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Green Nanotechnology for Antimicrobial Resistance: Plant-Derived Nanantibiotics

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Abstract: Antimicrobial resistance (AMR) is accelerating globally, reducing the effectiveness of conventional antibiotics and increasing the burden of persistent infections. Plant-derived antimicrobials such as polyphenols, terpenoids, alkaloids, and essential oils offer broad bioactivity and chemical diversity, but their clinical translation is often limited by poor water solubility, instability, rapid clearance, and variable potency. "Nanoantibiotics" integrate antimicrobial agents with nanoscale carriers or are nanomaterials with intrinsic antimicrobial activity, enabling higher local drug concentration, improved bioavailability, controlled release, and antibiofilm performance. This review summarizes plant-derived nanoantibiotics, focusing on green-synthesized metal/metal-oxide nanoparticles using plant extracts, nanoencapsulated phytochemicals, and phytochemical-functionalized nanocarriers. This review discusses mechanisms of action (membrane disruption, reactive oxygen species generation, enzyme inhibition, and quorum-sensing interference), formulation strategies, antibiofilm and wound-healing applications, and current challenges including standardization, toxicity, and regulatory pathways. Finally, this review outlines future directions such as stimuli-responsive systems, synergistic phytochemical antibiotic co-delivery and scalable green manufacturing.

Keywords: Antibiofilm, Antimicrobial resistance, Green synthesis, Nanoformulation, Polymeric nanoparticles.

1. Introduction

AMR has emerged as one of the most serious threats to public health, driven by antibiotic overuse, limited discovery of new antibiotic classes, and rapid microbial adaptation. Resistant bacteria frequently form biofilms structured communities embedded in extracellular polymeric substances making them up to 10–1000× less susceptible to antimicrobials [1-3]. Natural products from plants have historically contributed to drug discovery and remain a rich source of antibacterial, antifungal, and antivirulence compounds [4-5]. However, many phytochemicals suffer from low solubility, poor stability under light/heat/oxygen, and inconsistent composition across plant sources [6-7].

Nanotechnology provides a route to overcome these barriers. Nano-antibiotics can enhance solubility and protect labile compounds, enable sustained or targeted delivery, improve penetration into biofilms and infected tissues, reduce required dose and off-target toxicity,enable multi-mechanistic killing that reduces resistance development [8-9].

Plant-derived nanoantibiotics broadly fall into three overlapping categories: (i) plant-extract-mediated "green" nanoparticles (e.g., AgNPs synthesized using plant extracts), (ii) nanocarriers encapsulating phytochemicals (e.g., curcumin-loaded polymeric nanoparticles), and (iii) phytochemical-functionalized nanomaterials (e.g., catechin-coated nanoparticles) that combine carrier and active chemistry [3,10,11].

2. Plant-Derived Antimicrobials: Classes and Limitations

2.1. Major Classes of Antimicrobial Phytochemicals

Plant-derived phytochemicals constitute a diverse group of bioactive compounds with well-documented antimicrobial properties. Their mechanisms are often multi-targeted, which reduces the likelihood of resistance development compared to conventional antibiotics. The major classes include polyphenols, terpenoids, alkaloids, and organosulfur compounds, each characterized by distinct chemical features, biological activities, and formulation challenges as shown in **Table1**.

a) Polyphenols (Flavonoids, Tannins, Phenolic Acids)

Polyphenols are one of the most extensively studied classes of plant secondary metabolites, widely distributed in fruits, vegetables, tea, wine, and medicinal plants. Structurally, they contain multiple phenolic hydroxyl groups, which contribute to their redox activity and strong interactions with biological macromolecules.

Antimicrobial mechanisms:

1. **Membrane perturbation:** Polyphenols can interact with bacterial lipid bilayers through hydrogen bonding

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and hydrophobic interactions, leading to altered membrane fluidity, increased permeability, and leakage of intracellular contents.

2. **Enzyme inhibition:** Flavonoids such as quercetin and catechins inhibit key bacterial enzymes involved in cell wall synthesis, fatty acid metabolism, and energy production by binding to active or allosteric sites.
3. **Metal chelation:** Phenolic acids and tannins chelate essential metal ions (Fe^{2+}, Zn^{2+}, Cu^{2+}), depriving microorganisms of cofactors required for enzymatic activity and oxidative stress defense.
4. **Quorum sensing (QS) interference:** Several polyphenols disrupt bacterial communication systems by inhibiting autoinducer synthesis or receptor binding, thereby reducing virulence factor expression and biofilm formation.

Advantages:

1. Broad-spectrum antimicrobial and antibiofilm activity
2. Strong antioxidant and anti-inflammatory properties
3. Synergistic effects with antibiotics and nanoparticles

Limitations:

1. Poor aqueous solubility
2. Low stability under physiological conditions
3. Limited bioavailability

Nanocarrier-based delivery systems (liposomes, polymeric nanoparticles, metal–polyphenol networks) have shown promise in overcoming these limitations [12-14].

b) Terpenoids and Essential Oils (Thymol, Carvacrol, Eugenol)

Terpenoids are lipophilic compounds derived from isoprene units and are major constituents of essential oils. They are particularly abundant in aromatic plants such as thyme, oregano, clove, and cinnamon.

Antimicrobial mechanisms:

1. **Strong membrane disruption:** Due to their hydrophobic nature, terpenoids readily partition into bacterial membranes, causing structural disorganization, proton motive force dissipation, and cell lysis.
2. **Ion leakage and ATP depletion:** Membrane damage leads to uncontrolled ion flux and rapid loss of ATP, resulting in metabolic collapse.
3. **Synergistic interactions:** Terpenoids enhance the penetration of antibiotics and other phytochemicals by increasing membrane permeability.

Advantages:

1. Rapid bactericidal activity
2. Effective against Gram-positive bacteria and fungi
3. Low propensity for resistance development

Limitations:

1. High volatility and chemical instability
2. Sensitivity to light, heat, and oxygen
3. Potential cytotoxicity at higher concentrations

Encapsulation in nanoemulsions, solid lipid nanoparticles, or cyclodextrin complexes significantly improves their stability and controlled release [15-16].

c) Alkaloids *(Berberine, Quinine-like Scaffolds)*

Alkaloids are nitrogen-containing heterocyclic compounds known for their potent pharmacological activities. Many traditional antimicrobial remedies derive their efficacy from alkaloid-rich extracts.

Antimicrobial mechanisms:

1. **DNA intercalation and replication inhibition:** Alkaloids such as berberine intercalate into DNA, disrupting replication and transcription processes.
2. **Efflux pump interactions:** Certain alkaloids inhibit bacterial multidrug efflux pumps (e.g., NorA in *Staphylococcus aureus*), increasing intracellular antibiotic accumulation.
3. **Protein synthesis disruption:** Some alkaloids interfere with ribosomal function and protein translation.

Advantages:

a) Potent activity at low concentrations
b) Effective against multidrug-resistant strains
c) Well-defined molecular targets

Limitations:

a) Poor oral bioavailability
b) Rapid metabolism and systemic clearance
c) Potential toxicity and narrow therapeutic window

Nano-formulation strategies, including polymeric nanoparticles and co-delivery systems with antibiotics, significantly enhance alkaloid efficacy and safety [17-18].

d) Organosulfur Compounds (Allicin and Related Thiosulfinates)

Organosulfur compounds, particularly allicin from garlic (*Allium sativum*), exhibit broad-spectrum antimicrobial activity against bacteria, fungi, and viruses.

Antimicrobial mechanisms:

1. **Reaction with thiol-containing enzymes:** Allicin reacts with cysteine residues in essential bacterial enzymes, leading to irreversible enzyme inactivation.

2. **Redox imbalance induction:** Organosulfur compounds disrupt intracellular redox homeostasis, inducing oxidative stress and metabolic dysfunction.
3. **Multi-target action:** Their high chemical reactivity allows simultaneous interference with multiple cellular pathways.

Advantages:

a) Broad-spectrum antimicrobial activity

b) Low resistance development

c) Effective against biofilms and dormant cells

Limitations:

a) High chemical instability

b) Rapid degradation in aqueous and biological environments

c) Strong odor and formulation challenges

Encapsulation in lipid-based or polymeric nanocarriers has been shown to protect organosulfur compounds from degradation and improve their antimicrobial persistence [19].

Table 1: Phytochemical – Nanomaterial Synergy in Antimicrobial Therapy

Photochemical Class	Representative Compounds	Primary Antimicrobial Mechanisms	Key Advantages	Major Limitations
Polyphones	Flavonoids (quercetin, catechins), tannins, phenolic acids	• Membrane permeability alteration • Enzyme inhibition (cell wall, metabolic enzymes) • Metal ion chelation (Fe^{2+}, Zn^{2+}) • Quorum sensing and biofilm inhibition	• Broad-spectrum activity • Strong antibiofilm and antivirulence effects • Antioxidant and anti-inflammatory properties • Synergistic with antibiotics and nanomaterials	• Poor solubility • Low stability in physiological conditions • Limited bioavailability
Terpenoids & Essential Oils	Thymol, carvacrol, eugenol	• Severe membrane disruption • Ion leakage and proton motive force collapse • ATP depletion and metabolic arrest	• Rapid bactericidal action • Effective against Gram-positive bacteria and fungi • Low resistance development	• High volatility • Chemical instability (light, heat, oxygen) • Potential cytotoxicity at high doses
Alkaloids	Berberine, quinine-like scaffolds	• DNA intercalation • Inhibition of DNA replication/transcription • Efflux pump inhibition • Protein synthesis disruption	• High potency at low concentrations • Activity against multidrug-resistant pathogens • Well-defined molecular targets	• Poor oral bioavailability • Rapid metabolism and clearance • Potential toxicity and narrow therapeutic index
Organosulfur Compounds	Allicin, thiosulfinates	• Reaction with thiol-containing enzymes • Redox imbalance and oxidative stress induction • Multi-target cellular disruption	• Broad-spectrum antimicrobial activity • Effective against biofilms and dormant cells • Low likelihood of resistance	• High chemical instability • Rapid degradation in biological systems • Strong odor and formulation challenges

2.2 Need for Nanoformulation

Despite the promising antimicrobial potential of phytochemicals, their direct clinical and industrial translation remains limited due to several inherent physicochemical and biological constraints. Nanoformulation has emerged as a powerful strategy to overcome these limitations by improving stability, bioavailability, and antimicrobial efficacy.

2.2.1 Key Challenges of Conventional Phytochemical Formulations

a) Poor aqueous solubility: Many bioactive phytochemicals, including curcumin and most terpenoids, exhibit extremely low water solubility. This limits their dissolution, absorption, and effective concentration at infection sites, resulting in suboptimal antimicrobial performance.

b) Chemical instability: Phytochemicals are often prone to degradation via oxidation, hydrolysis, and photodegradation. Compounds such as polyphenols and organosulfur molecules rapidly lose activity when exposed to light, oxygen, or physiological P^H conditions, reducing shelf-life and therapeutic effectiveness.

c) Low permeability and rapid metabolism: Several phytochemicals suffer from poor membrane permeability and undergo rapid metabolic transformation in the gastrointestinal tract or systemic circulation. This leads to low bioavailability and short half-life, necessitating higher or repeated dosing.

d) Batch-to-batch variability in plant extracts: Natural extracts are subject to significant compositional variability due to differences in plant species, growth conditions, harvesting time, and extraction methods. This variability complicates dose standardization and reproducibility in antimicrobial applications.

e) Insufficient biofilm penetration: Bacterial biofilms present a dense extracellular polymeric substance (EPS) matrix that severely restricts the penetration of free phytochemicals, resulting in reduced efficacy against chronic and device-associated infections.

2.2.2. Advantages of Nanoformulation in Antimicrobial Delivery

Nano-based delivery systems including polymeric nanoparticles, lipid-based carriers, nanoemulsions, and inorganic Nanomaterials offer several critical advantages:

a) Protection of active compounds from chemical and enzymatic degradation

b) Improved solubility and dispersion of hydrophobic phytochemicals

c) Enhanced cellular uptake and tissue penetration, including biofilms

d) Sustained and controlled release, maintaining therapeutic concentrations over extended periods

e) Localized delivery, minimizing systemic exposure and toxicity

By increasing local drug concentrations at infection sites and enabling multi-target antimicrobial action, nanoformulations can enhance efficacy while potentially reducing the selective pressure that drives antimicrobial resistance. Overall, nanoformulation represents a crucial enabling technology for translating phytochemical antimicrobials into effective therapeutic agents as shown in **Fig.1**. The rational design of nanocarriers tailored to specific phytochemical classes and infection environments holds significant promise for next-generation antimicrobial strategies [3,20].

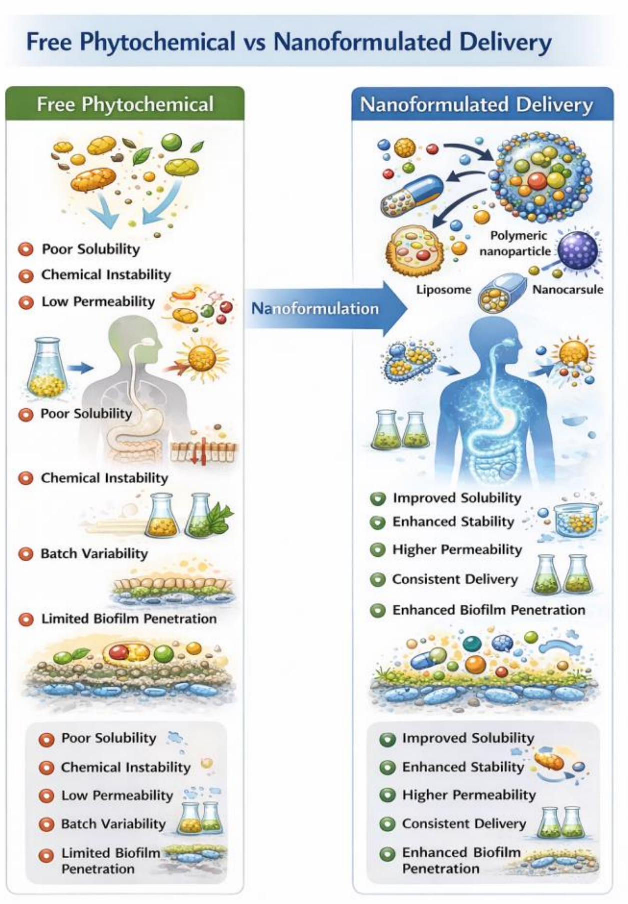

Fig .1: Schematic illustration of free phytochemicals versus nanoformulated delivery systems

3. Nanoantibiotics

Nanoantibiotics refer to nanoscale systems that exhibit antimicrobial activity either intrinsically or through the delivery of antimicrobial agents. Intrinsic nanoantibiotics include materials such as metal and metal-oxide nanoparticles (e.g., silver, zinc oxide, titanium dioxide), which exert antimicrobial effects via mechanisms such as reactive oxygen species (ROS) generation, membrane disruption, and ion release as shown in **Fig.2**. In contrast, carrier-based nanoantibiotics function by encapsulating or conjugating antimicrobial agents including antibiotics, phytochemicals, and essential oils thereby enhancing their stability, bioavailability, and targeted delivery [20].

The antimicrobial performance of nanoantibiotics is strongly governed by their physicochemical properties, including particle size, shape, surface charge, coating chemistry, and release kinetics. Nanoscale dimensions facilitate close interaction with bacterial cell envelopes, while surface functionalization enables selective binding to microbial membranes and biofilms. Furthermore, controlled release profiles can be engineered to maintain therapeutic concentrations over extended durations or to respond to specific stimuli such as P^H, enzymes, light, or redox conditions [21].

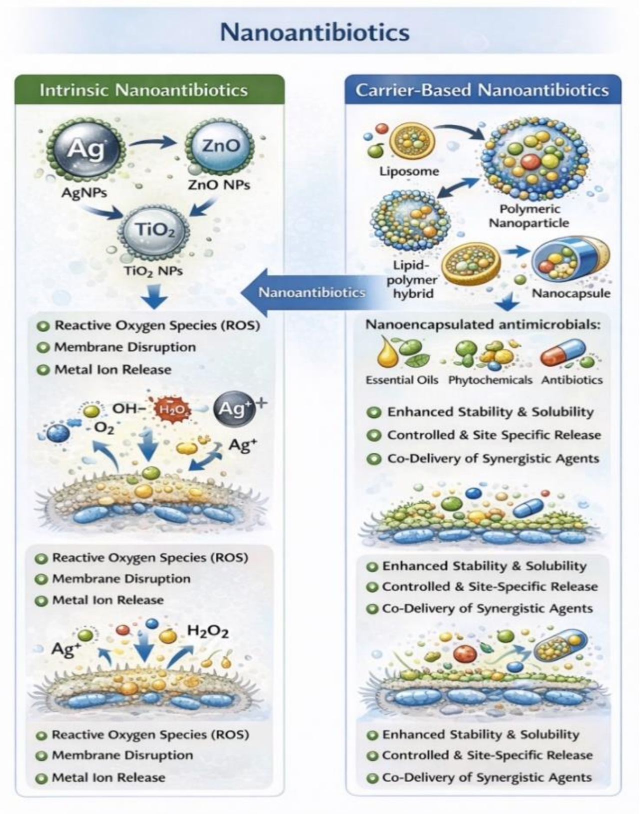

Fig. 2: Intrinsic versus carrier-based nanoantibiotics: mechanisms and delivery strategies

3.1 Core Advantages of Nanoantibiotics

Nanoantibiotics offer several distinct advantages over conventional antimicrobial formulations:

A. **Multiple simultaneous mechanisms of action:** Nanoantibiotics often act through combined pathways such as membrane disruption, oxidative stress induction, intracellular interference, and drug delivery, making it more difficult for microorganisms to develop resistance.

B. **Enhanced interaction with bacterial membranes:** Their high surface-area-to-volume ratio promotes strong adhesion to bacterial surfaces, leading to improved membrane perturbation and cellular uptake.

C. **Controlled and stimuli-responsive release:** Nanoformulations can be designed to release antimicrobial agents in a sustained or trigger-dependent manner, optimizing therapeutic efficacy while minimizing off-target toxicity.

D. **Co-delivery of synergistic antimicrobial pairs:** Nanoantibiotics enable the simultaneous delivery of multiple agents, such as a phytochemical combined with a conventional antibiotic, thereby enhancing antimicrobial potency and restoring antibiotic susceptibility in resistant strains.

Perspective

By integrating material science with microbiology and pharmacology, nanoantibiotics represent a promising next-generation strategy to combat antimicrobial resistance. Their ability to combine physical, chemical, and biological modes of action positions them as versatile tools for treating complex infections, particularly those involving biofilms and multidrug-resistant pathogens [22].

4. Design Strategies for Plant-Derived Nanoantibiotics

The rational design of plant-derived nanoantibiotics integrates principles from green chemistry, nanotechnology, and microbiology. Depending on whether the antimicrobial function arises intrinsically from the nanomaterial or primarily from the delivered phytochemical, different design strategies can be employed. Broadly, these strategies include green synthesis of nanoparticles using plant extracts, nanoencapsulation of phytochemicals, and surface functionalization of nanomaterials with bioactive plant compounds [23].

4.1 Green-Synthesized Nanoparticles Using Plant Extracts

Green synthesis employs plant extracts as eco-friendly alternatives to conventional chemical reducing and stabilizing agents. Phytochemicals such as polyphenols, flavonoids, terpenoids, sugars, and proteins present in the extracts act simultaneously as reducing agents, converting metal salts into nanoparticles, and as capping agents, stabilizing the nanoparticle surface and preventing aggregation [24].

4.1.2 Common green-synthesized nanoantibiotic systems include:

a) Silver nanoparticles (AgNPs): AgNPs are among the most widely studied green-synthesized nanoantibiotics due to their broad-spectrum antimicrobial activity. They exert antimicrobial effects through silver ion release, ROS generation, and membrane disruption, and often display strong antibiofilm activity against both Gram-positive and Gram-negative bacteria.

b) Gold nanoparticles (AuNPs): AuNPs exhibit excellent biocompatibility and chemical stability. While their intrinsic antimicrobial activity is moderate, they are highly valuable as platforms for surface functionalization and for combination strategies such as photothermal or photodynamic antimicrobial therapy.

c) Metal-oxide nanoparticles (ZnO, TiO_2, CuO): These nanoparticles exert antimicrobial activity primarily through ROS generation and membrane damage. ZnO and TiO_2 are particularly attractive due to their relative safety profiles and photocatalytic properties, while CuO nanoparticles provide strong antimicrobial effects but require careful toxicity control [25] .

4.2 Key design variables:

The physicochemical properties and antimicrobial performance of green-synthesized nanoparticles are highly sensitive to synthesis parameters, including:

a) Composition and concentration of plant extract

b) pH of the reaction medium

c) Temperature and reaction time

d) Ionic strength

e) Metal precursor type and concentration

Standardization and precise control of these variables are essential to ensure reproducibility, scalability, and consistent antimicrobial efficacy.

4.3 Nanoencapsulation of Phytochemicals (Delivery-First Approach)

In this strategy, the primary antimicrobial activity arises from the phytochemical itself, while the nanocarrier functions to improve solubility, stability, bioavailability, and targeted delivery. This approach is particularly suitable for chemically unstable or poorly soluble plant-derived antimicrobials.

a) Polymeric nanoparticles (PLGA, chitosan, alginate): Polymeric nanoparticles enable sustained and controlled release of encapsulated phytochemicals. Chitosan-based systems are especially attractive, as chitosan carries a positive surface charge that enhances bacterial membrane interaction and provides intrinsic antibacterial activity.

b) Lipid-based systems (liposomes, solid lipid nanoparticles, nanostructured lipid carriers): These carriers are well suited for hydrophobic compounds such as essential oils and terpenoids. Lipid-based systems improve chemical stability, enhance skin and mucosal delivery, and facilitate fusion with bacterial membranes.

c) Cyclodextrin inclusion complexes: Cyclodextrins form host–guest complexes with hydrophobic phytochemicals such as thymol and eugenol, significantly improving their aqueous solubility, stability, and handling without altering chemical structure.

d) Nanoemulsions: Nanoemulsions are particularly effective for essential oil delivery. Their small droplet size enhances dispersion, increases surface contact with bacterial membranes, and improves antimicrobial efficacy at lower doses [26-28] .

4.4 Phytochemical-Functionalized Nanomaterials (Surface Engineering)

Surface engineering represents a hybrid strategy in which phytochemicals are grafted, adsorbed, or coated onto preformed nanomaterials. This approach combines the intrinsic properties of the nanomaterial with the biological activity of the phytochemical. Phytochemical functionalization can be designed to Stabilize nanoparticles and prevent aggregation, Improve biocompatibility and reduce nonspecific toxicity, Introduce antibiofilm and antivirulence properties, such as quorum-sensing inhibition and Create multi-hit antimicrobial activity, combining membrane disruption, oxidative stress, and intracellular interference as shown in **Fig.3.**

Such multifunctional systems are particularly promising for combating biofilm-associated and multidrug-resistant infections. Together, these design strategies highlight the versatility of plant-derived nanoantibiotics . By carefully selecting synthesis routes, carrier systems, and surface functionalization approaches, it is possible to tailor nanoantibiotics with enhanced efficacy, reduced toxicity, and lower resistance potential [29-30].

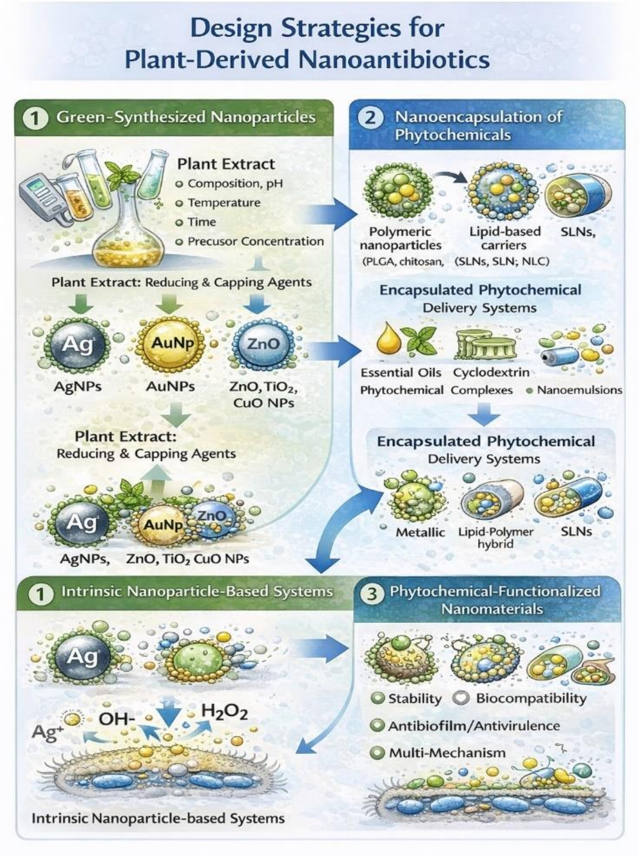

Fig. 3: Design Strategies for Plant-Derived Nanoantibiotics

5. Mechanisms of Antimicrobial Action

5.1 Membrane disruption

Hydrophobic phytochemicals (thymol, carvacrol) and cationic carriers (chitosan) increase membrane permeability, causing leakage of ions and metabolites.

5.2 Reactive oxygen species (ROS) generation

Metal/metal-oxide nanoparticles can generate ROS (especially under light for some oxides), damaging proteins, lipids, and DNA.

5.3 Intracellular target interference

Some phytochemical inhibit enzymes (e.g., cell wall synthesis enzymes), disrupt energy metabolism, or interfere with DNA replication/transcription.

5.4 Quorum sensing and biofilm inhibition

Plant polyphenols and some terpenoids suppress quorum sensing, reduce EPS formation, and impair adhesion making bacteria more susceptible.

5.5 Efflux pump modulation and synergy

Certain phytochemicals can inhibit efflux pumps or increase membrane permeability, restoring antibiotic susceptibility. Nano co-delivery intensifies this effect.

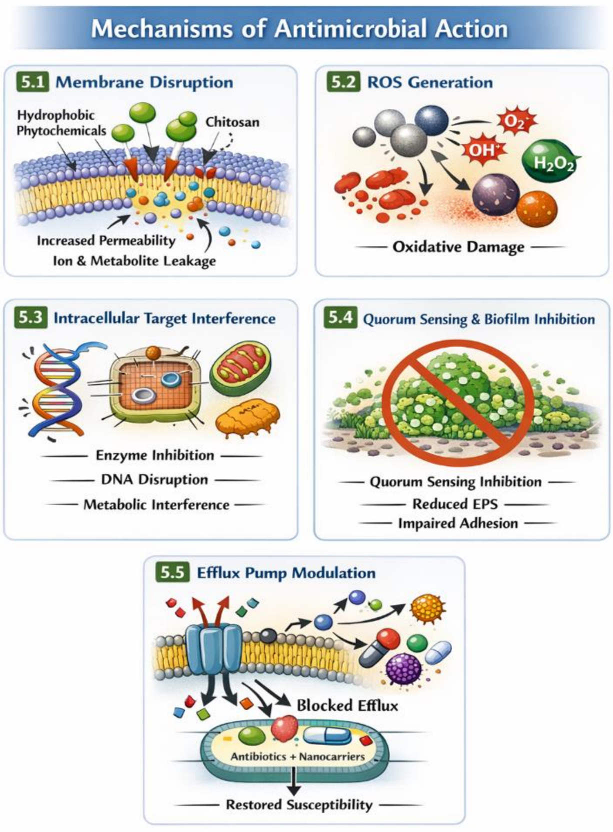

Fig. 4: Mechanisms of Antimicrobial Action

6. Advanced Design Strategies for Smart Nanoantimicrobial Systems

6.1 Stimuli-Responsive Delivery Systems

Stimuli-responsive nanoantimicrobial platforms are designed to release their active payload selectively in response to specific physicochemical or biological cues associated with infected tissues, thereby enhancing therapeutic efficacy while minimizing off-target toxicity.

a) pH-responsive release systems

Many infection sites and biofilm microenvironments exhibit localized acidity due to bacterial metabolism and host inflammatory responses. pH-responsive nanocarriers exploit this characteristic by remaining stable under physiological pH (~7.4) and undergoing structural changes or accelerated drug release under acidic conditions (pH 5.0–6.5). Such systems improve site-specific delivery of phytochemicals and antibiotics, increasing antimicrobial concentration at the infection focus while reducing systemic exposure.

b) Enzyme-responsive carriers

Enzyme-triggered nanocarriers are engineered to respond to bacterial enzymes such as β-lactamases, proteases, lipases, or phospholipases that are overexpressed during infection. These enzymes selectively degrade carrier components (e.g., polymer backbones or peptide linkers), leading to controlled payload release directly at the bacterial site. This strategy enhances selectivity and helps overcome resistance mechanisms by synchronizing drug release with bacterial activity.

c) Light- and thermal-responsive systems

Externally triggered systems utilizing light or thermal stimuli offer precise spatiotemporal control over drug release. Photothermal materials most notably gold-based nanostructures (AuNPs, nanorods, nanoshells) convert near-infrared (NIR) light into localized heat. This heat can disrupt bacterial membranes, weaken biofilm matrices, and simultaneously trigger the release of loaded antimicrobial agents. The combination of photothermal therapy with chemical antimicrobial action provides a dual-killing mechanism that is particularly effective against biofilm-associated infections.

6.2 Co-Delivery and Combination Therapy Approaches

Co-delivery strategies aim to harness synergistic interactions between multiple antimicrobial agents, improving efficacy and reducing the likelihood of resistance development.

a) Phytochemical antibioticco delivery

The simultaneous delivery of phytochemicals and conventional antibiotics (e.g., curcumin + ciprofloxacin) has demonstrated enhanced antibacterial activity through complementary mechanisms. Phytochemicals can disrupt bacterial membranes, inhibit efflux pumps, or modulate quorum sensing, thereby sensitizing bacteria to antibiotics. Encapsulation within a single nanocarrier ensures synchronized release, improved bioavailability of poorly soluble phytochemicals, and sustained synergistic effects.

b) Dualphyto chemical delivery

Co-encapsulation of two or more phytochemicals (e.g., thymol + eugenol) enables spectrum broadening and multi-target antimicrobial action. These compounds often act on distinct cellular pathways, such as membrane destabilization and enzyme inhibition, reducing the probability of resistance emergence. Nanoformulation further enhances stability, controlled release, and penetration into biofilms.

6.3 Surface Charge Engineering and Targeting Strategies

Surface charge plays a critical role in determining nanoantimicrobial interactions with bacterial cells and biofilms. Bacterial cell walls and extracellular polymeric substances (EPS) in biofilms are predominantly negatively charged. Accordingly, nanocarriers with cationic surfaces exhibit enhanced electrostatic attraction, promoting stronger adhesion, deeper biofilm penetration, and increased local drug concentration at the infection site [31]. In addition to charge-based targeting, surface functionalization with ligands such as antimicrobial peptides, sugars, or antibodies can further improve bacterial specificity and therapeutic outcomes while minimizing interactions with host cells.

7. Applications

7.1 Wound and skin infections

Plant-derived nanoantibiotics are highly suited for topical use:

a) sustained release in hydrogels/films,

b) antibiofilm action against *Staphylococcus aureus* and *Pseudomonas aeruginosa*,

c) potential anti-inflammatory and antioxidant benefits aiding healing.

Common formats: chitosan films, alginate dressings, nanofiber mats, hydrogel composites with green-synthesized nanoparticles.

7.2 Medical device coatings

Catheters and implants are prone to biofilm formation. Nano-coatings containing phytochemicals or green-synthesized nanoparticles can reduce colonization.

7.3 Respiratory and gastrointestinal infections (emerging)

Oral and inhalable nanoformulations are under exploration but require stricter safety, mucosal compatibility, and scalability evidence.

7.4 Food packaging and surface disinfection

Nanoemulsified essential oils and plant-capped nanoparticles can inhibit spoilage and pathogens on surfaces, but migration/toxicity evaluation is critical [32-33].

8. Safety, Toxicity, and Standardization Challenges

8.1 Toxicity considerations

a) Metal nanoparticles can pose cytotoxicity risks depending on size, dose, dissolution, and coatings.

b) Essential oils at high concentrations can irritate tissues; nanoencapsulation may reduce irritation but must be validated.

c) Long-term exposure and environmental release require assessment.

8.2 Reproducibility and quality control

Plant extracts vary with species, season, soil, extraction solvent, and storage. This impacts nanoparticle synthesis and activity. Recommended controls:

a) chemical fingerprinting (HPLC/GC-MS),

b) standardized extraction protocols,

c) nanoparticle characterization (size, zeta potential, morphology, stability),

d) standardized antimicrobial testing (MIC, MBC, time-kill, biofilm assays).

8.3 Regulatory hurdles

Complex natural mixtures and nanoscale behavior complicate approvals. Clear definition of active components, stability, and manufacturing controls are essential [34-36].

9. Future Perspectives

Key directions likely to accelerate translation:

1. Standardized green synthesis with validated fingerprints and batch-to-batch performance.
2. Biofilm-first product design (penetration + EPS disruption + sustained release).
3. Synergistic co-delivery pairing phytochemicals with existing antibiotics to revive potency.
4. Smart wound platforms (pH/enzymatic triggers, antibacterial + healing support).
5. Scalable manufacturing (continuous-flow synthesis, greener solvents, robust QA).
6. Resistance monitoring to confirm reduced propensity for resistance development compared with monotherapies.

10. Conclusions

Plant-derived nanoantibiotics represent a promising, multi-mechanistic strategy to address AMR and biofilm-associated infections. By combining phytochemicals' chemical diversity with nanoscale delivery or intrinsic nanoactivity, these systems can improve solubility, stability, targeting, and antibiofilm performance. Continued progress depends on rigorous standardization of plant materials, careful toxicity profiling, and scalable manufacturing pathways. Each phytochemical class exhibits distinct yet complementary antimicrobial mechanisms, making them highly suitable for combination therapies and nano-enabled delivery platforms. Integrating phytochemicals with nanotechnology offers a promising strategy to enhance stability, bioavailability, and therapeutic efficacy while addressing the growing challenge of antimicrobial resistance. With these advances, plant-based nanoantibiotics can move from laboratory concepts toward clinically relevant antimicrobial solutions.

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