Review

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Arid Zone Phytochemicals as a Source of Novel Antimicrobials: Synergistic Effects with Nanotechnology in Antibiotic Resistance Microbes

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Antibiotic resistance has emerged as one of the most critical global health challenges, exacerbated by the overuse and misuse of antibiotics in healthcare. Resistant bacterial strains pose a greater threat to human health than cancer. This crisis has prompted an urgent search for novel antimicrobial agents, particularly those derived from natural sources. This review explores the potential of arid zone plants as promising sources of new antimicrobial agents. They contain different types of bioactive compounds such as alkaloids, flavonoids, terpenoids, and phenolic acids with potent antimicrobial, antioxidant, and anti-inflammatory properties. These compounds target through a variety of mechanisms, such as disrupting bacterial cell membranes, inhibiting protein synthesis, and inhibiting DNA replication to effectively inhibit or kill the microbes, offering alternative therapeutic pathways. Furthermore, the integration of nanotechnology with phytochemicals enhances the therapeutic potential of nano-phytochemicals by improving bioavailability, controlled release, and enabling site-specific delivery. This innovative approach offers a promising strategy for combating multidrug-resistant (MDR) pathogens and overcoming biofilm-associated infections. However, challenges related to nanoparticle toxicity, biocompatibility, and regulatory hurdles persist. In this review, we discuss how an interdisciplinary approach to developing arid zone plant-based nanopharmaceuticals can offer an effective and sustainable solution to the escalating threat of MDR pathogens, thereby supporting global public health.

Keywords: antibiotic resistance; arid zone plants; phytochemicals; antimicrobial activity; nanoparticles

Introduction

Antibiotic-resistant bacteria have been recognized as one of the greatest challenges on a global scale in the 21st century [1]. The remarkable efficiency that antibiotics once possessed has been compromised by the spread of resistant pathogens, rendering them substantial threats. Moreover, the overuse and misappropriation of antibiotics in public health have played a part in the worsening of the situation [2,3]. According to the World Health Organization (WHO), antibiotic resistance leads to longer hospital stays, higher medical costs, and increased mortality, which ultimately jeopardizes public health [4]. It is estimated that globally, 10 million individuals could become victims of antibiotic-resistant pathogens, which is higher than the number of cancer patients. The emergence of bacterial strains (superbugs), resistant to multiple antibiotics has exacerbated the situation, emphasizing the critical need for new antimicrobial drugs [5]. This crisis has prompted scientists and researchers worldwide to look for new sources of antimicrobial medicines, particularly those derived from natural ingredients. Even though plant material has long been an important source of new pharmaceuticals and comes from a specific type of plant genus, there is a growing challenge to identify a novel group of antibiotics to combat the growing issue of antimicrobial resistance [6].

Besides the molecular and cellular mechanisms that cause drug resistance, the discovery of a novel class of drugs as well as their unique pathways to overcome microbial resistance remains a major area of interest in addressing the emergence of drug-resistant pathogens [7]. One of the promising avenues for identifying new antibiotics lies in exploring the native arid habitat plants [8]. These plants can grow in harsh environments like high temperatures and extreme weather conditions, developing stress-induced secondary metabolism in the production of unique secondary metabolites against pathogens. These arid plants are an underutilized source of new compounds, which are very efficient against resisting bacteria. Furthermore, plant-based treatments exhibit fewer side effects and pose a reduced

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

risk of developing resistance, making them appealing options for long-term therapy [9,10]. Various investigations have revealed that these bioactive chemicals have antibacterial properties and are effective against a broad spectrum of bacterial infections [10].

These bioactive chemicals function through various mechanisms such as disrupting bacterial cell membranes, inhibiting protein synthesis, and interference with DNA replication [11]. Compounds derived from arid zone plants may provide novel approaches to combat the escalating problem of antibiotic resistance by targeting these critical mechanisms (Fig. 1, Ref. [12]) [13]. Given the promising antimicrobial activities of arid zone plants, there is a growing interest in enhancing their efficacy through the integration of nanotechnology.

With the help of nanotechnology, we can improve the therapeutic potential of bioactive compounds [14,15]. Nanoparticles (NPs) can protect phytochemicals from getting degraded by the environment of the body and also facilitate controlled release over time [16]. This method enhances the antimicrobial activity of the compounds but also helps reduce side effects and the likelihood of resistance emergence. Moreover, the combination of nanotechnology with phytochemicals offers a novel strategy for overcoming antibiotic resistance [17]. When both plant-based compounds and conventional antibiotics are administered, synergistic effects may enhance the overall antimicrobial efficacy [18]. This synergism can help reduce the required antibiotic dose and thus minimize the selective pressure that leads to antibiotic resistance. Furthermore, nanocarriers can support the penetration of antimicrobial agents into biofilms, which are resistant structures that bacteria form that exhibit high resilience to antibiotics [19]. Therefore, these methods can be utilized to develop novel antimicrobial therapies, while promoting the sustainable management of natural resources, ultimately enhancing global health and conserving biodiversity.

Bioactive Compounds in Arid Zone Plants

In traditional medicine systems, plants from arid zones have been widely used in different treatments of diseases [20,21]. These plants can be classified based on their therapeutic applications and the specific plant parts utilized [22]. The challenges posed by extreme weather and drought conditions significantly drive the use of drought-resistant plant species in arid regions [9,10]. Characteristically, these plants often possess thick, waxy leaves or deep roots that serve as a reservoir of water and bioactive compounds. These plants are generally utilized for the treatment of ailments related to the skin, gastrointestinal, and respiratory systems, revealing the health challenges common in these climates [20,21,23]. These arid zone plants exhibit a wider variety of secondary metabolites including alkaloids, terpenoids, and phenolic compounds than any other flora from another region, protecting extreme environmental conditions [12,24]. These secondary metabolites have strong antimicrobial, antifungal, and antioxidant properties (Fig. 1) [25]. Consequently, they are particularly valuable in treating infections and inflammatory conditions, resulting in a rich diversity of compounds with potential pharmacological applications [26]. Additionally, they also help to enhance the shelf life of food materials through packaging materials [27].

Among the notable traditional medicines from arid zones is *Aloe vera*, which originates from the arid regions of the Arabian Peninsula [28]. Historically, *Aloe vera* has been used for many years for the relief of burns, wounds, and skin irritations mainly because of its soothing, anti-inflammatory, and antimicrobial properties [29]. The gel extracted from *Aloe vera* leaves remains a popular first-aid remedy worldwide [30]. Another well-known member of the arid zone flora is *creosote bush* (*Larrea tridentate*), native to North America. This shrub is the source of a substance called nordihydroguaiaretic acid (NDGA), which has demonstrated efficacy against both bacterial and viral infections [31,32]. NDGA has been traditionally utilized to address various conditions, including arthritis, skin infections, and even cancer, due to its powerful effects in fighting oxidative stress and microbial infection (Table 1, Ref. [28,29,31–72]). In the deserts of North Africa, the Berber tribes have traditionally used *Artemisia herba alba* to treat gastrointestinal disorders and respiratory infections, and as a general tonic [33,34]. The indigenous people of arid regions have used local plants for many years for treating a wide range of ailments, from simple infections like wounds and digestive disorders to more complicated diseases [73, 74]. For instance, leaves of *Calotropis procera* (*C. procera*) are used in the treatment of skin infections and rheumatism [35]. Extracts from *C. procera* have shown potential as antioxidants, and anticancer agents and exhibit antimicrobial activity against *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*) [36]. There are approximately 70 types of *Amaranthus species* with similar phytochemical profiles (Table 1), including β-cyanin, β-xanthin, betalain, gallic acid, quercetin equivalent, ferulic acid, sinapic acid, and apigenin [37,38]. These compounds exhibit several biological activities such as antioxidant, antibacterial, anti-nociceptive, anti-inflammatory, and anthelmintic properties [75–77]. The plant *Tephrosia purpurea* (*T. purpurea*) contains compounds such as tephrostachin, tephrosin, pongaglabol, semiglabrin, quercetin, rutin, β-sitosterol, and lupeol, which are responsible for its anti-inflammatory, antimicrobe, and anti-fungal activities [39–41]. Additionally, extracts of *Croton bonplandianum* extracts have been evaluated for their phytochemical properties and antimicrobial efficacy against pathogenic bacteria such as *Salmonella enterica* (*S. enterica*), and *Staphylococcus* species [42].

Moreover, the potential of many medicinal plants from arid zones remains unexplored, and their integration into

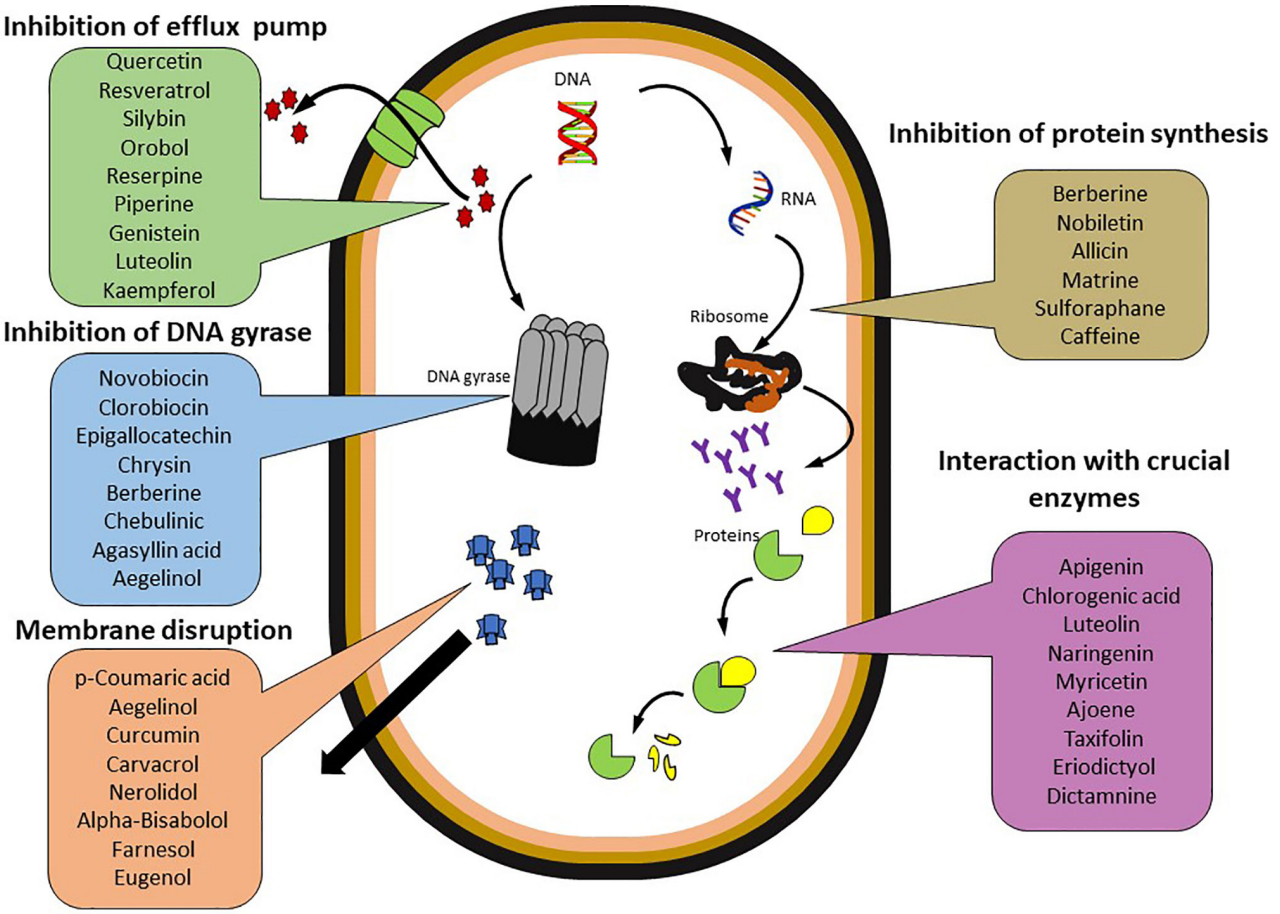

Fig. 1. Mechanisms to combat bacterial resistance by various natural compounds. These processes target crucial bacterial functions, playing a significant role in addressing antibiotic resistance. Efflux pump inhibitors, like quercetin and resveratrol, prevent bacteria from expelling antibiotics, thus allowing the drugs to accumulate inside the cells. DNA gyrase inhibitors, such as berberine and novobiocin, disrupt bacterial DNA replication, halting cell growth. Membrane disruptors like curcumin and eugenol break down bacterial cell membranes, causing leakage and death. Protein synthesis inhibitors, including sulforaphane and allicin, prevent the production of essential bacterial proteins. Additionally, certain compounds like apigenin interact with key enzymes, disrupting bacterial metabolism. These natural substances represent promising alternatives to traditional antibiotics in combating multidrug-resistant (MDR) pathogens, providing innovative solutions to the growing global health challenge of antibiotic resistance [12]. Reproduced the open-access image from the Frontiers Publishers [12].

contemporary medicine is still in its early stages despite their big potential. The exploration of these plants could lead to the development of innovative treatments for antibiotic resistance. Arid zone plants produce a variety of bioactive compounds, including alkaloids, flavonoids, terpenoids, phenolic acids, and essential oils (Table 1). These compounds play a crucial role in the survival of these plants under harsh conditions and provide intriguing opportunities for drug discovery. Their investigation may offer alternative strategies to address antibiotic resistance and related modern health challenges.

Alkaloids

Alkaloids are a class of natural nitrogenous compounds that are recognized for their significant biological effects. These compounds are recognized for their medical effects, such as analgesic, antimalarial, and anticancer effects [78,79]. The harsh conditions in arid zones often lead to the production of unique and potent alkaloids, which contribute to the plant's survival and hold great potential for the pharmaceutical industry. Various types of alkaloids are present in arid plants such as Tropane, Pyrrolizidine, Quinoline, Indole, Soquinoline, Steroidal, and Phenethylamine.

The alkaloid harmine, found in *Peganum harmala* (Syrian rue), is known to kill various microbes and human cancer cells [43,44]. The alkaloids found in *Catha edulis* (khat), exhibit stimulant and antimicrobial properties [45]. It is recommended to abstain from using Khat while taking Cytochrome P450 2D6 (CYP2D6) substrate drugs due to potential pharmacological interactions [46]. *Acacia nilotica* is rich in monocyclic and bicyclic alkaloids, including catecholamines such as nornuciferine and protopine, which

Table 1. Therapeutic properties in arid zone plants.

Plant	Bioactive compound	Compound type	Therapeutic properties	References
Aloe vera	Aloin	Phenolic acids	Anti-inflammatory, antimicrobial, soothing burns and skin irritations	[28,29]
Larrea tridentata	Nordihydroguaiaretic acid (NDGA)	Lignans, phenolic acids	Antioxidant, antibacterial, antiviral	[31,32]
Artemisia herba-alba	Artemisinin, cineole, camphor	Terpenoids	Antimicrobial, anticandidal, antioxidant, antiparasitic	[33,34]
Calotropis procera	Glycosides, calotropin	Alkaloids, terpenoids	Anticancer, antimicrobial, and antioxidant, used against *Escherichia coli* and *Staphylococcus aureus*	[35,36]
Amaranthus species	β-Cyanin, β-Xanthin, gallic acid	Flavonoids, phenolic acids	Antioxidant, antibacterial, anti-inflammatory, anti-nociceptive	[37,38]
Tephrosia purpurea	Tephrostachin, tephrosin	Flavonoids	Anti-inflammatory, antimicrobial, antifungal	[39–41]
Thymus vulgaris, Salvia officinalis folium	Alkaloids, flavonoids	Alkaloids, flavonoids	Antimicrobial, effective against *Salmonella enterica* and *Staphylococcus* sps.	[42]
Peganum harmala	Harmine, harmaline	Alkaloids	Antimicrobial, anticancer, antioxidant	[43,44]
Catha edulis	Cathine, cathinone	Alkaloids	Stimulant, antimicrobial	[45,46]
Acacia nilotica	Catecholamines (nornuciferine)	Alkaloids	Antibacterial, anti-inflammatory, anticancer	[47]
Ephedra species	Ephedrine, pseudoephedrine	Alkaloids	Bronchodilator, antimicrobial	[48]
Rauvolfia serpentina	Reserpine	Alkaloids	Antihypertensive, antipsychotic, anti-inflammatory	[49,50]
Nerium oleander	Oleandrin, neriine	Alkaloids	Anticancer, induces apoptosis in cancer cells	[51,52]
Prosopis cineraria	Quercetin, vitexin, kaempferol	Flavonoids	Antibacterial, antioxidant, anti-inflammatory	[53,54]
Ziziphus jujuba	Spinosin, ferulic acid, Rutin	Flavonoids, phenolic acids	Antioxidant, antibacterial, used for skin infections and digestive health	[55–57]
Capparis decidua	Rutin, kaempferol	Flavonoids	Anti-inflammatory, antioxidant, used for skin ailments	[58]
Artemisia annua	Artemisinin, flavonoids	Terpenoids, flavonoids	Antimalarial, antibacterial, antioxidant	[59,60]
Artemisia douglasiana	artemisia ketone, α-thujone, 1,8-cineole	Flavonoids	Antimicrobial	[61,62]
Commiphora myrrha (*Myrrh*)	Furanosesquiterpenes, curzerene	Terpenoids	Anti-inflammatory, analgesic, antimicrobial	[63,64]
Boswellia sacra (frankincense)	Boswellic acids	Triterpenoids	Anti-inflammatory, antibacterial, and inflammatory diseases	[65]
Mentha longifolia	Menthol, pulegone	Terpenoids	Antibacterial, antiparasitic	[66]
Thymus vulgaris	Thymol, carvacrol	Essential oils	Antibacterial, antifungal, effective against Methicillin-resistant *Staphylococcus aureus* (MRSA)	[67,68]
Lavandula angustifolia	Linalool, camphor	Essential oils	Antibacterial, antifungal, antioxidant	[69–72]

MRSA, Methicillin-resistant *Staphylococcus aureus*.

are capable of killing many bacterial strains [47]. One of the most promising alkaloids derived from *Ephedra* species is ephedrine, which is an efficient treatment for asthma and bronchitis in modern medicine [48]. *Rauvolfia serpentine* is the primary source of the alkaloid reserpine, known for its traditional antihypertensive and antipsychotic effects [49,50]. Furthermore, the plant *Nerium oleander* contains alkaloids such as oleandrin and nerine (Table 1), which have been shown to trigger apoptosis in cancer cells [51,52]. Through investigation into these unique substances, researchers can explore novel treatments for a variety of diseases, from cancer to infectious diseases, promoting both drug discovery and biodiversity preservation in arid areas.

Flavonoids

Flavonoids are a diverse group of polyphenolic compounds. The most studied flavanols are kaempferol, quercetin, and myricetin, which research attributes antioxidative properties and a potential role in ultraviolet (UV) defense through UV-screening mechanisms, making them critical for plant adaptation to climate change [80,81]. The flavonoid vitexin, puerarin, phloridzin, daidzein, and quercetin found in *Prosopis cineraria* (khejri), have been shown to possess strong antibacterial and antioxidant activities [53,54]. Quercetin has also been shown to inhibit the growth of various drug-resistant microorganisms [82]. The broad bactericidal efficacy of quercetin suggests that this compound (Table 1) can be employed as a natural antimicrobial agent [83]. Moreover, quercetin has been confirmed to inhibit the action of pro-inflammatory cytokines, minimize oxidative stress, and boost the activity of immune cells, contributing to cancer treatment [84,85]. Tian *et al.* [86] studied the anti-inflammatory and antioxidant activities of luteolin, kaempferol, apigenin, and quercetin by evaluating their effects on nitric oxide (NO) levels, phagocytic activity, free radical scavenging, and ferric ion reduction. Luteolin was found to inhibit viral mRNA and protein synthesis, and it disrupted microtubules and microfilaments [87].

The flavonoids apigenin and luteolin in *Teucrium polium* have demonstrated significant antioxidant and anti-inflammatory properties [88–90]. *Ziziphus jujuba*, commonly known as jujube or Chinese date, is an arid zone plant that contains a high concentration of flavonoids, including novel compounds such as spinosin, feruloylisospinosin, isospinosin, isovitexin, and rutin [55,56]. The crude extracts from *Ziziphus jujuba* could be used as natural antioxidants for the treatment of various diseases [57]. This study suggests that flavonoids extracted from *Z. jujuba* are promising candidates as natural antibacterial agents for pharmaceutical applications [91]. *Capparis decidua* (karir tree) contains a wide array of flavonoids, such as manghaslin, clitorin, rutin, kaempferol 3-neohesperidoside, Quercetin 3-neohesperidoside, nicotiflorin, and narcissin (Table 1), which have long been used for their medicinal properties such as treating skin problems, and rheumatism [58]. Rutin, another flavonoid, is well known for its strong antioxidant activity, anti-inflammatory, and/or anti-apoptotic properties [92,93]

Terpenoids

Terpenoids are one of the most diverse and widespread classes of natural products, with over 30,000 identified compounds. These substances are usually produced by plants through the isoprenoid pathway and play critical roles in various ecological and physiological functions [94, 95]. They have driven the evolution of unique terpenoid profiles in these plants, often endowing them with potent antimicrobial, anti-inflammatory, and anticancer properties [94,96]. The arid medicinal plants produce distinct terpenoids from plants such as *Cannabis sativa*, *Artemisia annua*, *Salvia miltiorrhiza*, *Ginkgo biloba*, and *Taxus media* [95]. The most prominent example of a medically important terpenoid is artemisinin from *Artemisia annua*, which is used in treating malaria [59]. *Artemisia* species have been documented to contain 75 types of phytoactive molecules with antibacterial properties and multiple modes of action. These molecules can disrupt bacterial cell walls and membranes, and interfere with DNA, proteins, and enzymes [60]. These phytoactive molecules exhibit strong antibiotic activity against *Bacillus subtilis* (*B. subtilis*), *E. coli*, *S. aureus*, *Proteus mirabilis* (*P. mirabilis*), and (*Pseudomonas aeruginosa*) *P. aeruginosa*, along with strong antioxidant capacity [97].

While *A. annua* is not a plant of arid zones, similar species, such as *Artemisia herba-alba*, which grow in arid areas, also produce the same terpenoids (Table 1), which possess excellent antibacterial, anticandidal, and antioxidant properties [98,99]. It yields a variety of terpenoids, including camphor, thujone, and cineole, known for their antimicrobial and antiparasitic activity [61,62]. *Artemisia douglasiana* has been shown to treat chronic bladder infections and has antimicrobial activity against *Bacillus cereus*, *S. aureus*, *E. coli*, *P. aeruginosa*, *C. albicans*, and *A. niger* [63]. *Commiphora myrrha*, the source of myrrh, produces resin enriched with terpenoids like furanoeudesma-1,3-diene and curzerene. Myrrh is a natural remedy known for its anti-inflammatory and analgesic properties [63,64]. Another arid zone plant, *Boswellia sacra*, produces a resin known as frankincense, which is rich in boswellic acids—triterpenoids with potent anti-inflammatory and antibacterial effects [65]. *Mentha longifolia* produces a range of terpenoids, including menthol, menthone, and pulegone with pulegone showing antibacterial effects against *S. aureus*, *Listeria monocytogenes* (*L. monocytogenes*), and *E. coli* [66].

These examples underscore the immense potential of terpenoids from arid zone plants in drug discovery and development. The unique environmental stresses in arid regions lead to the formation of these bioactive compounds,

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

some of which exhibit critical therapeutic properties. With the continued study of the plants that exist in such dry environments and their terpenoids, these natural chemical compounds are likely to be developed into treatments for various diseases, ranging from the signs of infectious diseases to chronic inflammation. The exploration of terpenoids from arid zone plants thus represents a promising frontier in the search for novel natural therapies.

Phenolic Acids

Phenolic acids, a significant subset of phenolic compounds, are the most diverse among the chemical candidates with emphasized biological activities, such as antioxidant, anti-inflammatory, and antimicrobial properties [100]. These compounds include well-known examples such as caffeic acid, gallic acid, vanillic, gentistic acid, salicylic acid, and ferulic acid, all of which play crucial roles in plant defense mechanisms [101]. Their ability to scavenge free radicals and inhibit the growth of pathogens is vital for plant survival. An arid region plant exhibiting great qualities of phenolic acids is the *creosote bush* (*Larrea tridentata*). Its medicinal properties have been partly attributed to its substantial levels of phenolic acids and lignans. NDGA, a lignan with strong phenolic features, has been extensively demonstrated as one of the most effective inhibitors of both prokaryote and eukaryote microorganisms [102]. Similarly, phenolic acids such as gallic acid and ferulic acid contribute to its impressive defense mechanisms. Gallic acid is widely recognized for its broad activity against both bacterial and fungal pathogens, making it highly effective in inhibiting infections [103].

Acacia nilotica contains significant quantities of gallotannins, such as gallic acid, which have been prominent in traditional medicine for the treatment of infections and inflammatory diseases. *Zygophyllum dumosum* can produce considerable quantities of different types of ferulic acids and phenolics. These compounds are the most important components of the plant that help it withstand the harsh conditions of desert environments. They also exhibit antioxidant, anti-inflammatory, and antimicrobial activities, which may assist the plant in becoming more resistant to the effects of other stress elements [104].

Essential Oils

The bioactive potential and possible uses of essential oils extracted from arid zone plants have become the focus of many studies due to their antioxidants and antibacterial properties. This study underscores the significance of essential oils, not only for plant survival but also as valuable natural products for human use [67]. Plants such as sage (*Salvia officinalis*), *Micromeria* sps., *Marrubium* sps., and *Thymus vulgaris* (thyme), which grow in arid regions, have been identified as new sources of essential oils, each with unique components. Sage oil is rich in compounds like germacrene-B and geranyl linalool, while *Micromeria* oil contains caryophyllene oxide and α-bisabolol. *Marrubium* oil's main ingredients include thymol and myristicin, with thymol also being the dominant compound in thyme oil (TEO). These oils are primarily composed of sesquiterpenes and oxygenated monoterpenes, offering potential new uses for their natural properties [68].

The essential oil (EO) of thyme, with thymol and carvacrol as its main components, has demonstrated activity against Methicillin-resistant *Staphylococcus aureus* (MRSA) [105]. This bacterium is a significant problem in healthcare settings because it shows resistance to many antibiotics [106]. Studies have shown that these compounds can cause lipid bilayer disruption, resulting in cell death, indicating that thyme essential oil could be used as an alternative, or in combination with, antibiotic therapy for persistent infections caused by drug-resistant bacteria [107,108]. Pectin-based active films incorporated with TEO successfully exhibited antioxidant and antibacterial activities [109]. Another study suggested the synergistic antibacterial effect of clove/thyme against *Malassezia furfur* (*M. furfur*). Results of the fungal growth curve, fungal morphology, and cell membrane permeability revealed that the EO combination has a negative effect on the membrane of fungal cells [110]. A comprehensive study on *Mentha longifolia* essential oil investigated chemical composition and bioactivity. The study identified menthol, 1,8-cineol, limonene, α-terpineol, carvone, piperitone oxide, pulegone, and menthone as the primary components responsible for their antimicrobial and insecticidal properties [69]. The essential oil demonstrated strong activity against a range of bacterial and fungal pathogens. The essential oil from *Lavandula angustifolia*, containing apigenin, kaempferol, and caftaric acid, significantly inhibited the growth of selected Gram-negative and Gram-positive bacteria as well as *Candida* yeasts. Inhibition of mold growth was observed at an extract dose of at least 1 mL/100 mL [70]. The antibacterial activity of lavender oil against various bacteria commonly associated with skin infections, including *Propionibacterium acnes* and *Staphylococcus epidermidis* [111]. The results indicated that lavender essential oil effectively inhibited bacterial growth, suggesting its potential use in treating acne and other skin conditions [71,72]. These findings open avenues for further research into the bioactive capabilities of essential oils from plants in arid areas as well as highlighting their potential usage as natural antimicrobial, antifungal, and anticancer agents in medicine.

To Evaluate the Potential Mechanisms in Addressing Antibiotic Resistance

Arid zone plants possess unique phytochemicals with diverse mechanisms of action against bacterial pathogens. These compounds can inhibit or kill bacteria through various mechanisms, such as disrupting cell walls, interfering with protein synthesis, and inhibiting DNA replication

(Fig. 1). This section discusses these mechanisms, provides examples of arid zone plants with demonstrated antimicrobial activity, and explores the challenges and opportunities in developing plant-based antibiotics.

Disruption of Cell Membrane Integrity

The disruption of cell membrane integrity is a crucial way in which phytochemicals from plants confer antimicrobial activity [112]. Plant oils and terpenoids, such as thymol and carvacrol, possess strong antibacterial activity because of their inherent lipophilicity [113]. The membrane of bacterial cells is made up of lipids, and it is the physical structure that holds the cell together, maintaining membrane integrity is necessary for the survival and function of bacterial cells [114]. Lipophilic molecules such as thymol and carvacrol affect the inner structure of the bacteria, causing disruption and leakage of cellular components, including ions and metabolites, thereby altering membrane structure and function [115]. Mitochondrial membrane potential is the driving force of several metabolic pathways, such as adenosine triphosphate (ATP) generation through oxidative phosphorylation and the translocation of nutrients into the cell [116]. Damaging the membrane structure severely impacts the synthesis of proteins, DNA repair, and other vital processes like the production of heat shock proteins [114]. One particular study showed that thymol alters the permeability of some bacteria by breaking down the integrity of cell membranes, leading to membrane disruption and cell lysis [117]. Thymol essential oil showed a significant reduction in mature *Salmonella enteritidis* (*S. enteritidis*) biofilm at 624 µg/mL, while a combination of carvacrol and thymol reduced *Salmonella* spp. cells on polypropylene [118].

Similarly, carvacrol and oregano have also received much attention for their antimicrobial properties [119]. Luteolin (LUT) has predominantly bactericidal effects by inducing oxidative stress in bacterial cells, resulting in severe cellular damage, suppression of metabolic and respiratory activities, and abnormalities in energy metabolism, ultimately causing bacterial cell death [120]. Essential oil containing α-pinene, o-cymene, sabinene, and β-myrcene from *Juniperus communis* has demonstrated antibacterial and antibiofilm properties [121]. Moreover, thymol and carvacrol, lipid-soluble compounds, can be penetrated through membrane barriers, disrupting key elements of bacterial membranes and affecting their pump functions. Developing new antimicrobial protocols is promising, particularly in the context of growing antibiotic resistance.

Inhibition of Cell Wall Synthesis

Phytochemicals derived from arid zone plants are highly effective in inhibiting the synthesis of peptidoglycan, a crucial component of the bacterial cell wall [122]. The bacterial cell wall is very important for maintaining structural integrity, allowing cells to resist high osmotic pressure and other physical stressors [123]. When the cell wall is not properly functioning, bacteria become very sensitive and ultimately undergo lysis and death [115]. Among these, flavonoids like quercetin and kaempferol are the most potent inhibitors of peptidoglycan synthesis. These compounds are effective against the bacteria by blocking the activity of enzymes needed to synthesize peptidoglycan, trans-glycosylase, and transpeptidase [124].

Quercetin blocks the function of the enzyme trans-glycosylase by inhibiting the elongation of glycan strands that form the cell wall structure by anchoring to the active sites of trans-glycosylase enzymes [125]. This inhibition slows down cell wall metabolism, significantly reducing bacterial number [126]. Similarly, kaempferol interferes with the activity of linking peptide chains, which contributes to the strength of the peptidoglycan matrix [127,128]. Prosojuliflavone, from *Prosopis juliflora*, has been shown to inhibit bacterial growth by targeting peptidoglycan synthesis [129]. Quercetin-treated bacteria exhibited cell wall defects, making them more susceptible to external stressors [130].

Inhibition of Protein Synthesis

The inhibition of protein synthesis is a critical mechanism through which certain phytochemicals exert their antimicrobial effects [131]. Protein synthesis is essential for bacterial cell growth, function, and reproduction. Bioactive substances from arid zone plants are capable of altering the bacterial protein synthesis in microbes [132]. For instance, berberine, found in arid zone plants like *Berberis* and *Argemone* species, inhibits protein synthesis in bacteria. Berberine, a physiologically active natural chemical derived from medicinal plants, effectively prevents the growth of *Streptococci*, and its synergistic action with conventional antibiotics can enhance antibacterial properties [133]. Berberine, at a concentration of 20 µg/mL, inhibited the growth of *E. coli*, showcasing its potential as an antibacterial agent [134]. The immense toxicity of pathogenic bacteria has resulted in significant morbidity and mortality worldwide, prompting the demand for stronger antibacterial agents with long-term efficacy. Berberine can specifically target the bacterial ribosomal subunit 50S, which is the integral component of the translation process. Hence, by disrupting this translational process, berberine prevents the formation of the functional ribosome complex required for protein synthesis [135]. As a result, the bacteria are deprived of the proteins and enzymes necessary for cellular metabolism, division, and structural integrity, leading to cell death [136–138]. Additionally, berberine may inhibit DNA synthesis by affecting the activity of DNA topoisomerase and blocking translation through tRNA binding and ribosomal translocation [139]. Another phytochemical, gallic acid is a potent DNA gyrase inhibitor for bacterial DNA. Other phytochemicals such as gallate and dodecyl gallate also have the potential to inhibit bacterial DNA gyrase [140]. Target-driven screening was applied for phytochemicals that can inhibit

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

the activity of *S. aureus* DNA gyrase [141]. The antimicrobial activity of these compounds, particularly against a wide range of bacterial pathogens, highlights their potential as alternative treatments in the context of increasing antibiotic resistance.

Inhibition of Quorum Sensing (QS) and Biofilm Formation

The inhibition of QS and biofilm formation is a highly effective antimicrobial strategy employed by certain phytochemicals from arid zone plants [142]. Quorum sensing is a bacterial communication system that regulates collective behaviors, such as biofilm formation, virulence factor production, and antibiotic resistance [143]. Biofilms help bacteria evade the immune system and develop high resilience to antibiotic treatment [144,145]. Bioactive compounds have been proven to disrupt the QS mechanism through the interaction with signaling molecules, such as acyl-homoserine lactones (AHLs), used by Gram-negative bacteria for communication [146,147]. This disruption inhibits biofilm formation, thus making the bacteria unable to perform their essential functions [143,148]. The key findings highlight plant phenolics such as phenyl propanoids, gallotannins, stilbenes, flavonoids, benzoates proanthocyanidins, and coumarins as well as terpenes as significant inhibitors of both QS and biofilm formation [149]. Terpenes like carvacrol have been shown to reduce the production of virulence factors and inhibit biofilm formation in bacteria like *Pseudomonas aeruginosa* (*P. aeruginosa*) [150]. Carvacrol also inhibits biofilm formation in *Chromobacterium violaceum* (*C. violaceum*), *Salmonella* sps. and *S. aureus* by disrupting bacterial signaling pathways, thereby enhancing the efficacy of antibiotic treatments [150–152].

Additionally, furanones, which are structurally similar to AHLs, can competitively inhibit AHL binding to bacterial receptors [153]. This competition prevents the activation of QS-regulated genes, thereby inhibiting biofilm formation and reducing bacterial virulence [154,155]. For example, the crude extraction of *Proteus mirabilis* has been investigated for its anti-infective properties against biofilm-forming bacteria [156]. Essential oils such as MLT-EO (containing piperitenone, carvone, and piperitone) have shown inhibitory effects against *Candida parapsilosis* [157]. The components of *Ferula asafoetida* L. (*Ferula*) and *Dorema aucheri* (*Dorema*) have been shown to exhibit anti-quorum sensing effects against *P. aeruginosa* at a 25 µg/mL concentration [158]. Furthermore, berberine from *Coptidis rhizoma* and other herbs showed significant antibacterial and biofilm inhibition effects [159]. Study also demonstrates that compounds like octyl gallate, scutellarein, and wedelolactone can inhibit the pathways of biofilm formation in *E. coli* [160]. Phytochemicals from *Passiflora edulis* have been shown to significantly reduce violacein production, AHLs, extracellular polymeric substance (EPS), and biofilm formation, thus inhibiting quorum sensing [161]. This disruption reduces bacterial pathogenicity and makes them more vulnerable to conventional antibiotics. The anti-QS and antibiofilm properties of these compounds need to be explored future for potential pharmacological applications.

Integration of Nanotechnology and Phytochemicals for Overcoming Antibiotic Resistance

In recent years, the combination of nanotechnology with phytochemicals has emerged as a promising potential for developing next-generation antimicrobial agents [162]. Phytochemicals—bioactive compounds derived from plants have been well-recognized for their antimicrobial traits. However, their clinical application is limited by factors such as poor solubility, stability, bioavailability, and rapid degradation in the body. Nanotechnology offers a solution to overcome these limitations by enabling the encapsulation, targeted delivery, and controlled release of phytochemicals, thereby enhancing their therapeutic potential [163]. Nanoparticles (NPs) have played important roles in addressing neurological, bone, and cardiovascular diseases for human health [164–168]. The section covers various aspects of targeted delivery, controlled release, enhanced biofilm penetration, antibiotic synergies, multi-functional antimicrobial actions, and methods to combat multi-drug resistance (Fig. 2) [169].

Targeted Delivery and Controlled Release

One of the primary advantages of integrating nanotechnology with phytochemicals is the ability to achieve targeted delivery and controlled release of antimicrobial agents [162,170]. NPs such as liposomes, polymeric NPs, and metallic NPs as ideal carriers for phytochemicals, due to their small size, biocompatibility, and ability to be functionalized with targeting ligands [171]. These NPs can be engineered to specifically target bacterial cells or infected tissues by exploiting differences in pH, temperature, or specific bacterial markers [172]. For instance, NPs can be designed to release their cargo molecule in response to the acidic environment of the infection site, where the pH is typically lower than in healthy tissues. This pH-sensitive release mechanism ensures that the phytochemicals are delivered directly to the site of infection, thus avoiding off-target effects and enhancement of antimicrobial activity [173]. Moreover, NPs can be functionalized with ligands that recognize and bind to bacterial surface proteins or polysaccharides, further enhancing the specificity of delivery [174]. For example, NPs coated with antibodies or peptides that target bacterial adhesins can selectively bind to bacteria, ensuring that the phytochemicals are released close to the bacterial cells, where they can exert their strong antimicrobial effects [175]. The controlled release of phytochemicals from NPs can be achieved through var-

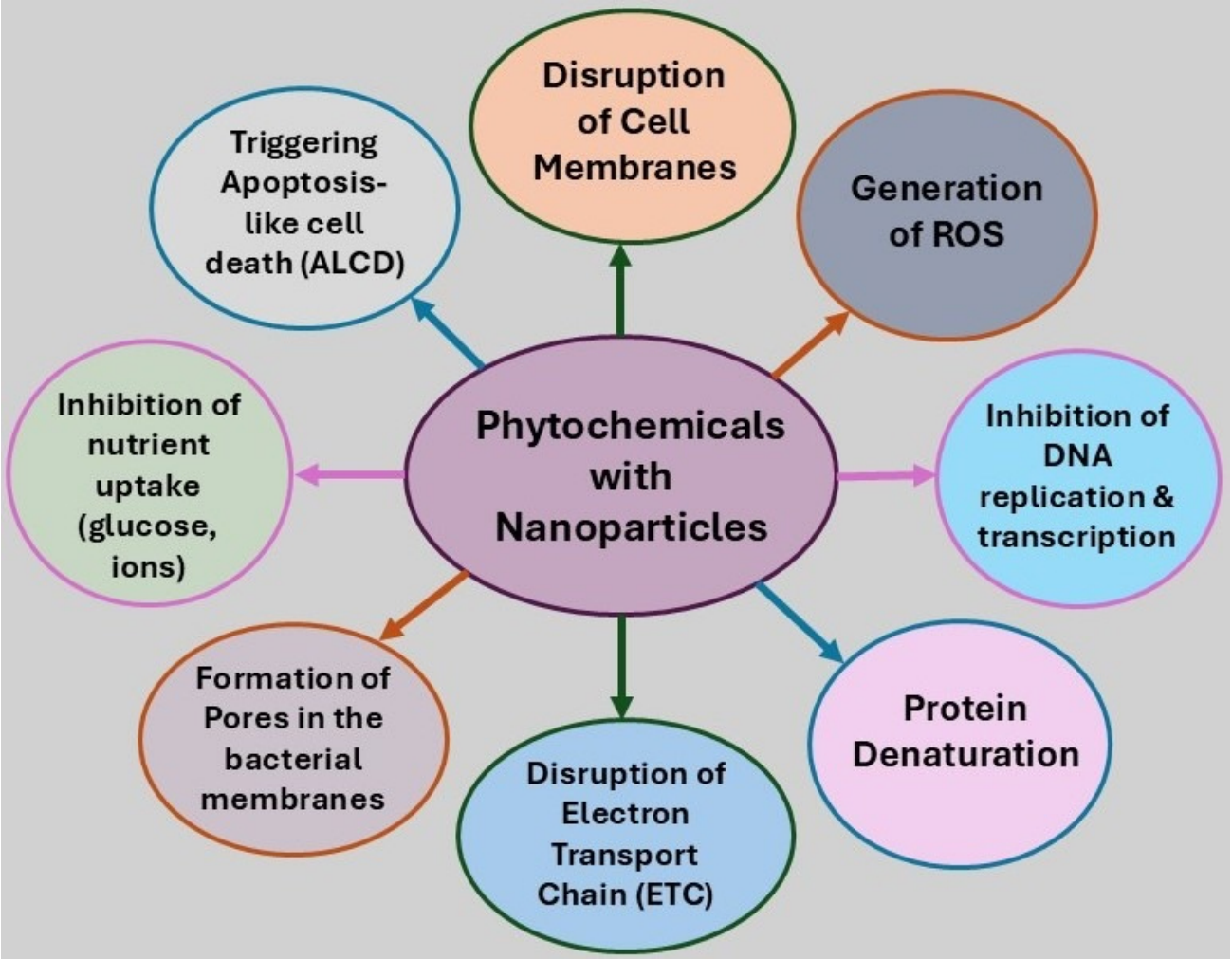

Fig. 2. The advantages of integrating nanotechnology with phytochemicals involve different modes of action on bacterial cells. ROS, reactive oxygen species.

ious mechanisms, including diffusion, degradation of the nanoparticle matrix, or external triggers such as light, temperature, or magnetic fields [176–178]. This controlled release allows for a sustained release of the antimicrobial agents over an extended period, maintaining therapeutic concentrations at the infection site and reducing the need for frequent dosing [16]. This is particularly advantageous in the treatment of chronic infections, where continuous exposure to antimicrobial agents is necessary to eradicate persistent bacterial populations [179].

Huang *et al*. [180] conducted a systematic study on the potential of liposomal encapsulation for flavonoids such as luteolin, quercetin, and kaempferol. Liposomes loaded with quercetin exhibited higher stability and stronger antioxidant capacity than those loaded with other flavonoids. Quercetin nanoliposomes (QT-NLs) were prepared to induce apoptosis in MCF-7 human breast cancer cells for cancer treatment [181]. Carrageenan/Ag-NPs hydrogel beads with encapsulated extract of *Citrullus colocynthis* showed significant antibacterial activity against *S. aureus*, MRSA, *P. aeruginosa*, and *E. coli* [182]. Copper oxide nanorods (CuO NRs) loaded with the extract of *Momordica charantia* demonstrated significant antimicrobial activity against various resistant human pathogens, including Gram-positive and Gram-negative bacteria [183].

Enhanced Penetration and Disruption of Biofilms

Biofilms are a major cause of persistent bacterial infections because they exhibit natural resistance to most antibiotics [184]. The structural organization of biofilms involves bacteria embedded in an EPS matrix which prevents the penetration of antimicrobials and immune defenses [185]. Another factor leading to biofilm resistance is the dormancy of bacterial cells, where their metabolic activity decreases and prevents the action of bactericidal antibiotics [186]. Phytochemicals have shown promise in interfering with and disrupting biofilms, although their ability to penetrate the EPS matrix is often limited [187]. The employment of nanotechnology is a promising solution to address this issue by increasing the penetration of phyto-

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

chemicals into biofilms. Because of their small size, NPs can be produced with surface modifications to achieve more efficient biofilm structure penetration than free drugs [188]. The NPs can release their phytochemical cargo, which interacts with either the EPS or the bacterial cells [173]. Besides, NPs can be designed to have components comprised of different antibacterial agents that are synergistically administered in combination with phytochemicals and conventional antibiotics [189].

Many of these features are present in both natural systems isolated from plants and in manufactured systems such as NPs and nanocomposites. We emphasize the benefits and efficacy of several natural and synthetic chemicals as a new treatment method to manage bacterial biofilms and address MDR in bacteria [169]. The intrinsic anti-bacterial effects of these metal NPs are mostly attributable to the generation of reactive oxygen species (ROS), which target bacterial DNA, proteins, and membranes, leading to cell death. Plant compounds can be incorporated into NPs to further disrupt and kill bacteria within biofilms [190]. Moreover, the surface of NPs can also be functionalized with bioactive molecules such as enzymes that cleave and degrade the EPS matrix, allowing penetration and enhanced antimicrobial action in biofilms [191].

This strategy enhances the effectiveness of phytochemicals in disrupting biofilms and decreasing antibiotic resistance in bacteria. Silver (AgNPs), copper (CuNPs), and zinc oxide nanoparticles (ZnONPs) have been evaluated for their antibacterial and biofilm removal effectiveness against *Enterococcus gallinarum*, *Staphylococcus haemolyticus*, *Enterobacter aerogenes*, and *Salmonella enterica*. These results suggest that NPs can be effectively utilized as antimicrobial agents and biofilm disruptors, offering a promising approach to managing microbial pathogens responsible for severe infections [191]. Ag-doped CuO nanoparticles synthesized using the extract of *Heracleum persicum* exhibited antibacterial activity against *S. aureus*, *Enterococcus faecalis*, *E. coli*, and *Klebsiella pneumoniae* (*K. pneumoniae*) [192]. Another biogenic cerium oxide-supported osmium oxide nanoalloy (CeO_2/OsO_4 NA), synthesized using the extract of *Oldenlandia umbellata* plant exhibited 93% antimicrobial activity against *E. coli*, *S. aureus*, *K. pneumoniae*, *Bacillus subtilis*, and MDR *P. aeruginosa* [193]. The antimicrobial activity of the plant extracts of Prickly Pear and AgNPs was evaluated against standard strains of Gram-positive bacteria (*S. aureus*, *E. faecalis*, *S. mitis*, *K. pneumoniae*, and *S. epidermidis*), as well as Gram-negative bacteria (*E. coli* and *P. aeruginosa*) [194]. AgNPs and CuNPs derived from *Prosopis cineraria* showed enhanced antimicrobial activity against MDR human pathogens, including Gram-positive and Gram-negative bacteria [195]. Gallic acid-coated ZnO NPs and tobramycin-coated contact lenses exhibited significant antibacterial, antifungal, and antibiofilm activity against MDR bacteria [196]. The chitosan–AuNPs synthesized from *Punica granatum* L. extract improved the antibacterial activity against antibiotic-resistant bacteria [197]. The antimicrobial activities of the NPs from *Cotyledon orbiculata*, were reported to have antimicrobial effects against skin pathogens like *S. aureus*, *S. epidermidis*, *P. aeruginosa,* and *C. albicans*. The nanofibrous dressings made from poly-ϵ-caprolactone/gelatin loaded with the antibiotic minocycline and infused with *Gymnema sylvestre* extracts demonstrated potent antimicrobial and antibiofilm properties [198]. Curcumin-encapsulated AgNPs nanofibers demonstrated synergistic antibacterial activities [199]. The antibacterial properties of myrrh/poly(vinyl alcohol)/*Thymus vulgaris* (PVA/TG) nanofibers produced by electrospinning showed increased zone of inhibition activity against *Escherichia fergusonii* (*E. fergusonii*), *P. mirabilis*, *Aeromonas enteropelogenes*, and *S. aureus* with an increased ratio of myrrh extract [200]. The phytochemicals of *Thymus vulgaris*, *Salvia officinalis folium*, and *Hyperici herba* were combined with PVA nanofiber and evaluated for significant antimicrobial activity [42]. The chitosan NPs with phytochemicals derived from *Pelargonium graveolens* exhibited positive effects on the infected area [42].

Synergistic Effects of Nano-Phytomedicine with Conventional Antibiotics

The combination of nanotechnology, phytochemicals, and traditional antibiotics presents an opportunity to utilize synergistic effects for enhanced antimicrobial action [201]. Antibiotic resistance often arises from bacterial mechanisms such as the overexpression of efflux pumps, modification of drug targets, and the production of enzymes that degrade antibiotics. Phytochemicals can interfere with these resistance mechanisms, restoring the effectiveness of antibiotics against resistant microbes [174]. NPs allow for the co-delivery of phytochemicals and antibiotics at specific target sites with appropriate molecule compositions, which can be effective in overcoming resistance mechanisms [202].

Phytochemicals have been shown to inhibit bacterial efflux pumps, which are responsible for the efflux of antibiotics from bacterial cells, thus reducing the intracellular concentration of the drug [203]. By inhibiting these efflux pumps, phytochemicals can improve the intracellular accumulation of antibiotics, increasing their efficacy against resistant bacteria [204]. The combination of phytochemicals with antibiotics can reduce the minimum inhibitory concentration (MIC) of antibiotics, leading to a decrease in drug dosage and thus reducing the side effects associated with high antibiotic concentrations [201,205]. NPs can encapsulate these antibiotics, shielding them from degradation until they reach the bacterial cells [206,207]. Upon reaching the bacteria, the NPs can release the antibiotics, allowing them to exert their bactericidal effects [208]. Phytochemicals can further enhance this effect by inhibiting the pro-

duction or activity of beta-lactamases, ensuring that antibiotics remain effective [209]. Nano-phytomedicines are biocompatible, safe, well-defined, and offer an alternative to conventional antibiotics [210]. Moreover, phytochemical-loaded NPs have shown increased interaction with bacterial cells, providing an opportunity to harness synergistic effects by combining nanotechnology with antimicrobial agents [211]. Antibiotic resistance frequently arises from mechanisms like the overexpression of efflux pumps, modification of drug targets, and the production of enzymes that degrade antibiotics [208]. However, phytochemicals can counter these resistance mechanisms, even in resistant bacteria, thereby restoring the effectiveness of antibiotics [188,212]. Nanocarriers can be engineered to deliver phytochemicals and antibiotics together in synergistic proportions, which can be particularly powerful in overcoming resistance mechanisms [213].

For example, antibiotics of amoxicillin and potassium clavulanate were co-encapsulated using mesoporous iron carboxylate metal-organic framework (nanoMOF) NPs and have been shown to effectively reduce bacterial infection of *S. aureus* [214]. *In vitro* evaluation of antibiotic-loaded hybrid NPs against *P. aeruginosa* biofilms, consisting of poly (lactic-co-glycolic acid), phosphatidylcholine, and levofloxacin, demonstrated slower antibiotic release due to lipid inclusion. However, these NPs demonstrated increased antibacterial activity against biofilm cells than polymeric NPs, exhibiting increased effectiveness in antibiotic mechanism, and release rate against MDR [215]. The NPs encapsulated with rifampin and azithromycin have competently targeted infected cells, and reduced microbial burden, with combination therapy proving more effective than individual drugs on antibiotic-resistant bacteria *Chlamydia trachomatis* and *C. pneumoniae* [216]. Novel antibiotic SV7 shows promise against MRSA infection, but its low solubility is a challenge. Costabile *et al*. [217] demonstrated that poly(lactic-co-glycolic) acid (PLGA) NPs encapsulated with SV7 improved solubility and sustained release as a potential therapy for MRSA lung infections. The poly(ethylene glycol) (PEG)–PLGA NPs loaded with ciprofloxacin showed controlled and effective delivery to target sites, combating *E. faecalis* infections [218]. Moreover, *in vitro* study showed that phytochemicals from plants like *Berberis aristata*, *Syzygium aromaticum*, *Rhus cotinus*, *Phyllanthus emblica*, and *Allium sativum* exhibited synergistic antibacterial action by inhibiting efflux pumps in *S. typhimurium*, highlighting their potential as powerful antimicrobial agents [219].

Overcoming Multidrug Resistance

The treatment of bacterial infections is significantly hindered by MDR, which now has become a bigger issue that decreases the sensitivity to antibiotics on microbes and is occurring regardless of the mechanism [220]. The nanotechnology integrated with phytochemicals would be the conceivable approach to reduce the infection of MDR [221]. The development of NPs with phytochemicals aims to co-deliver drugs along with efflux pump inhibitors, thus protecting the activity of the antibiotic (Fig. 3). The co-delivery system can bring about a reversal of resistance in MDR-bacteria and enhance the effectiveness of current antibiotics [207,222]. Another approach involves the use of NPs to circumvent conventional mechanisms of resistance [223]. The design of NPs can penetrate bacterial membranes and cause a type of rupture that does not rely on bacterial resistance mechanisms [213]. NPs themselves can demonstrate antimicrobial properties, which could be augmented when they are combined with phytochemicals [188]. There are ongoing clinical and preclinical studies combining phytochemicals with nanotechnology. Preclinical studies have shown great potential in combining phytochemicals with nanotechnology for various therapeutic applications. One such example involves thyme, an alkaloid found in plant *Thymus vulgaris*, known for its antimicrobial and anticancer properties, and has limited clinical use due to low bioavailability [67,68]. In a preclinical study, the nanoparticle formulations improved the antimicrobial activity of TEO, showing higher antibacterial efficacy *in vitro*. *In vivo* studies in mice with bacterial infections demonstrated that EO-loaded nanoparticles significantly reduced bacterial load without causing toxicity, suggesting this combination could be a novel approach for treating resistant bacterial infections. The quercetin nanoliposomes have shown enhanced stability and stronger antioxidant properties compared to free quercetin [181]. These nanoliposomes have been evaluated in the treatment of cancer cells like MCF-7, showing promising apoptotic effects. Azizi *et al*. (2017) [182] developed a nanocomposite with silver nanoparticles (AgNPs) encapsulated in carrageenan and loaded with *Citrullus colocynthis* extract. This formulation demonstrated effective antibacterial activity against multidrug-resistant strains *P. aeruginosa*, and *E. coli*. This preclinical study evaluated copper oxide nanorods combined with *Momordica charantia* extract, demonstrating significant antimicrobial effects against both gram-positive and Gram-negative bacteria [183]. Metallic NPs such as silver (Ag), gold (Au), zinc oxide (ZnO), and titanium dioxide (TiO_2) NPs are recognized for their broad-spectrum antimicrobial activity. The combination of metallic NPs and phytochemicals will increase the effectiveness in the killing of MDR bacteria [224]. These NPs can kill bacteria through several different mechanisms, including the production of ROS, disruption of cell membranes, interference with bacterial enzyme function, and repression of DNA replication [213]. The AuNPs, which are principally capable of generating ROS can be combined with medicinal herbs such as ginseng or garlic, which possess properties that inhibit kinases or promote the breakage of DNA strands [225].

Garcinia mangostana was used to synthesize AgNPs, AuNPs, and platinum (Pt)NPs in a green route demon-

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

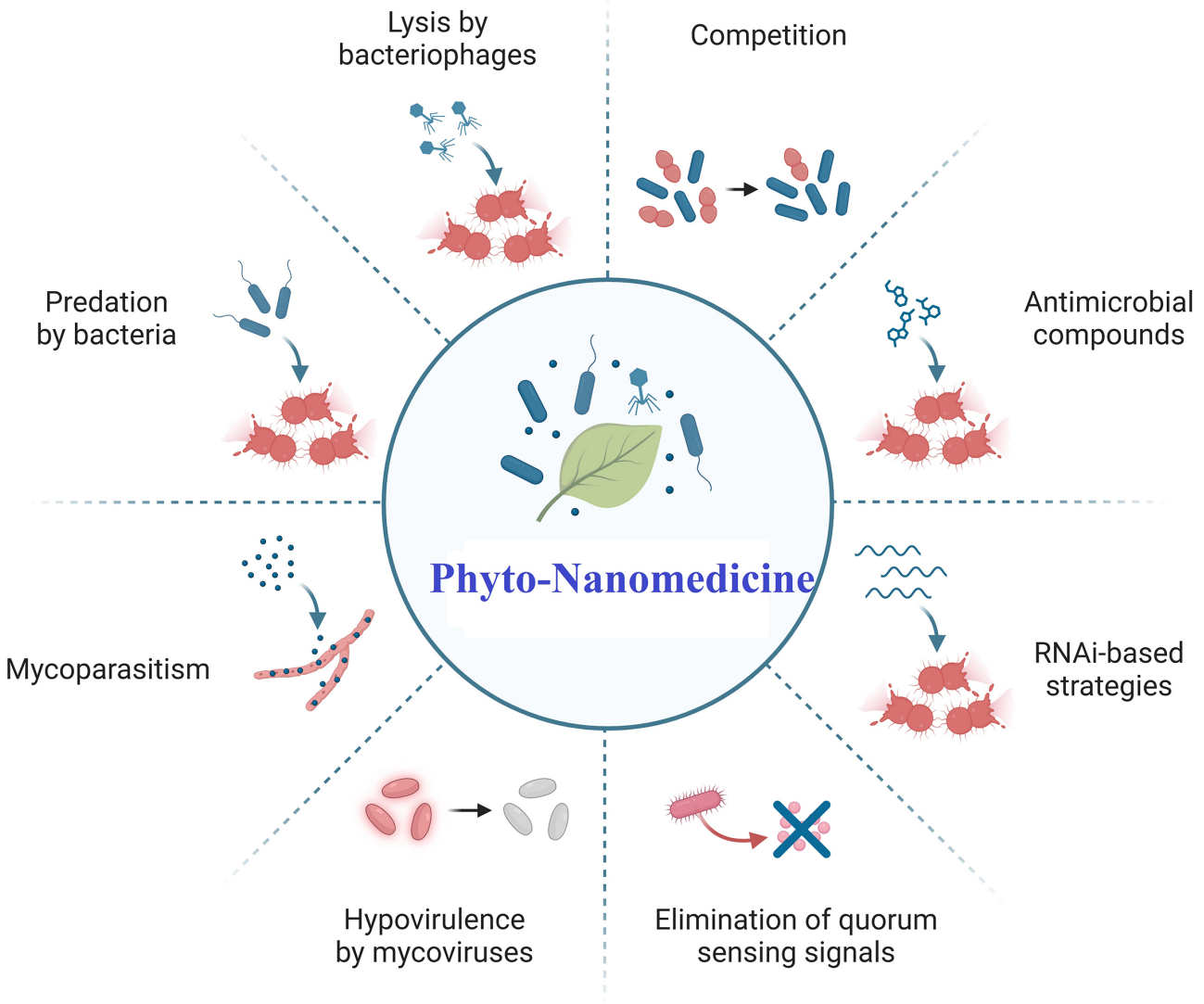

Fig. 3. Schematic representation of various modes of action of phyto-nanomedicine to overcome MDR. This figure was drawn using the BioRender tool (https://www.biorender.com/).

strating antibacterial synergism. Notably, *Bacillus* species resistant to streptomycin became highly sensitive when coupled with AuNPs. This study indicates the potential therapeutic implications of combining NPs with antibiotics to treat antibiotic-resistant bacteria [226]. Another study demonstrated the use of AgNPs synthesized using *Anastatica hierochuntica* and *Artemisia absinthium* as a feasible approach for large-scale manufacturing of antibacterial molecules [227]. Myricetin (MYR)-coated ZnO nanocomposites have shown antibacterial properties, making them effective candidates for treating *Clostridium perfringens* infections [228]. Another study explored that myricetin/tannic acid NPs and chitosan-derived microgels were combined to create antimicrobial films that were designed to eradicate harmful microorganisms [229].

The germicidal plasmid-curing agents are effective in curtailing the dissemination of resistant plasmids in bacterial populations, thus increasing bacterial sensitivity to antibiotics. The delivery of bacteriophages that infect and inhibit/kill bacteria, can be improved by NPs that also hinder the movement of efflux pumps and plasmids [230]. Bacteriophages can be combined with nanocarrier to produce dual-action antimicrobial therapy [231]. Phytochemicals and bacteriophages-loaded NPs ensure that both are delivered simultaneously to the site of infection [223]. The phage preparation lyses the target bacterium, while the phytochemicals are targeted to inhibit resistance mechanisms, leading to more effective treatment. Elsayed *et al.* [232] suggested that *L. monocytogenes* phage (LMP3) and Ag-NPs could be used in combination for effective and eco-friendly antibacterial treatments against multidrug-resistant *L. monocytogenes* in livestock. Encapsulating MRSA-specific phages with chitosan-based NPs increased their lytic activity and resilience under adverse circumstances,

indicating a feasible technique for controlling multidrug-resistant MRSA in poultry farms [233]. This combined approach efficiently delivers plasmid-curing agents, targeting and destroying plasmids responsible for antibiotic-resistance genes [234].

Discussion

Nanotechnology enhances the therapeutic capacity of arid zone plant-sourced phytochemical antimicrobial drugs, representing a breakthrough in the fight against antibiotic resistance. By improving drug delivery, bioavailability, and targeted action, NPs ensure that phytochemicals can effectively reach the targeted sites of infection for effective therapeutics. Controlled release capabilities minimize toxicity and reduce the risk of resistance formation. The administration of arid plant-based antimicrobial drugs in combination with conventional antibiotics through nanocarriers can trigger excellent synergistic effects, significantly enhancing antibiotic activity against resistant bacteria, reducing required dosages, and minimizing selective pressure for resistance, thus slowing the emergence of resistance among microbes. Therefore, this strategy holds great potential for addressing MDR-related challenges. Here, we discussed some key areas for future consideration, which include:

I. **Phytochemical Delivery with Optimization of Nanocarriers**: The optimization of nanocarrier types employed for the delivery of phytochemicals needs to be the main emphasis of studies in the future. Liposomes, polymeric nanoparticles, metallic nanoparticles, and nanocomposites, amongst others, must be further studied for their role in protecting antimicrobial drugs from degradation and enabling controlled release at the site of infection or disease.

II. **Mechanistic Studies**: More research is required to fully understand the mechanisms by which nanotechnology enhances the bioavailability and efficacy of phytochemicals. Studies should explore the interaction between different types of nanoparticles and phytochemicals at the molecular level, and their effects on MDR bacterial cells and biofilms for future therapeutic applications.

III. **Synergistic Effects**: Combining phytochemicals with conventional antibiotics or other therapeutic agents offers a promising strategy. Future studies should aim to explore the synergistic effects between nanotechnology-enhanced phytochemicals and existing other antimicrobial agents/drugs to reduce antibiotic resistance, enhance antimicrobial activity, and improve therapeutic outcomes in other diseases like cancer and inflammation.

IV. **Targeted Delivery Systems**: There is a need for the design and development of sophisticated next-generation targeted delivery systems to ensure the delivery of phytochemicals directly into infected or diseased tissues, whether they are bacterial infections, tumors, or other diseases. Moreover, novel nanocarriers triggered by pH, temperature, or other biological stimuli should be studied for site-specific drug release.

V. **Toxicity and Biocompatibility**: Ensuring the biocompatibility and non-toxicity of nanocarriers and nanocomposites is a major challenge in clinical applications. Some nanoparticles, particularly metallic nanoparticles, can accumulate in the body, causing potential long-term side effects. Future studies must rigorously assess the safety and biocompatibility of these nanomaterials.

VI. **Scalability and Cost**: The large-scale synthesis of nanoparticles/nanocarriers and nanocomposites for targeted drug delivery is technologically challenging and costly. For phytochemical-loaded nanoparticles/nanocarriers to be clinically viable, production methods must be cost-effective without compromising stability and functionality.

VII. **Regulatory Hurdles**: The nanotechnology-based therapeutics have to go through stringent regulatory approval procedures, which may be cumbersome and time-consuming. Combining phytochemicals with nanotechnology in the preparation of formulations brings complexity, as both the natural phytochemicals and the nanosystems fulfill the standards for safety and efficacy for human use.

VIII. **Clinical Translation and Long-term Efficacy**: Despite promising preclinical studies, translating nanotechnology-enhanced phytochemicals into clinical settings remains a challenge. Long-term studies assessing the efficacy and safety of these systems in humans are still limited. The variability in human responses to natural compounds, coupled with the novel nature of nanotechnology, makes it difficult to predict outcomes in clinical trials.

IX. **Addressing Multidrug Resistance**: Although MDR remains a challenge, nanotechnology-improved phytochemicals have immense potential in surmounting multidrug resistance. The problem of MDR is very complex and multifactorial in nature; therefore, further studies are warranted to ascertain how well these combinations prevent tachyphylaxis (rapid adaptation of bacteria) in environments where bacterial resistance evolves quickly. The results of plant-based antimicrobials and nanotechnology are a strong strategy for overcoming multidrug resistance.

Conclusions

The emerging threat of antibiotic resistance demands the discovery of new antimicrobial agents, wherein arid zone plants are a potential source. These plants synthesize several types of bioactive compounds such as alkaloids, flavonoids, terpenoids, and phenolic acids, which have demonstrated excellent efficacy as antimicrobials, antioxidants, and anti-inflammatory agents. These phytochemicals act against the bacterial cell membrane, inhibit protein

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

synthesis, or interfere with DNA replication, thereby acting as a natural alternate choice to conventional synthetic antibiotics. Nanotechnology has emerged as an important means of augmenting the usefulness of arid plant phytochemicals. Nanoparticles, including those of silver, gold, and zinc oxide, stabilize the phytoconstituents and enhance their bioavailability with controlled release. Further, it enables better permeation through biofilms and site-specific delivery to infection sites, thereby enhancing the *in vivo* antimicrobial activity while minimizing adverse side effects.

Preclinical studies have demonstrated encouraging results, showing improved antimicrobial activities against multidrug-resistant strains. Nevertheless, several challenges remain for clinical translation, including nanoparticle toxicity, biocompatibility, and the scalability of production methods. Approval by the corresponding regulatory agencies is rather complicated, while longer clinical studies on humans are urgently needed concerning safety and efficacy. The battle against antibiotic resistance in the future will require a coordinated effort that integrates bio-based solutions, precision technologies, and eco-friendly products from natural resources. Collaborative research and development initiatives focused on drought-resistant plants, and medicinal plants with synergistic effects should be prioritized by both industry and government agencies.

Availability of Data and Materials

This article is a review and does not involve the generation or use of original data. All data discussed are available in the cited reference.

Author Contributions

TG: Conceptualization, Methodology, Data curation, Writing-original draft, Investigation, Visualization, Writing-review & editing. SSH: Data curation, Writing-original draft. KBN: Investigation, Visualization, Data curation, Writing -original draft, Investigation. EM: Methodology, Supervision, Visualization. RB: Data curation, Supervision, Writing-review & editing. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest.

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