbacks, such as a lack of site-specific delivery and the possibility that the compound would break down or be eliminated before it reaches the target. Additionally, when large dosages of therapeutic substances are administered using traditional drug delivery techniques (such as oral, inhalation, or injection), there is a higher chance of systemic toxicity. Thus, scientists seek to overcome these limitations using various approaches [6]. As a result, nanotechnology came into the field to overcome all these drawbacks. Nanoparticles (NPs), sometimes known as invisible particulate matter, are extremely important in modern research. They have a diameter of between 1- 100 nanometers (nm). They are a special delivery and antibacterial agent in various ways because of their high surface area to volume ratio [1]. There are various nanoparticles for targeted drug delivery, including liposomes, polymeric nanoparticles, dendrimers, and inorganic nanoparticles [7]. These biomedical nanotechnology systems are significantly enhancing the therapeutic effects of traditional medications and could potentially alter the effectiveness of antibiotics that are currently available in the market [8]**.** Lipid nanocarriers (LNCs) have been shown to enhance the effectiveness of current bioactive medications and are regarded as appealing antimicrobial carriers due to their biocompatibility and adaptability. Even though bioactive compounds incorporated nanoparticles are being used, metal and metal oxide-based nanoparticles are also been synthesized and used as better antimicrobial agents. For example, certain metals such as silver, gold, copper, titanium, zinc and their oxide form are used as antimicrobial agents by producing nanoparticles form it. Since, this nanoparticle includes metals it can cause toxicity to the human body, not only that using of pure drug in a nano-formulation for targeted drug delivery for antimicrobial activity can also have some side effects in human. So, in order to reduce the toxicity and to overcome these issues researchers are nowadays studying the hybridization of metal nanoparticle and bioactive compounds in a nano formulation and they proved that these hybridization of compound had shown the synergetic effects and reduced side effects. so, this review examines the potential benefits of hybrid nanoparticles in treating antibiotic resistance by targeting resistant microorganisms and improving therapeutic efficacy while resolving issues such as toxicity, scalability, and regulatory barriers. It highlights recent developments and potential future possibilities for incorporating hybrid nanoparticles into antimicrobial strategies.

2.ANTI-MICROBIAL DRUGS AND ANTIMICROBIAL RESISTANCE- OVERVIEW

Antimicrobial resistance remains a significant concern worldwide for *carbapenemase-producing Enterobacterales* (CPE) [9]. The most common carbapenemases found in *carbapenemase-producing Enterobacteriaceae (CPE)* in Europe and the United States are described as *Klebsiella pneumoniae carbapenemases (KPC)* [10]. Although *metallo-β-lactamase (MBL)* are widespread globally, in India, MBL was predominantly found in New Delhi. *Carbapenem-resistant Gram-negative bacteria (CRGN)* are a major cause of death; they are becoming increasingly prevalent and can lead to bloodstream infections. [11] and they are less susceptible to beta-lactamase inhibitors such as avictam, vaporbactam and relebactam. The combination of ceftazidime-avibactam (CZA) and aztreonam (ATM) has been found to reduce the risk of death compared to regimens containing colistin [12]. Also, according to existing guidelines, it is recommended as a first-line treatment against MBL [13].

The main purpose of ceftazidime–avibactam in combination with aztreonam is to treat severe infections caused by metallo-β-lactamase–producing carbapenem-resistant Enterobacterales like *Escherichia coli* and *Klebsiella.* Ceftazidime–avibactam (2.5g) is administered intravenously every 8 hours**,** in combination with aztreonam (2 g) intravenously every 8 hours. Nafithromycin is used for bacteria infection of the lungs and the respiration system like community-Acquired bacteria pneumonia. It is administered at a dose of 800mg orally once daily. Rezafungin is used for first

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(3), 2951-2962 | ISSN:2251-6727

line initial therapy for candidemia/IC except for central nervous system, urinary tract infection or eye. Three echinocandins were previously approved by the Food and Drug Administration (FDA), all of which are available only as intravenous (IV) formulations dosed once daily [14]. The following susceptible microorganisms are responsible for causing community-acquired bacterial pneumonia (CABP) in adults, for which lefamulin is recommended as a treatment: Streptococcus pneumoniae, Staphylococcus aureus. The in vitro antibacterial profile of lefamulin covers a wide range of prevalent bacterial pathogens that are responsible for skin and skin structure infections as well as respiratory tract and sexually transmitted infections. It's a semi-synthetic antibacterial drug that may be taken intravenously (IV) or orally. 150 mg intravenously administered over 60 minutes (repeated doses every 12 hours); 2 hours after or an hour before eating, take 600 mg orally (every 12 hours for multiple doses) [15]. Cefiderocol drug used for emerging option for bloodstream infection for potent against NDM and other MBLs. It is administered at a dose of 2 g intravenously every 8 hours, infused over 3 hours [11]. Meropenem and Vaborbactam is treatment of complicated urinary tract infections, including pyelonephritis, caused by susceptible *Escherichia coli*, *Klebsiella pneumoniae*, or *Enterobacter cloacae* species complex. Meropenem–vaborbactam was administered as 2 g/2 g intravenously every 8 hours, infused over 3 hours, with dose adjustment based on renal function. Imipenem/cilastatin/relebactam is used for complicated urinary tract infection, and complicated intra-abdominal infections, and pyelonephritis caused by gram-negative bacteria. It is recently approved by anti-infective combination of a β-lactam and a new β-lactamase inhibitor [16]. Plazomicin is a broad spectrum aminoglycoside antibiotic that is usually used iv to treat moderate-to-severe pyelonephritis or urinary tract infections. Although there is not much clinical use of plazomicin, it has not been linked to any incidences of clinically significant liver damage or elevated serum enzyme levels during treatment. Under the brand name Zemdri, plazomicin, it is sold in solution in 10-mL single-dose vials containing 500 mg (50 mg/mL), having been authorized for usage in the US in 2018. Adults usually get an intravenous infusion of 15 mg/kg every 24 hours for 4–7 days [16]. Table 1 represents Food and Drug Administration (FDA) approved by New antibiotic and antibiotic combination for clinical use in infection caused by Multi drug resistance (MDR) Bacteria.

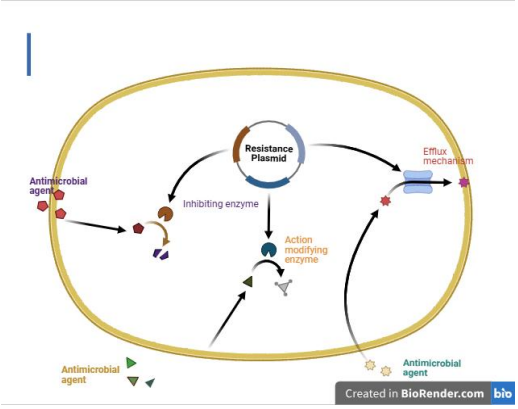

Figure 1 Mechanism of Anti-microbial resistance

Table1: Food and Drug Administration (FDA) approved by New antibiotic and antibiotic combination for clinical use in infection caused by MDR Bacteria.

Antibiotic / Antibiotic Combination	Multidrug resistance Bacteria	Year of sanction	Class	MOA
Delafloxacin	*Methicillin-Resistant Staphylococcus aureus*	2017	Fluoroquinolone	Inhibition of DNA gyrase and bacterial DNA topoisomerase IV halts DNA replication [17].
Lasculfloxacin	*Methicillin-Resistant Staphylococcus aureus*	2019	Fluoroquinolone	Inhibition of bacterial DNA topoisomerase IV and DNA gyrase (topoisomerase II), thereby interfering with DNA replication [18].

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(3), 2951-2962 | ISSN:2251-6727

Alalevonadifloxacin	*Methicillin-Resistant Staphylococcus aureus*	2020	Fluoroquinolone	By stopping bacterial DNA topoisomerase IV and DNA gyrase (topoisomerase II), one may upset DNA replication [19].
Meropenem/Vaborbactam	*Carbapenem-Resistant Enterobacterales*	2017	β-Lactam (Carbapenem) / Boronate β-lactamase inhibitor	Inhibition of cell wall synthesis by blockage of PBPs (BLI protects from inactivation by class A β-lactamases) [20].
Imipenem/Relebactam	*Carbapenem-Resistant Enterobacterales*	2019	β-Lactam (Carbapenem) / Diazabicyclooctane β-lactamase inhibitor	By inhibiting cell wall production through obstruction of PBPs (BLI protects against inactivation by class A β-lactamases) [21].
Aztreonam/Avibactam	*Carbapenem-Resistant Enterobacterales*	2025	β-Lactam (Monobactam) / Diazabicyclooctane β-lactamase inhibitor	Interruption of cell wall creation by obstruction of PBPs; avibactam prevents from class A and D β-lactamases [22].
Cefepime/Enmetazobactam	*Extended-Spectrum β-Lactamase–producing Enterobacterales*	2024	β-Lactam (Cephalosporin) / Penicillanic acid sulfone β-lactamase inhibitor	Blocking of PBPs inhibits cell wall synthesis; by this way, BLI protects from ESBL-type β-lactamases [23].
Meropenem/Nacubactam	*Carbapenem-Resistant Enterobacterales*	2019	β-Lactam (Carbapenem) / Diazabicyclooctane β-lactamase inhibitor	Inhibition of cell wall synthesis by blockage of PBPs (BLI protects from class A, C, and some D β-lactamases) [24].
Eravacycline	*Carbapenem-Resistant Enterobacterales*	2018	Tetracycline	At site A of the 30S ribosomal subunit, inhibition of protein synthesis [25].
Omadacycline	*Methicillin-Resistant Staphylococcus aureus*	2018	Tetracycline	At position A of the 30S ribosomal subunit, inhibition of protein synthesis [26].
Cefiderocol	CR-E, CR-PA, CR-AB	2019	β-Lactam (Cephalosporin)	Siderophore-mediated entrance through iron transport systems next inhibition of cell wall synthesis [27].
Plazomicin	*Carbapenem-Resistant Enterobacterales*	2018	Aminoglycoside	Distortion of the 30S ribosomal subunit results in aberrant protein synthesis and membrane permeability [28].
Sulbactam/Durlobactam	*Carbapenem-Resistant*	2023	β-Lactam–β-lactamase inhibitor	PBP3 inhibition of cell wall creation protects against class

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(3), 2951-2962 | ISSN:2251-6727

	Acinetobacter baumannii		/ Diazabicyclooctane β-lactamase inhibitor	A, C, and D β-lactamases [29].
Pretomanid	*Pre-Extensively Drug-Resistant Mycobacterium tuberculosis*	2019	Nitroimidazole	Respiratory chain toxicity suppression and mycolic acid synthesis inhibition decrease intracellular ATP [30].
Contezolid	*Methicillin-Resistant Staphylococcus aureus*	2021	Oxazolidinone	Prevention of 70S initiation complex formation thus inhibits protein synthesis at the 50S ribosomal subunit [31].
Lefamulin	*Penicillin-Non-Susceptible*	2019	Pleuromutilin	Inhibition of protein production at the peptidyl transferase center of the 50S ribosome unit [15].

3. DRUG DELIVERY STRATEGIES FOR ANTIMICROBIAL AGENTS

3.1 LIPID-BASED NANOPARTICLES

Nanoparticles made from lipids have been extensively researched and crafted for applications in the antimicrobial activity. Lipid- based nanocarriers similar as liposomes, solid lipid nanoparticles(SLN), and nanostructured lipid carriers(NLC) are used to effectively deliver a variety of drug [32]. Liposomes are spherical lipid vesicles made up of amphiphilic lipid molecules with a bilayer membrane structure. The liposome contains a hydrophilic core as well as a hydrophobic exterior. Consequently, liposomes can deliver both hydrophilic and lipophilic medications by hybridization them in their internal aqueous core and lipid bilayer membrane configuration, respectively. Furthermore, liposome delivery improves the stability of the bactericidal agent by preventing its degradation. Adsorption, endocytosis, lipid exchange, and liposome fusion with the bacterial cell membrane are some of the ways that the two surfaces can interact [33]. Researchers are interested in fusogenic liposomes because they may be attached to membranes of bacteria and improve the efficiency of antimicrobial drug delivery. By using a combined mechanism, fusogenic liposomes break down the bacterial membrane, release their helpful payload, and eradicate the bacterial cells [34].

With a solid lipid core held up by surfactants, SLNs are comparatively amorphous structures made up of separated bilayers. SLNs are suitable for the delivery of lipophilic medications due to the structure of their lipid particle core. The stability of the medication is enhanced, and SLNs can be scaled up for large-scale industrial production [35]. The hydrophilic drug's application in SLN is limited, though. NLC was developed to overcome the hydrophilic drug's SLN restriction. The NLC system uses liquid lipids to preserve the structure, allowing for a two-phase drug release profile that includes a rapid release at the beginning and a sustained release.

Increasing antibiotic efficacy while offering protection against metabolic elimination and fusogenicity is one advantage of liposomal antimicrobial nanocarriers. The requirement for deep killing to stop infection recurrence is one of the more difficult parts of clinical infection therapy. To help destroy bacteria that many antimicrobials cannot reach because they hide in mammalian cells, it is also worthwhile to look into the possibility of developing liposomal antimicrobial nanocarriers.

3.2 DENDRIMER

Dendrimers are molecules that are shaped like stars and have many branches. They are made up of three parts: the central core, the inner dendritic structure and the outer surface groups. Dendrimers have a defined three-

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(3), 2951-2962 | ISSN:2251-6727

dimensional structure with available groups that can attach to other things, which makes it easier to predict how they will interact with antibiotics. Dendrimers can carry drugs that're either hydrophilic or lipophilic. Attached to the outer surface groups, dendrimers are good at mimicking cell membranes, which makes them a good way to deliver drugs. They can help drugs dissolve better and get into the body easily and they can release the drugs in a controlled way [35]. Dendrimers can be used to deliver antibiotics. It can even be used to create coatings that resist bacteria. They can also be used as antibiotics on their own attacking cells or toxins. This is because dendrimers are shaped like balls and have groups on their surface which allows them to interact with bacteria in a powerful way. Some dendrimers, called glycodendrimers are very specific which can target specific bacteria. Others, called dendrimers are broader and can attack many types of bacteria [36]. They can be used alone or with drugs to create a powerful antibiotic. There are also dendrimers, which are a mix of cationic and hydrophobic residues. These work by destroying membranes but are more selective than other types of dendrimers. Even though dendrimers are promising there is still a lot to learn about them. Many of the studies that have been done far have only looked at a small number of chemical structures and more research is needed to understand how the structure of dendrimers affects their activity [37]. This means that there are opportunities for further study and development of dendrimers as antimicrobial agents. Dendrimers are an interesting area of research and scientists are still learning about the many ways that dendrimers can be used to fight bacteria and deliver drugs. Dendrimers have the potential to be a tool in the fight against bacterial infections and more research, on dendrimers is needed to fully understand their potential [38].

3.3 POLYMERIC NANOPARTICLES

Antibiotic conjugated polymeric nanoparticles for multidrug-resistant bacteria have been the subject of extensive research [39]. Antibiotic-carrying polymeric nanoparticles have been created using natural and synthetic polymers that are biocompatible and biodegradable. Covalent and non-covalent bonds have been used to attach bactericidal agents to the surface of a polymer or to encapsulate them in the interior of a polymeric core.

Along with providing drug protection through steric hindrance, these polymeric nanoparticles are usually modified to release the drug in response to stimuli [40]. Polymeric nanoparticles use both passive and active targeting to deliver the antibiotic to bacterial cells. The polymer increases the porosity of the bacterial membrane by causing structural disruptions when it interacts with cell membranes which is passive targeting. By binding with a specific antibody and aptamer enhancement a bacterial infection protein, the polymer engages in active targeting, which allows the drug to enter the bacterial cells. Antimicrobial polymeric nanoparticles are innovative alternatives to traditional antibiotics because of their natural antimicrobial properties [41]. Antibiotic combined nanoparticles of polymers for multidrug-resistant organisms have been the subject to multiple studies [39].

4. NANO FORMULATION OF BIOACTIVE COMPOUNDS FOR ENHANCING ANTIMICROBIAL ACTIVITY

Many bioactive compounds that show antimicrobial activity have been formulated using nanocarriers for better action. For instance, Thymol and carvacrol are the two active phenolic ingredients from terpenoids group that are detected in the essential oil extracted from several plants. Studies have proved that these two compounds have potent antibacterial activity by inducing lipid peroxidation in the cell membrane of bacteria. Liposomal encapsulation of essential oil has improved its stability and dissolution, which has been proven by several investigations [42]. Similarly, clove oil also studied for its antimicrobial activity, in which the activity of encapsulated clove oil shows more potential than the free form. The MBC (Minimum Bactericidal concentration) of clove oil was reached up to 5 mg/ml, whereas with a liposomal clove concentration, it reached up to 0.5 mg/ml only, and hence the antibacterial activity of clove oil was enhanced by 10 times when clove oil was carried on liposomes [43]. Likewise, bioactive compounds extracted from the Melissa officinalis plant show higher antibacterial activity when compared to the free form, where the encapsulated one shows 4.68 µg/ml, and for the free form, it is 9.375 µg/mL against Staphylococcus aureus [44]. Like liposomes, there are different nanocarriers that have been used for the encapsulation of certain bioactive compounds for

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(3), 2951-2962 | ISSN:2251-6727

enhanced activity. Polymeric micelles are a type of nanocarrier that are made from a certain polymer. The plant Inula helenium L, which is rich in sesquiterpene lactones have antimicrobial activity that has been studied for inhibition of biofilm formation. In that research, they mentioned that the bioactive extract of the plant Inula helenium L, has shown potent antibacterial activity when it is encapsulated with the polymeric micelles. These encapsulated plant extract shows more inhibition of biofilm formation when compared to the non-encapsulated extract. The bioactive compound-loaded polymeric micelles shows 50 % and 61.87% when it is tested against P.aeruginosa and s.aureus which is higher than the free form [45]. Dendrimer G4 Poloxamer nanoparticles are another type of nanoparticle that has been studied for antimicrobial activity against methicillin-resistant Staphylococcus aureus. In this study, the Dendrimer G4 Poloxamer loaded with coumarin (DG4-polox-coumarin nanoparticles) shows stronger antibacterial activity against MRSA than that of the pure form. The DG4-polox-coumarin nanoparticles show MIC at 1.12 µg/ml after 24 hrs. whereas, the free form shows 4.17 µg/ml after 24 hrs [46]. Like antibacterial activity, many studies have been done for antifungal activity using bioactive compounds. For instance, Curcumin is a bioactive compound that is highly present in Turmeric. This compound, when tested in free form against Candida albicans and Aspergillus niger, has a MIC of 64 µg/ml and 128 µg/ml, but when it is tested after loading in a lipid nanoparticle, it shows a MIC of 8 µg/ml and 16 µg/ml against C.albicans and A. niger. From this demonstration, researchers have concluded that curcumin, when it is loaded in lipid nanoparticles have potential antifungal activity compared to free bioactive form [47].

5. METAL NANOPARTICLES FOR ANTIMICROBIAL ACTIVITY

Even if we enhance the antimicrobial activity of bioactive compounds by nanoformulation, these compounds, When used in pure form, they have certain negative effects and toxicity that change with dosage. To overcome the drawbacks caused by bioactive compounds, researchers have begun to work with metals by synthesizing metal nanoparticles. Several studies indicate the potent antibacterial properties of these metal nanoparticles against bacteria that cause infections. For instance, the silver nanoparticles were synthesized and studied against certain bacteria, such as *Escherichia coli, Klebsiella pneumoniae, Salmonella typhimurium, and Salmonella enteritidis,* which show a MIC and MBC of 7.8, 3.9, 3.9, 3.9 µg/ml and 7.8, 3.9, 7.8, 3.9 µg/ml. From these experimental researchers have proved that the silver nanoparticles have significant antibacterial activity [48]. Likewise, in another study, the silver nanoparticles have tested on *S. aureus, S.epidermidis, B.subtilis and P. aeruginosa,* which shows MIC at 10.8, 9.74, 8.9, 12, and 9.85 µg/ml, showing significant antibacterial activity when compared to standard antibiotics, such as amoxicillin [49]. Not only silver, but also different metals have been used to synthesize for antimicrobial activity, such as copper, zinc, and many. The antifungal activity of metal nanoparticles has been studied using copper nanoparticles. These copper nanoparticles have tested against some fungal strains such as Fusarium solani, Neofusicoccum sp and Fusarium oxysporum, which shows IRG (Inhibition of radial growth) at a concentration of 0.75 mg/ml. In this concentration, 100% of fungal radial growth has been inhibited. so, from this demonstration, scientists conclude that this copper nanoparticle has good antifungal activity [50]. Likewise, zinc has also been studied for antimicrobial activity, especially in bacteria and fungi. The antibacterial effectiveness of zinc nanoparticles is studied against strains such as *B. subtilis, P. aeruginosa, S. aureus, and E. coli.* In this study, they have analyzed the structure of these bacteria after exposing them to zinc nanoparticles, in which they could see rupture of the bacterial cell wall. From this experimental analysis scientist have proved that the zinc nanoparticles have potent antibacterial activity [51]. Similarly, this zinc nanoparticle has been studied for antifungal activity using the strain C. albicans, in which it shows a MIC of 80 µg/ml, which proves that the zinc nanoparticle has effective antifungal activity [52].

6. HYBRIDIZATION OF A BIOACTIVE COMPOUND AND A METAL NANOPARTICLE IN A NANOFORMULATION

Even though scientists synthesize metal nanoparticles to overcome the dose-dependent toxic effects of bioactive compounds, these metal nanoparticles also have similar effects on humans. To achieve lower toxicity and higher efficiency, researchers have focused on hybrid metal-

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(3), 2951-2962 | ISSN:2251-6727

bioactive compound-based nanoparticles. The main focus of this study is to have each metal and bioactive compound in a certain ratio and load them in a nanocarrier, which will have both the compound in minimal quantity, and thereby it will have an effective antimicrobial with minimal toxicity when compared to the previous formulation. Certain studies have proved that these hybrid nanoparticles have effective antimicrobial activity. For instance, the curcumin and silver nanoparticles have been synthesized as a hybrid that has been studied for its capacity to eliminate P. aeruginosa and S. aureus. The demonstration proved that the hybrid nanoparticle, which is curcumin and silver loaded nanoparticles, produced the most potent antibacterial activity when tested on its own, compared to curcumin and silver nanoparticles [53]. Similarly, the copper and tannins have made as a hybrid nanoparticle and studied for HO free radical generating activity. The ESR data of this study show that these tannin and copper hybrid nanoparticles show high generation of the HO free radical, and that mechanism can be utilized for antimicrobial activity for wound healing. In this study, they discussed that when this hybrid nanoparticle is applied on wound, because of its high free radical-generating ability, it can act on the microbial cell wall, which are present on the wound, and thereby it prevents the microbial infection [54].

7. CELLULAR AND MOLECULAR MECHANISMS OF ANTIMICROBIAL ACTIVITY OF BIOACTIVE COMPOUNDS AND METAL NANOPARTICLES

These natural substances have different mechanisms of action that are unique and specific in directing their antibacterial activity. The mechanisms of action of some of these drugs involve the destruction of the microbial cell membrane, which ultimately leads to the leakage of cellular contents and the death of the microbes. The mechanisms of action of some involve the suppression of protein and DNA incorporation. Additionally, some involve the disruption of vital enzymatic processes that are essential to microbial life. It is intriguing to note that the mechanisms of action of most of these drugs are not well understood. However, future studies should aim at utilizing different and innovative procedures to understand the intricate mechanisms of action of the antibacterial properties of these endophyte-derived substances The exploration and discovery of natural antimicrobial substances derived from endophytes have great potential in the development of novel antibiotics, as indicated in the conclusion. Future studies could involve the use of computers and other structural biology and OMICS strategies to determine the bonds between these substances and microbes. Thus, in conclusion, the exploration and discovery of natural antimicrobial substances derived from endophytes have great potential in the development of novel antibiotics [55]. Among other things, the mechanism of action of metallic nanoparticles includes: (i) disruption of the cell walls, resulting in their permeability due to the electrostatic interaction between the positively charged nanoparticles and the negatively charged molecules of the cell wall of the microorganism, leading to the leakage of the cellular content and the disruption of the membrane potential; (ii) another mechanism involves the generation of toxic ROS. The oxidative stress leads to the oxidation of the glutathione, thereby disrupting the antioxidant defense system of the bacteria against ROS. The overproduced ROS leads to the disruption of the redox balance, resulting in oxidative stress, affecting the membrane lipids, the DNA, and the protein structure; (iii) an additional mechanism involves the binding of the nanoparticles to the intracellular components, among other things, resulting in the damage of the DNA, the proteins, and the inhibition of the enzymes. The DNA may be damaged or sheared by the metallic nanoparticles, thereby disrupting the cell division. Moreover, the denaturation of the ribosomes leads to the inhibition of the synthesis of the proteins. (iv) The apoptotic cell death occurs finally due to the overall effects of the processes mentioned above [56]. Hence the combined cellular effect of bioactive and metal nanoparticiles (Figure 2) will be the great solution for anti biotic resistance along with reduced toxicity and dose requirement.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(3), 2951-2962 | ISSN:2251-6727

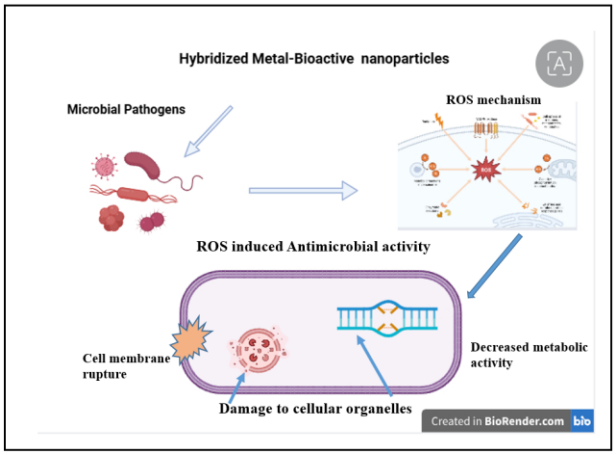

Figure 2 Mechanism of action hybridized Bio-active metal nanoparticles in antimicrobial action.

8. CONCLUSION AND FUTURE PERSPECTIVE:

The use of antibiotics played a major role in those days in curing microbial infections. After a certain number of years, because of evolution and genetic variation, these antibiotics become resistant towards certain microbial organism which turns the microbes into multi-drug resistant (MDR) strains. Because of this reason, many problematic conditions have created, and many people have died. So, to overcome this situation scientist have developed a nano formulation of a drug obtained from a plant, which is known as bioactive compounds that have potent antimicrobial activity. These bioactive compounds, if we take as free form, will have less bioavailability and a lack of site specificity. To overcome this problem scientist have started to encapsulate the bioactive drug into nanocarriers, which have increased its activity. Likewise, metal nanoparticles have also been synthesized to study antimicrobial activity to overcome the drawbacks caused by the nano-formulated bioactive compound, which shows good antimicrobial activity, but still, since it is a metal, it shows toxicity in a dose-dependent manner. So to overcome all these problems, scientists focused to synthesized hybrid-based nanoparticles in which the bioactive compounds and the metal nanoparticles are encapsulated into a nanocarrier. These hybrid formulations, as shown in a certain study, are more effective than other formulations in reducing toxicity and enhancing antimicrobial activity at minimal concentrations. But there is not much study on this hybrid-based nanoformulation, so much research has to be done in this field to overcome the MDR strain and make the people more protective form the pathogenic microbes.

DECLARATION

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors discloses no conflict of interest.

9. REFERENCES:

1. Sharmin S, Rahaman MM, Sarkar C, Atolani O, Islam MT, Adeyemi OS. Nanoparticles as antimicrobial and antiviral agents: A literature-based perspective study. Heliyon. 2021 Mar 1;7(3).
2. Wang L, Hu C, Shao L. The antimicrobial activity of nanoparticles: present situation and prospects for the future. International journal of nanomedicine. 2017 Feb 14:1227-49.
3. Raza S, Wdowiak M, Grotek M, Adamkiewicz W, Nikiforow K, Mente P, Paczesny J. Enhancing the antimicrobial activity of silver nanoparticles against ESKAPE bacteria and emerging fungal pathogens by using tea extracts. Nanoscale Adv 5 (21): 5786–5798 [Internet]. 2023
4. Nikaido H. Multidrug resistance in bacteria. Annual review of biochemistry. 2009 Jul 7;78(1):119-46.
5. Bertagnolio S, Dobreva Z, Centner CM, Olaru ID, Donà D, Burzo S, Huttner BD, Chaillon A, Gebreselassie N, Wi T, Hasso-Agopsowicz M. WHO global research priorities for antimicrobial resistance in human health. The Lancet Microbe. 2024 Nov 1;5(11).
6. Ahsan A, Thomas N, Barnes TJ, Subramaniam S, Loh TC, Joyce P, Prestidge CA. Lipid nanocarriers-enabled delivery of antibiotics and antimicrobial adjuvants to overcome bacterial biofilms. Pharmaceutics. 2024 Mar 14;16(3):396.
7. Mondal SK, Chakraborty S, Manna S, Mandal SM. Antimicrobial nanoparticles: current landscape and future challenges. RSC Pharmaceutics. 2024;1(3):388-402.
8. Ferreira M, Ogren M, Dias JN, Silva M, Gil S, Tavares L, Aires-da-Silva F, Gaspar MM, Aguiar SI.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(3), 2951-2962 | ISSN:2251-6727

Liposomes as antibiotic delivery systems: a promising nanotechnological strategy against antimicrobial resistance. Molecules. 2021 Apr 2;26(7):2047.
9. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, Van Duin D, Clancy CJ. Infectious Diseases Society of America guidance on the treatment of extended-spectrum β-lactamase producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with difficult-to-treat resistance (DTR-P. aeruginosa). Clinical Infectious Diseases. 2021 Apr 1;72(7):e169-83.
10. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, Pulcini C, Kahlmeter G, Kluytmans J, Carmeli Y, Ouellette M. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. The Lancet infectious diseases. 2018 Mar 1;18(3):318-27.
11. Falcone M, Tiseo G, Nicastro M, Leonildi A, Vecchione A, Casella C, Forfori F, Malacarne P, Guarracino F, Barnini S, Menichetti F. Cefiderocol as rescue therapy for Acinetobacter baumannii and other carbapenem-resistant Gram-negative infections in intensive care unit patients. Clinical Infectious Diseases. 2021 Jun 1;72(11):2021-4.
12. Falcone M, Daikos GL, Tiseo G, Bassoulis D, Giordano C, Galfo V, Leonildi A, Tagliaferri E, Barnini S, Sani S, Farcomeni A. Efficacy of ceftazidime-avibactam plus aztreonam in patients with bloodstream infections caused by metallo-β-lactamase–producing Enterobacterales. Clinical infectious diseases. 2021 Jun 1;72(11):1871-8.
13. Paul M, Carrara E, Retamar P, Tängdén T, Bitterman R, Bonomo RA, De Waele J, Daikos GL, Akova M, Harbarth S, Pulcini C. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). Clinical Microbiology and Infection. 2022 Apr 1;28(4):521-47.
14. Smith HL, Bensman TJ, Mishra S, Li X, Dixon CA, Sheikh J, McMaster OG, Joshi A, Rubin DB, Goodwin A, Miller TJ. Regulatory considerations in the approval of rezafungin (REZZAYO) for the treatment of candidemia and invasive candidiasis in adults. The Journal of Infectious Diseases. 2024 Aug 15;230(2):505-13.
15. Kozhokar L, Levien TL, Baker DE. Lefamulin. Hospital Pharmacy. 2022 Dec;57(6):704-11
16. Mansour H, Ouweini AE, Chahine EB, Karaoui LR. Imipenem/cilastatin/relebactam: A new carbapenem β-lactamase inhibitor combination. American Journal of Health-System Pharmacy. 2021 Apr 15;78(8):674-83.
17. Turban A, Guérin F, Dinh A, Cattoir V. Updated review on clinically-relevant properties of delafloxacin. Antibiotics. 2023 Jul 28;12(8):1241.
18. Thakare R, Singh S, Dasgupta A, Chopra S. Lascufloxacin hydrochloride to treat bacterial infection. Drugs Today. 2020 Jun 1;56(6):365.
19. Bhagwat SS, Nandanwar M, Kansagara A, Patel A, Takalkar S, Chavan R, Periasamy H, Yeole R, Deshpande PK, Bhavsar S, Bhatia A. Levonadifloxacin, a novel broad-spectrum anti-MRSA benzoquinolizine quinolone agent: review of current evidence. Drug design, development and therapy. 2019 Dec 24:4351-65.
20. Matlock A, Garcia JA, Moussavi K, Long B, Liang SY. Advances in novel antibiotics to treat multidrug-resistant gram-negative bacterial infections. Internal and Emergency Medicine. 2021 Nov;16(8):2231-41.
21. Johnston BD, Thuras P, Porter SB, Anacker M, VonBank B, Vagnone PS, Witwer M, Castanheira M, Johnson JR. Activity of imipenem-relebactam against carbapenem-resistant Escherichia coli isolates from the United States in relation to clonal background, resistance genes, coresistance, and region. Antimicrobial agents and chemotherapy. 2020 Apr 21;64(5):10-128.
22. Karlowsky JA, Kazmierczak KM, de Jonge BL, Hackel MA, Sahm DF, Bradford PA. In vitro activity of aztreonam-avibactam against Enterobacteriaceae and Pseudomonas aeruginosa isolated by clinical laboratories in 40 countries from 2012 to 2015. Antimicrobial agents and chemotherapy. 2017 Sep;61(9):10-128.
23. Bhowmick T, Canton R, Pea F, Quevedo J, Santerre Henriksen A, Timsit JF, Kaye KS. Cefepime-enmetazobactam: first approved cefepime-β-lactamase inhibitor combination for multi-drug

resistant Enterobacterales. Future Microbiology. 2025 Mar 4;20(4):277-86.
24. Asempa TE, Motos A, Abdelraouf K, Bissantz C, Zampaloni C, Nicolau DP. Meropenem–nacubactam activity against AmpC-overproducing and KPC-expressing Pseudomonas aeruginosa in a neutropenic murine lung infection model. International journal of antimicrobial agents. 2020 Feb 1;55(2):105838.
25. Scott LJ. Eravacycline: a review in complicated intra-abdominal infections. Drugs. 2019 Feb 28;79(3):315-24.
26. Zhanel GG, Esquivel J, Zelenitsky S, Lawrence CK, Adam HJ, Golden A, Hink R, Berry L, Schweizer F, Zhanel MA, Bay D. Omadacycline: a novel oral and intravenous aminomethylcycline antibiotic agent. Drugs. 2020 Feb;80(3):285-313.
27. YY. Cefiderocol: a review in serious Gram-negative bacterial infections. Drugs. 2021 Sep;81(13):1559-71.
28. Clark JA, Burgess DS. Plazomicin: a new aminoglycoside in the fight against antimicrobial resistance. Therapeutic advances in infectious disease. 2020 Sep;7:2049936120952604.
29. El-Ghali A, Kunz Coyne AJ, Caniff K, Bleick C, Rybak MJ. Sulbactam-durlobactam: A novel β-lactam-β-lactamase inhibitor combination targeting carbapenem-resistant Acinetobacter baumannii infections. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2023 Jun;43(6):502-13.
30. Kadura S, King N, Nakhoul M, Zhu H, Theron G, Köser CU, Farhat M. Systematic review of mutations associated with resistance to the new and repurposed Mycobacterium tuberculosis drugs bedaquiline, clofazimine, linezolid, delamanid and pretomanid. Journal of Antimicrobial Chemotherapy. 2020 Aug;75(8):2031-43.
31. Hoy SM. Contezolid: first approval. Drugs. 2021 Sep;81(13):1587-91.
32. Kumar R. Lipid-based nanoparticles for drug-delivery systems. InNanocarriers for drug delivery 2019 Jan 1 (pp. 249-284). Elsevier.
33. Yadav D. Liposomes for drug delivery. Journal of Biotechnology & Biomaterials. 2017 Jan 1.
34. Watarai S, Iwase T, Tajima T, Yuba E, Kono K, Sekiya Y. Application of pH-sensitive fusogenic polymer-modified liposomes for development of mucosal vaccines. Veterinary immunology and immunopathology. 2014 Mar 15;158(1-2):62-72. Hajibonabi A, Yekani M, Sharifi S, Nahad JS, Dizaj SM, Memar MY. Antimicrobial activity of nanoformulations of carvacrol and thymol: New trend and applications. OpenNano. 2023 Sep 1;13:100170.
35. Karaman DŞ, Manner S, Fallarero A, Rosenholm JM. Current approaches for exploration of nanoparticles as antibacterial agents. Antibacterial agents. 2017 May 31;61.
36. Abbasi E, Aval SF, Akbarzadeh A, Milani M, Nasrabadi HT, Joo SW, Hanifehpour Y, Nejati-Koshki K, Pashaei-Asl R. Dendrimers: synthesis, applications, and properties. Nanoscale research letters. 2014 May 21;9(1):247.
37. Wang J, Li B, Qiu L, Qiao X, Yang H. Dendrimer-based drug delivery systems: History, challenges, and latest developments. Journal of biological engineering. 2022 Jul 25;16(1):18.
38. Chauhan AS. Dendrimers for drug delivery. Molecules. 2018 Apr 18;23(4):938.
39. Michalak G, Głuszek K, Piktel E, Deptuła P, Puszkarz I, Niemirowicz K, Bucki R. Polymeric nanoparticles–a novel solution for delivery of antimicrobial agents. Medical Studies/Studia Medyczne. 2016 Jan 1;32(1):56-62.
40. Kavruk M, Celikbicak O, Ozalp VC, Borsa BA, Hernandez FJ, Bayramoglu G, Salih BE, Arica MY. Antibiotic loaded nanocapsules functionalized with aptamer gates for targeted destruction of pathogens. Chemical communications. 2015;51(40):8492-5.
41. Barreras US, Méndez FT, Martínez RE, Valencia CS, Rodríguez PR, Rodríguez JP. Chitosan nanoparticles enhance the antibacterial activity of chlorhexidine in collagen membranes used for periapical guided tissue regeneration. Materials Science and Engineering: C. 2016 Jan 1;58:1182-7.
42. Hajibonabi A, Yekani M, Sharifi S, Nahad JS, Dizaj SM, Memar MY. Antimicrobial activity of nanoformulations of carvacrol and thymol: New trend and applications. OpenNano. 2023 Sep 1;13:100170.
43. Haggag MG, Shafaa MW, Kareem HS, El-Gamil AM, El-Hendawy HH. Screening and enhancement of the antimicrobial activity of some plant oils using

liposomes as nanoscale carrier. Bulletin of the National Research Centre. 2021 Feb 6;45(1):38.
44. Nizam N, Taner G, Cagal MM. Nanoliposomal system for augmented antibacterial and antiproliferative efficacy of Melissa officinalis L. extract. Toxicology Research. 2024 Dec;13(6):tfae198.
45. Stancheva R, Damyanova T, Paunova-Krasteva T, Veleva R, Topouzova-Hristova T, Ivanova V, Trendafilova A, Dimitrov I, Rangelov S, Haladjova E. Cationic Polymer Micelles as Carriers of Bioactive Sesquiterpene Lactones from Inula Helenium L. for Effective Treatment of Bacterial Biofilms. Pharmaceutics. 2025 Jun 19;17(6):800.
46. Foudah AI, Alqarni MH, Ross SA, Alam A, Salkini MA, Kumar P. Site-specific evaluation of bioactive coumarin-loaded dendrimer G4 nanoparticles against methicillin resistant Staphylococcus aureus. ACS omega. 2022 Sep 22;7(39):34990-6.
47. T.M. V, Yadav S, Bhushan Patil M, Sindhu YR, Patel J, S. Uttekar P, et al. Nanoformulation of Phytochemicals to Increase Antifungal Effectiveness Against Pathogens Resistant to Drugs. J Neonatal Surg [Internet]. 2025 Apr. 1 [cited 2026 Feb. 5];14(10S):479-87.
48. Loo YY, Rukayadi Y, Nor-Khaizura MA, Kuan CH, Chieng BW, Nishibuchi M, Radu S. In vitro antimicrobial activity of green synthesized silver nanoparticles against selected gram-negative foodborne pathogens. Frontiers in microbiology. 2018 Jul 16;9:1555.
49. Bali, M. & Shukla, S. (2022). Formulation and Characterization of Silver Nanoparticles Using Casiatora and Evaluation of Antimicrobial and Antioxidant Activities. Der Pharma Chemica, 14(9), 16–23. DOI: 10.4172/0975-413X.14.9.16-23.
50. Pariona N, Mtz-Enriquez AI, Sánchez-Rangel D, Carrión G, Paraguay-Delgado F, Rosas-Saito G. Green-synthesized copper nanoparticles as a potential antifungal against plant pathogens. RSC advances. 2019;9(33):18835-43.
51. Mendes CR, Dilarri G, Forsan CF, Sapata VD, Lopes PR, de Moraes PB, Montagnolli RN, Ferreira H, Bidoia ED. Antibacterial action and target mechanisms of zinc oxide nanoparticles against bacterial pathogens. Scientific reports. 2022 Feb 16;12(1):2658.
52. Djearamane S, Xiu LJ, Wong LS, Rajamani R, Bharathi D, Kayarohanam S, De Cruz AE, Tey LH, Janakiraman AK, Aminuzzaman M, Selvaraj S. Antifungal properties of zinc oxide nanoparticles on Candida albicans. Coatings. 2022 Nov 30;12(12):1864.
53. Loo CY, Rohanizadeh R, Young PM, Traini D, Cavaliere R, Whitchurch CB, Lee WH. Combination of silver nanoparticles and curcumin nanoparticles for enhanced anti-biofilm activities. Journal of agricultural and food chemistry. 2016 Mar 30;64(12):2513-22.
54. Zhiye Zheng, Yan Chen, Binxue Zhang, Mengting Huang & Aikebaier Rehman, A Type of Metal-Tannin Nanoparticles: Featuring Oxidative Antibacterial Effects Applied in Wound Healing, Transactions on Materials, Biotechnology and Life Sciences, Volume 2, BBBS 2023, published April 2024.
55. Eshboev F, Mamadalieva N, Nazarov PA, Hussain H, Katanaev V, Egamberdieva D, Azimova S. Antimicrobial action mechanisms of natural compounds isolated from endophytic microorganisms. Antibiotics. 2024 Mar 18;13(3):271.
56. Skłodowski K, Chmielewska-Deptuła SJ, Piktel E, Wolak P, Wollny T, Bucki R. Metallic nanosystems in the development of antimicrobial strategies with high antimicrobial activity and high biocompatibility. International journal of molecular sciences. 2023 Jan 20;24(3):2104