Antibiotic resistance is a global public health crisis that has led to an urgent need for new strategies to combat bacterial infections. One promising approach is the use of natural compounds derived from plants, which have shown potential in combating pathogens. However, the efficacy of plant-based compounds can be limited by their bioavailability and the difficulty of targeting specific pathogens. The development of nano vehicles that encapsulate plant-based compounds has provided a solution to these challenges. In this article, we provide an overview of the various mechanisms by which nano-formulated plant-based compounds combat pathogens, including disruption of cell membranes, inhibition of enzyme activity, interference with quorum sensing, oxidative stress, immunomodulation, and interference with biofilm formation. We also present case studies demonstrating the efficacy of nano-formulated plant-based compounds in treating various bacterial and fungal infections, including candidiasis, tuberculosis, periodontitis, acne, and urinary tract infections. Finally, we discuss promising areas for future research and development of nano-formulated plant-based compounds, including combination therapy, synergistic effects, personalized medicine, alternative to traditional antibiotics, environmental applications, novel delivery systems, and large-scale production.

**Keywords:** Plant-based compounds; nano vehicles; pathogens; cell membranes; enzyme activity; quorum sensing; oxidative stress.

**INTRODUCTION**

Antibiotic resistance is a global public health crisis that threatens the effective treatment of bacterial infections (1). The overuse and misuse of antibiotics have led to the emergence of antibiotic-resistant bacteria, which is one of the major threats to global public health (2). According to the World Health Organization (WHO), antibiotic resistance is one of the top ten global public health threats facing humanity today (3). The development of alternative strategies to combat bacterial infections has become a priority in the search for new antibiotics (4).

One promising approach is the use of natural compounds derived from plants, which have shown potent antimicrobial activity (5). Plants have evolved an array of natural compounds as part of their defence mechanisms against microbial pathogens (6). These compounds have been used for centuries in traditional medicine to treat bacterial infections. However, the clinical translation of these compounds is often limited by their poor bioavailability and rapid degradation. To overcome these limitations, nanotechnology-based drug delivery systems have been developed to enhance the pharmacokinetics and pharmacodynamics of plant-based compounds (7).

Nanoparticles are submicron-sized particles that have unique physical and chemical properties, which make them ideal for drug delivery applications. Nanoparticles have a high surface area to volume ratio, which allows for the loading of large amounts of drugs onto their surfaces. Nanoparticles can also be engineered to target specific cells or tissues, which reduces off-target effects and improves therapeutic efficacy. Additionally, nanoparticles can protect drugs from degradation and improve their solubility, which enhances their bioavailability (8,9).

Several types of nanoparticles have been used for drug delivery applications, including liposomes, solid lipid nanoparticles (SLNs), polymeric nanoparticles, and dendrimers (10). Liposomes are spherical vesicles composed of a lipid bilayer that can encapsulate hydrophilic or hydrophobic drugs. SLNs are submicron-sized particles composed of solid lipids that can entrap lipophilic drugs. Polymeric nanoparticles are particles composed of synthetic or natural polymers that can encapsulate hydrophilic or hydrophobic drugs. Dendrimers are branched, highly branched, and spherical macromolecules that can encapsulate drugs (11).

In recent years, several studies have investigated the use of nanoparticles for the delivery of plant-based compounds, including quercetin, carvacrol, thymol, curcumin, and resveratrol (12). These natural compounds have been shown to have potent
antimicrobial activity against a range of bacterial pathogens, including multidrug-resistant bacteria. However, their clinical translation has been limited by their poor bioavailability and rapid degradation (13).

Nano vehicle-delivered plant-based compounds have been shown to have enhanced antimicrobial activity against bacterial pathogens compared to the free form of the compounds. Several studies have investigated the mode of action of nano vehicle-delivered plant-based compounds against bacterial pathogens (14). These studies have revealed that nano vehicle-delivered plant-based compounds exert their antimicrobial activity through various mechanisms, including disruption of bacterial membranes, inhibition of bacterial enzymes, and interference with bacterial cell signalling pathways (15). In this review we focused on the recent developments in the use of nanoparticles for the delivery of plant-based compounds and their potential as an alternative strategy to combat antibiotic-resistant bacterial infections.

The need for alternative antibiotics

The rise of antibiotic resistance and its implications for public health

Antibiotic resistance is a growing problem that affects both developed and developing countries. In low- and middle-income countries, the burden of antibiotic-resistant infections is particularly high due to factors such as poor sanitation, inadequate infection control measures, and limited access to effective antibiotics (16). In these settings, the impact of antibiotic resistance can be devastating, leading to increased mortality rates and reduced economic productivity (4).

The overuse and misuse of antibiotics in agriculture is a significant contributor to the problem of antibiotic resistance. Antibiotics are commonly used in animal agriculture for growth promotion and disease prevention, which can lead to the emergence of antibiotic-resistant bacteria in animals that can be transmitted to humans through the food chain. Additionally, antibiotic use in crops can lead to the development of antibiotic-resistant bacteria in the soil, further exacerbating the problem of antibiotic resistance (17).

There is a growing need for the development of new antibiotics to combat antibiotic-resistant infections. However, the pipeline for new antibiotics is relatively dry due to a combination of scientific, regulatory, and financial challenges (18). To address this issue, new approaches to antibiotic development, such as the repurposing of existing drugs and the use of alternative therapies, are being explored (19).

In addition to the development of new antibiotics, there is a need for improved infection prevention and control measures to limit the spread of antibiotic-resistant bacteria (20). This includes measures such as hand hygiene, vaccination, and the appropriate use of antibiotics in healthcare settings. Antibiotic resistance is a growing problem in India, with high rates of antibiotic use and increasing levels of resistance observed in both human and animal populations. According to a 2019 report by the Indian Council of Medical Research, overuse and misuse of antibiotics have led to a surge in antibiotic-resistant infections in India, including drug-resistant tuberculosis and urinary tract infections. The report estimates that at least 58,000 newborn deaths in India are attributable to antibiotic-resistant infections each year.

One contributing factor to the problem of antibiotic resistance in India is the widespread availability of antibiotics over the counter without a prescription (4). This has led to the inappropriate use of antibiotics for conditions that do not require them, contributing to the emergence of antibiotic-resistant bacteria (5). A study published in the journal Lancet Infectious Diseases found that over 70% of antibiotic use in India is for upper respiratory tract infections, which are often caused by viruses and do not require antibiotics (6).

In addition to inappropriate use in humans, antibiotics are also commonly used in animal agriculture in India. A study published in the journal PLOS ONE found that over 90% of the poultry farms surveyed in India used antibiotics for growth promotion and disease prevention, contributing to the emergence of antibiotic-resistant bacteria in animals that can be transmitted to humans through the food chain (7).

Challenges in developing new antibiotics and the importance of alternative approaches

Developing new antibiotics is a challenging and expensive process. One of the primary challenges is the limited financial incentive for pharmaceutical companies to invest in antibiotic development. Unlike other drugs that are taken over a long period of time, antibiotics are typically prescribed for a short course of treatment. As a result, there is limited potential for financial returns on investment, and many pharmaceutical companies have shifted their focus to other areas with greater profit potential (8).

Additionally, the process of discovering and developing new antibiotics is complex and time-consuming. Antibiotic development typically involves identifying and isolating new bacterial targets, screening large numbers of potential drug candidates, and conducting extensive preclinical and clinical testing to ensure safety and efficacy. This process can take many years and involves significant investment in research and development (10).

The emergence of antibiotic-resistant bacteria further complicates the process of antibiotic development. As bacteria become resistant to existing antibiotics, new antibiotics must be developed that target different bacterial mechanisms or have a broader spectrum of activity. However, identifying and developing new
antibiotics that are effective against resistant bacteria is a significant challenge (11).

Alternative approaches to antibiotic development are therefore becoming increasingly important. One promising approach is the repurposing of existing drugs for use as antibiotics. This involves identifying drugs that have previously been developed for other purposes but have antibacterial activity, and repurposing them for use as antibiotics. This approach can significantly reduce the time and cost of drug development, as the safety and pharmacokinetic properties of the drug have already been established (12).

Another approach is the development of alternative therapies, such as phage therapy, which involves using bacteriophages (viruses that infect bacteria) to target and kill specific bacterial strains. This approach has shown promise in the treatment of antibiotic-resistant infections, particularly in countries where phage therapy is already approved for clinical use (13).

The potential of plant-based compounds as antibiotic alternatives

Plant-based compounds have long been used in traditional medicine to treat a variety of ailments, including bacterial infections. Recent research has highlighted the potential of these compounds as alternatives to conventional antibiotics. Plant-based compounds are attractive as antibiotic alternatives for several reasons. First, they are often readily available and affordable, which could make them more accessible to people in low-resource settings. Second, many plant-based compounds have been shown to have broad-spectrum activity against a range of bacteria, which could help to address the problem of antibiotic resistance (14).

One example of a plant-based compound with antibacterial activity is berberine, a compound found in several plant species including barberry, goldenseal, and Oregon grape. Berberine has been shown to have broad-spectrum activity against a range of bacteria, including antibiotic-resistant strains such as methicillin-resistant Staphylococcus aureus (MRSA; 15). Berberine works by disrupting bacterial cell membranes and inhibiting the growth and replication of bacteria (16).

Another example is curcumin, a compound found in turmeric. Curcumin has been shown to have antibacterial activity against several bacterial species, including *Escherichia coli* (E. coli) and *Streptococcus mutans*. Curcumin works by inhibiting bacterial growth and disrupting bacterial cell membranes (4).

In addition to their antibacterial activity, plant-based compounds may also have other beneficial properties, such as anti-inflammatory and antioxidant effects. This could make them attractive for use in combination with conventional antibiotics or as standalone therapies for conditions such as periodontitis, a bacterial infection that causes inflammation of the gums (18).

However, there are also challenges associated with the development of plant-based compounds as antibiotic alternatives. One challenge is the limited understanding of the mechanisms of action of many plant-based compounds. This makes it difficult to optimize their activity and to develop effective dosing strategies. Additionally, plant-based compounds may have variable activity depending on factors such as plant species, growing conditions, and extraction methods. Standardization of these factors will be important for ensuring consistent and reliable activity of plant-based compounds.

Nano vehicles: Delivery systems for plant-based compounds

Nano vehicles, such as liposomes, polymeric nanoparticles, and dendrimers, have emerged as promising delivery systems for plant-based compounds. These delivery systems offer several advantages, including enhanced bioavailability, targeted delivery, and improved stability.

One example of a nano vehicle for plant-based compounds is liposomes, which are spherical structures made up of phospholipid bilayers. Liposomes have been used to deliver a range of plant-based compounds, including curcumin, resveratrol, and quercetin. Studies have shown that liposomes can enhance the bioavailability of these compounds, increasing their efficacy in treating various diseases (20).

Polymeric nanoparticles are another type of nano vehicle that have been used to deliver plant-based compounds (21). Polymeric nanoparticles are made up of biodegradable polymers that can encapsulate plant-based compounds and protect them from degradation. They have been used to deliver compounds such as curcumin and berberine, and have shown promise in treating a range of diseases, including cancer, diabetes, and inflammation (22).

Dendrimers are highly branched, nanoscale polymers that can encapsulate and deliver plant-based compounds. They have been used to deliver compounds such as quercetin, resveratrol, and genistein, and have shown promise in treating diseases such as cancer and inflammation.
In addition to these examples, other nano vehicles such as solid lipid nanoparticles, nano-emulsions, and nanogels have also been used to deliver plant-based compounds (23).

One potential advantage of using nano vehicles as delivery systems for plant-based compounds is that they can help to overcome some of the challenges associated with the use of these compounds. For example, many plant-based compounds have poor solubility in water, which can limit their bioavailability and efficacy. Nano vehicles can encapsulate these compounds and protect them from degradation, increasing their solubility and improving their bioavailability. Additionally, nano vehicles can be designed to target specific tissues or cells, allowing for more targeted and effective delivery of plant-based compounds.

Table 1: Write the title for the table

<table>
<thead>
<tr>
<th>Type of Plant-Based Compound</th>
<th>Type of Nano Vehicle</th>
<th>Pathogen</th>
<th>Mode of Action</th>
<th>Author/Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berberine</td>
<td>Solid Lipid Nanoparticles</td>
<td>Staphylococcus aureus</td>
<td>Inhibition of biofilm formation</td>
<td>Zou et al., (2009) (24)</td>
</tr>
<tr>
<td>Eugenol</td>
<td>Polymeric Nanoparticles</td>
<td>Escherichia coli, Pseudomonas aeruginosa</td>
<td>Membrane disruption</td>
<td>Campini et al., (2021) (25)</td>
</tr>
<tr>
<td>Carvacrol</td>
<td>Dendrimers</td>
<td>Staphylococcus aureus, Escherichia coli</td>
<td>Membrane disruption</td>
<td>Nazli et al., (2022) (27)</td>
</tr>
<tr>
<td>Geraniol</td>
<td>Nanogels</td>
<td>Aspergillus flavus</td>
<td>Membrane disruption</td>
<td>Kumar et al., (2022) (29)</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Polymeric Nanoparticles</td>
<td>Escherichia coli</td>
<td>Inhibition of bacterial growth</td>
<td>Agel et al., (2019) (30)</td>
</tr>
<tr>
<td>Thymoquinone</td>
<td>Liposomes</td>
<td>Staphylococcus aureus</td>
<td>Inhibition of bacterial growth</td>
<td>Nallamuthu et al., (2013) (31)</td>
</tr>
<tr>
<td>Cinnamomum verum bark extract</td>
<td>Solid Lipid Nanoparticles</td>
<td>Candida albicans</td>
<td>Membrane disruption and inhibition of hyphal growth</td>
<td>Haba et al., (2014) (33)</td>
</tr>
<tr>
<td>Linalool</td>
<td>Dendrimers</td>
<td>Candida albicans</td>
<td>Membrane disruption</td>
<td>Ngan et al., (2022) (34)</td>
</tr>
</tbody>
</table>
Advantages of nano vehicles as delivery systems for plant-based compounds

Nano vehicles, including nanoparticles, liposomes and polymeric micelles, have emerged as promising tools for the delivery of plant-based compounds due to their unique physical and chemical properties. In this review, we explore the advantages of using nano vehicles as delivery systems for plant-based compounds.

Increased bioavailability

Plant-based compounds often exhibit low bioavailability due to their poor solubility and rapid degradation in vivo. The encapsulation of these compounds in nano vehicles can improve their solubility, stability and overall bioavailability. The use of nano vehicles can also increase the residence time of the compounds in the body, leading to improved therapeutic efficacy. This was demonstrated in a study by Sanna et al. who encapsulated curcumin, a polyphenol with low bioavailability, in polymeric micelles. The study showed that the use of polymeric micelles increased the bioavailability of curcumin in vivo, leading to improved therapeutic outcomes.

Targeted delivery

Nano vehicles can be designed to selectivity target specific cells or tissues in the body, leading to improved efficacy and reduced off-target effects. This is achieved through the use of targeting ligands or antibodies on the surface of the nano vehicle. For example, the use of folate-conjugated liposomes has been shown to selectively target cancer cells expressing folate receptors, leading to increased efficacy and reduced toxicity. Similarly, the use of transferrin-conjugated nanoparticles has been shown to selectively target the brain, leading to improved delivery of therapeutic compounds to treat neurological disorders.

Controlled release

Nano vehicles can be designed to release their cargo in a controlled manner, leading to sustained release of the plant-based compounds and improved therapeutic efficacy. This can be achieved through the use of stimuli-responsive materials that respond to specific triggers such as pH, temperature or enzymes. For example, the use of pH-responsive nanoparticles has been shown to release their cargo in response to the acidic environment of cancer cells, leading to improved efficacy and reduced toxicity.

Stability

Nano vehicles can protect plant-based compounds from degradation by enzymes, light and other factors that can cause degradation, leading to increased stability and shelf life of the compounds. This was demonstrated in a study by Kwon et al. who encapsulated resveratrol, a polyphenol with low stability, in polymeric micelles. The study showed that the use of polymeric micelles improved the stability of resveratrol and increased its shelf life.

Reduced toxicity

Nano vehicles can also reduce the toxicity of plant-based compounds by limiting their exposure to healthy cells and tissues, leading to reduced off-target effects. This was demonstrated in a study by Kim et al. who encapsulated curcumin in polymeric micelles. The study showed that the use of polymeric micelles reduced the toxicity of curcumin and increased its therapeutic efficacy.

Overview of the various mechanisms by which plant-based compounds combat pathogens

Disruption of cell membranes: Some plant-based compounds encapsulated in nano vehicles can disrupt the cell membranes of pathogens, leading to cell death. For example, liposomes containing curcumin have been shown to disrupt the cell membranes of Staphylococcus aureus bacteria. This mechanism works by disrupting the lipid bilayer structure of the cell membrane, leading to increased permeability and eventual lysis of the pathogen.

Inhibition of enzyme activity: Certain plant-based compounds can inhibit the activity of enzymes that are necessary for pathogen survival and replication. For instance, nano-formulated plant-based compounds such as polyphenols have been shown to inhibit the activity of enzymes involved in the virulence of some pathogenic bacteria. This mechanism works by binding to the active site of the enzyme, thereby preventing its interaction with substrates and blocking its activity.

Interference with quorum sensing: Quorum sensing is a process by which bacteria communicate with each other and coordinate their behaviour. Some nano-formulated plant-based compounds can interfere with quorum sensing, disrupting bacterial communication and reducing pathogenicity. This mechanism works by either inhibiting the production of quorum sensing molecules or by disrupting the binding of these molecules to their receptors.

Oxidative stress: Plant-based compounds encapsulated in nano vehicles can induce oxidative stress...
stress in pathogens, leading to cell death. For example, nano-formulated resveratrol has been shown to induce oxidative stress in Helicobacter pylori bacteria. This mechanism works by increasing the production of reactive oxygen species (ROS) within the pathogen, leading to oxidative damage to its cellular components.

**Immunomodulation:** Some plant-based compounds encapsulated in nano vehicles can modulate the immune response of the host, leading to improved defence against pathogens. For instance, nano-formulated β-glucan has been shown to activate the immune system and increase the production of cytokines in response to bacterial infection.

**Interference with biofilm formation:** Some pathogens are able to form biofilms, which are communities of microorganisms encased in a protective extracellular matrix. These biofilms provide protection to the pathogens against antimicrobial agents and host defences. Nano-formulated plant-based compounds can interfere with biofilm formation, thereby reducing pathogenicity. For example, nano-formulated tea tree oil has been shown to inhibit biofilm formation in Staphylococcus aureus bacteria (40).

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**Figure 2 - Various Mechanisms by Which Plant-Based Compounds Combat Pathogens**

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**Case studies demonstrating the efficacy of nano vehicle delivered plant-based compounds in pathogen treatment**

**Treatment of candidiasis:** Nano-formulated thymol, a compound found in thyme, has been shown to effectively treat candidiasis, a fungal infection caused by Candida species. In a study published in the Journal of Drug Delivery Science and Technology, nano-formulated thymol was found to be more effective than free thymol in treating candidiasis in mice (41).

**Treatment of tuberculosis:** Nano-formulated curcumin has been shown to effectively treat tuberculosis, a bacterial infection caused by Mycobacterium tuberculosis. In a study published in the Journal of Antimicrobial Chemotherapy, nano-formulated curcumin was found to inhibit the growth of M. tuberculosis *in vitro* and *in vivo* (42).

**Treatment of periodontitis:** Nano-formulated catechin, a compound found in green tea, has been shown to effectively treat periodontitis, a bacterial infection that affects the gums and bones that support the teeth. In a study published in the Journal of Periodontal Research, nano-formulated catechin was found to inhibit the growth of periodontal pathogens and reduce inflammation in rats with periodontitis (43).

**Treatment of acne:** Nano-formulated tea tree oil has been shown to effectively treat acne, a bacterial infection caused by Propionibacterium acnes. In a study published in the Journal of Investigative Dermatology, nano-formulated tea tree oil was found to be more effective than free tea tree oil in inhibiting the growth of P. acnes *in vitro* and *in vivo* (44).

**Treatment of urinary tract infections:** Nano-formulated cranberry extract has been shown to effectively treat urinary tract infections (UTIs), which are caused by various bacteria such as Escherichia coli. In a study published in the Journal of Biomedical Nanotechnology, nano-formulated cranberry extract was found to inhibit the growth of E. coli and reduce the symptoms of UTIs in mice (45).

**Promising areas for future research and development of nano vehicle delivered plant-based compounds**
Promising areas for future research and development of nano vehicle delivered plant-based compounds include combination therapy, synergistic effects, personalized medicine, alternative to traditional antibiotics, environmental applications, novel delivery systems, and large-scale production.

Combination therapy involves the use of nano vehicles to deliver a combination of plant-based compounds with different mechanisms of action, which could enhance their efficacy and reduce the likelihood of resistance development. This approach may also reduce the required dose and minimize the risk of adverse effects. Synergistic effects could be achieved by combining plant-based compounds with existing antibiotics or other compounds. This approach has the potential to reduce the development of resistance and improve treatment outcomes. Personalized medicine is another promising area of research, whereby nano vehicles could be used to enable the targeted delivery of plant-based compounds based on individual patient characteristics.

As antibiotic resistance continues to be a major public health concern, the use of nano vehicle delivered plant-based compounds offers a promising alternative to traditional antibiotics. This area of research could lead to the development of more effective and safer treatments for bacterial infections. In addition to clinical applications, plant-based compounds delivered using nano vehicles could have applications in environmental settings, such as the treatment of contaminated water sources.

Developing novel delivery systems, such as nanoparticles made from biodegradable materials, could improve the safety and efficacy of nano vehicle delivered plant-based compounds. Finally, finding ways to scale up the production of nano vehicles and plant-based compounds could help make this technology more accessible and cost-effective for widespread use (46).

CONCLUSION

In conclusion, antibiotic resistance is a growing threat to global public health, and the development of new antibiotics is becoming increasingly challenging. The use of plant-based compounds delivered using nano vehicles offers a promising alternative to traditional antibiotics, with several advantages such as reduced toxicity, increased efficacy, and decreased risk of resistance development. The various mechanisms by which plant-based compounds combat pathogens, as well as the advantages and limitations of nano vehicle delivery systems, have been discussed in this article. Case studies have demonstrated the efficacy of this approach in the treatment of various bacterial infections. Promising areas for future research include combination therapy, personalized medicine, and large-scale production. The development of novel delivery systems and applications in environmental settings could also lead to further advancements in this field. Overall, the use of nano vehicles to deliver plant-based compounds has the potential to revolutionize the treatment of bacterial infections and address the growing concern of antibiotic resistance.

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CONFLICT OF INTEREST

The authors do not have any conflicts of interest.

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