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A comprehensive review of plant-based compounds as alternatives and adjuvants to conventional antibiotics

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ABSTRACT

Antimicrobial resistance (AMR) is the biggest threat to global public well-being in the 21st century, causing millions of deaths yearly if we do not do anything to get rid of this problem. The reduced effectiveness of currently used antibiotics, along with a festering drug development pipeline, requires the study of new treatment decisions. Plant-derived phytochemicals, such as alkaloids, flavonoids, terpenoids, tannins, phenolic acids, essential oils, and saponins, have appeared as attractive options due to their structural variety and multi-target actions. To combat drug-resistant infections, these chemicals disrupt cell membranes, flow pumps, and quorum sensing while also producing reactive oxygen species. Also, the possibility of synergy with existing antibiotics gives an approach for restoring the effectiveness of older medications. This study critically evaluates the antibacterial efficacy of essential plant compounds against WHO priority-specific resistance infections, investigates the mechanisms behind resistance change, and examines ethnobotanical evidence from traditional medicinal systems. Regulatory hurdles, such as a lack of bioavailability, a lack of standardisation, and translation issues, are also addressed. Future initiatives, such as nanotechnology-based delivery systems and metabolomics powered by artificial intelligence, are identified as feasible paths to speed the integration of plant compounds into standard antimicrobial therapy.

Key Words: *Phytochemicals; Plant-derived compounds; Drug-resistant infections; Antibiotic resistance*

Introduction

2.1 The Global Antimicrobial Resistance (AMR) Crisis

When bacteria develop resistance against the antibiotic that previously worked against the same organism, exposure to those bacteria. And because this ability has been developed in bacteria, it is hard to treat, causing higher severity and sometimes death, and it raises a question about the decade of medicinal progress often declared as a silent pandemic.[1] These causes lead to health problems in the 21st century; the deaths due to AMR are very shocking and well-established. Groundbreaking global research predicted that 4.95 million fatalities were connected with bacterial AMR, with 1.27 million directly due to it in 2019 alone, across 204 nations and territories.[2] MRSA (methicillin-resistant Staphylococcus aureus) is one of the most hazardous drug-resistant bacteria, accounting for a large number of deaths from AMR infections worldwide. Nonetheless, around 3.5% of current TB and 18% of previously treated patients globally have MDR-TB (multidrug-resistant tuberculosis), raising concerns about XDR-TB among many MDR-TB cases.[3]

A complete Lancet study estimated that between 1990 and 2021, the total number of deaths and DALYs from 22 pathogens, 84 combinations of pathogens and drugs attributable to bacterial AMR was 94.[4]

On the WHO Bacterial Priority Pathogens List 2024, carbapenem-resistant Acinetobacter baumannii, third-generation cephalosporin-resistant Enterobacterales, and rifampicin-resistant Mycobacterium tuberculosis were identified as critical

priority pathogens. The pathogen-drug combination with the greatest increase in attributable burden from 1990 to 2021 was MRSA, with deaths more than doubling, although it was listed as a high priority rather than a critical priority, partly because of its high treatability and medium preventability.[2]

Although antibiotics are essential for the treatment of bacterial infections, their overuse and abuse, including incorrect doses and durations, as well as unprofessional behaviour by chemists and health professionals over decades, have exerted selection pressure and resulted in the emergence of resistant bacteria. Beyond human healthcare, the incorrect use of antimicrobials in animal feed in many impoverished countries has played a crucial role in the spread of AMR. [5] Higher resistance causes severe infections, high complications, longer hospital admissions, and increased death rates. Overuse of antibiotics in pathogenic bacteria is a major public health concern at the global level.[6]

2.2 Historical Context of Plant Use in Traditional Medicine

Botanical entities have been the primary medicinal modality since antiquity. The World Health Organisation classified over 28,000 of the 374,000 identified plant species as therapeutic. This pharmaceutical use is supported by ancient documents such as the Indian Atharvaveda (c. 2000 BCE), Mesopotamian clay tablets (c. 1700 BCE), Egyptian Ebers Papyrus (c. 1550 BCE), Dioscorides' De Materia Medica (60-78 CE), and the Pen Ts'ao Ching (c. 200 CE).[7]

2.3 Ayurveda

The world's oldest medical system is often known as the "mother of all therapies".[8,9] Its description may be found in ancient literature such as the Rig-Veda and Atharva-Veda, which date from around 5000 BCE.[10] Ayurveda is a Sanskrit expression that means "knowledge of life" and refers to a combination of physiological and holistic treatment.[11] Alongside other basic medical systems of antiquity, such as Egyptian medicine, Greek humoral theory, and traditional Chinese medicine, this ancient therapeutic tradition developed, adding to the global framework of early healthcare knowledge .[8]

2.4 Traditional Chinese Medicine (TCM)

Although the origin of TCM is unknown, archaeological discoveries of acupuncture needles and remnants of herbal therapies imply that it has existed for 4000 to 8000 years. The Yijing (I Ching, or Book of Changes) and Huangdi Neijing (The Yellow Emperor's Classic of Internal Medicine) are the earliest documented accounts of TCM theory and clinical practice. TCM is a systematic healthcare approach based on clinical experience that uses unique ideas and methods to cure ailments and improve overall health. The core TCM ideas include the teaching of Yin and Yang and the Five Phases (Elements), which describe functional energies such as qi, blood (xue), and active and resting fluids (jin ye), as well as the differential diagnosis of disorders. Acupuncture and moxibustion are the most common practices, followed by Chinese herbal medicine and dietetics, Tuina, Qigong, and Taijiquan. Chinese herbal medicine uses the same diagnostic concepts as acupuncture and focuses on the therapeutic benefits of herbs and foods on the body, categorising them based on their thermal nature, sapour (flavour), organ network, and functional impact direction.[12]

2.5 Greek and Egyptian Medicine

The renowned Ebers Papyrus, written around 1550 BCE, included 876 prescriptions made up of 328 distinct substances, the majority of which came from plant species. It is the oldest and most extensive medical papyrus, acting as an encyclopaedia of medicine, with sections on helminthiasis, ophthalmology, dermatology, gynaecology, obstetrics, dentistry, and surgery, as well as over 700 verified formulae.[13] Ancient Egyptians found natural antibiotics, such as honey and onions, which were utilised to cure illnesses, as well as the anti-inflammatory qualities of olibanum tree incense. They also employed salicin from the willow tree to alleviate inflammation and discomfort.[14] Greek physicians such as Hippocrates, Dioscorides, and Galen helped to systematise plant medicine. Healing was inextricably linked to religion in ancient Egypt, with priests serving as healers, whereas Greek physicians during the Classical period made significant contributions through rational observation and naturalistic explanation of disease, collectively shaping the trajectory of Western herbal pharmacology for millennia. [15]

2.6 Rationale for Phytochemical Research

The rising AMR epidemic, along with a dangerously stalled antibiotic research pipeline, has resulted in an urgent need for alternative treatment approaches. Antimicrobial research and development lag far behind other sectors, such as cancer or HIV research, with considerable gaps in the creation of a strong and effective antibacterial medication pipeline.[16] Plants are a scientifically interesting and accessible resource in this setting. Plant secondary metabolites, known as phytochemicals, have structural and functional variety, allowing them to kill bacteria directly, disrupt essential cellular activities, and augment current antibiotics by evading microbial resistance mechanisms.[17] Several phytochemical classes have shown inhibitory activity against drug-resistant infections by targeting molecular determinants of resistance, such as biofilms, efflux pumps, and bacterial cell communication, making phytochemical research a scientifically justifiable priority.[18]

2.7 Scope and Objectives of the Review

This review deals with the convergence of the growing AMR burden and the under exploitation of plant components as structured pharmaceutical alternatives. Although interest in plant drugs has increased in recent years, additional research

is needed to fully understand the mechanisms of action and verify the safety of phytochemical antimicrobial agents. Therefore, this review aims to: (i) critically evaluate evidence of phytochemical activity against WHO priority drug-resistant pathogens; (ii)clarify key mechanisms, including the inhibition of efflux pump inhibition, the biofilm disruption and interference of quorum sensing;(iii) examine translation barriers, such as bioavailability, stability and standardization; and (iv) explore new strategies, including nanotechnology-based drug delivery and combination therapies. This review aims to provide a comprehensive framework for researchers and clinicians engaged in the global response to AMR by synthesising ethnopharmacological and contemporary molecular evidence.

Major Classes of Phytochemicals with Antibiotic Activity

Plants use phytochemicals as a wide range of secondary metabolites to protect themselves from harmful microorganisms.[19] Researchers are looking into these compounds more and more because they can fight multidrug-resistant (MDR) bacteria in different ways, such as by breaking down cell walls, stopping nucleic acid synthesis, and stopping efflux pumps.[20]

3.1 Alkaloids

Alkaloids are organic compounds that contain nitrogen and come from amino acids. They are very important for keeping plants safe from diseases.[19]

- Berberine is known to stop the growth of Staphylococcus aureus by attacking the cell membrane and stopping the FtsZ protein, which is needed for bacterial cells to divide.[21]
- Piperine: It may not always kill germs directly, but it is a strong efflux pump inhibitor. It greatly increases the effectiveness of other antibiotics, such as berberine, by stopping them from leaving bacterial cells.[21] It has also shown promise in stopping class C beta-lactamase enzymes in fungal pathogens.[22]

3.2 Flavonoids

Flavonoids are polyphenolic structures that are some of the strongest antimicrobial compounds found in plants.[19]

- Quercetin and Apigenin: These substances attack the membranes of bacteria's cytoplasm, making holes in them and damaging the phospholipid bilayers.[23]
- Mechanism: Quercetin specifically disrupts DNA-related metabolic processes by inhibiting enzymes such as DNA gyrase and topoisomerases, thereby effectively preventing bacterial replication.[20]

3.3 Terpenoids

Terpenoids are the biggest group of plant secondary metabolites. They are very lipophilic, which means they can easily interact with bacterial biomembranes.[19]

- Thymol and Carvacrol: These monoterpenes are effective against a wide range of bacteria, both Gram-positive and Gram-negative.
- Mechanism: They work by breaking down the outer membrane of bacteria, making it more fluid and permeable. This causes important parts of the cell to leak out, and the cell to die.[24,25]

3.4 Tannins

Large polyphenols called tannins bind to proteins and other substances, polysaccharides, often acting as bacteriostatic or bactericidal agents.

- Green tea's most potent polyphenol, epigallocatechin gallate (EGCG), physically damages the bacterial cell wall by binding to peptidoglycan.[26]
- It also has a strong synergistic effect with beta-lactam antibiotics against resistant strains such as methicillin-resistant Staphylococcus aureus (MRSA).[25]

3.5 Phenolic Acids

Almost all edible plants contain phenolic acids, which are associated with antimicrobial activity due to the presence of double bonds and hydroxyl groups.[19]

- Caffeic acid, found in coffee and propolis, has been shown to improve the efficacy of erythromycin and other antibiotics by inhibiting the bacterial RNA polymerase enzyme.[19,27]
- Gallic acid serves as an antimicrobial agent by disrupting membrane integrity and inhibiting viral RNA expression.[27]

3.6 Essential oils

Essential oils' antibacterial activity is primarily due to their complex active components, which include aldehydes and phenols.

- Eugenol and cinnamaldehyde use their hydrophobicity to penetrate lipid layers, destroying cell wall structures and allowing vital intracellular ions to exit.
- Cinnamaldehyde reduces bacterial membrane potential and impairs quorum sensing, thereby preventing biofilm formation.[28]

3.7 saponins

Saponins are glycosides that act as surfactants and can be found in many plant families.[19]

- Glycyrrhizin (Glycyrrhizic Acid) is a triterpenoid saponin derived from liquorice (Glycyrrhiza glabra). While it is best known for its anti-inflammatory and antiviral properties (for example, suppressing Hepatitis B surface antigens), it and its aglycone, glycyrrhetic acid, contribute significantly to the overall antimicrobial profile of liquorice extracts by altering membrane permeability.[29,30]

4. Mechanisms of Antimicrobial Action

Phytochemicals' structural variety allows them to sidestep traditional resistance mechanisms by using a multi-targeted strategy. Plant-derived medicines usually show pleiotropic effects, as opposed to many manufactured antibiotics, which only target one metabolic route.[31]

4.1 Cell Membrane and Wall Disruption

Lipophilic chemicals in garlic, such as monoterpenes (thymol and carvacrol) and organosulfur compounds, can enter the bacterial membrane. The interaction distorts membrane fluidity and changes permeability, leading to loss of critical ions like K^+ and ATP, resulting in osmotic collapse.[32,33] Furthermore, polyphenols like EGCG physically attach to peptidoglycan, undermining the structural integrity of the cell wall.[34]

4.2 Efflux Pump Inhibition (EPI)

One of the most significant clinical mechanisms is the suppression of efflux pumps. EPs are protein-based transporters that release antibiotics before they reach their intracellular destinations.[35] Piperine and other phytochemicals, as well as alkaloids, compete with or disrupt the proton motive force necessary for pump action, restoring the effectiveness of conventional medicines in MDR strains.

4.3 Biofilm Disruption and Quorum Sensing Interference

Biofilms are complex microbial communities that are enclosed in an extracellular polymeric substance (EPS) matrix, which protects microorganisms from human immune reactions and drugs.[35] Many phytochemicals, including cinnamaldehyde and flavonoids, inhibit quorum sensing (QS), the chemical communication mechanism utilised by bacteria to coordinate biofilm development.[36,37] These chemicals diminish virulence by interrupting QS pathways and preventing the creation of highly resistant biofilm formations.

4.4 ROS Generation and Nucleic Acid Inhibition

Certain phytochemicals induce the generation of reactive oxygen species (ROS) in bacterial cells, which causes oxidative damage to proteins and lipids.[32] Furthermore, flavonoids like quercetin block key enzymes such as DNA gyrase and topoisomerases, thereby preventing bacterial reproduction.[38]

5. Plant Sources and Ethnobotanical Evidence

Traditional medicinal systems have employed a range of strong herbs, and contemporary molecular research is now validating their antibacterial potency.[39]

- Allium sativum (garlic): contains allicin, which interacts with thiol groups in bacterial enzymes. It has demonstrated strong broad-spectrum action, notably against infections that cause respiratory and gastrointestinal discomfort.[33]
- Curcuma longa (Turmeric): Curcumin, the main bioactive, is a well-known antibacterial and anti-inflammatory drug that targets cell membrane integrity and inhibits virulence factors.[40]
- Azadirachta indica (Neem): Neem extracts, which are widely used in South Asian medicine, include azadirachtin and other limonoids that damage bacterial cell walls and have immunomodulatory activities.
- Zingiber officinale (Ginger): Gingerols and shogaols suppress bacterial metabolism and have been given priority in recent ethnobotanical rankings due to their medicinal effectiveness.
- Ocimum sanctum (Tulsi): Known as the "Queen of Herbs," its essential oils (rich in eugenol) have potent antibacterial and antioxidant capabilities, strengthening the immune system and directly targeting microorganisms.[41]

6. Synergistic Effect of Conventional Antibiotics

The combination of phytochemicals and conventional antibiotics is a "resistance-modifying" method that may salvage failed medications.

6.1 The concept of synergy and MIC reduction

Synergy occurs when the combined impact of two drugs outweighs the total of their separate effects. Phytochemicals can operate as "adjuvants" by reducing antibiotics' minimum inhibitory concentration (MIC), so rendering resistant bacteria vulnerable again.[42] For example, studies have shown that mixing essential oils with neomycin or tetracycline has synergistic or additive benefits.[32]

6.2 Mechanisms for neutralising resistance

Plant chemicals can facilitate antibiotic penetration by permeabilising the outer membrane or blocking enzymes that would otherwise break down the medication, such as β-lactamases (6).[43] These combinations strengthen the genetic barrier to resistance development by targeting many cellular processes at once.[31]

7. In Vitro vs. In Vivo Studies

7.1 Laboratory Efficacy vs. Real-World Challenges

While numerous plant-derived drugs have demonstrated excellent performance in laboratory settings, there is a clear gap in transferring these findings to therapeutic settings. According to recent evaluations of the WHO antibacterial clinical pipeline, research and development for novel antibacterials, especially those derived from natural materials, face considerable challenges as they proceed through clinical stages.[44] Systematic evaluations demonstrate that, while natural products have substantial effectiveness against priority pathogens in vitro, the intricacy of host-pathogen interactions needs more thorough in vivo validation.[45]

7.2 Bioavailability and Pharmacokinetic Hurdles (ADME)

The medicinal potential of phytochemicals is frequently hampered by their low bioavailability and complicated pharmacokinetic characteristics. Compounds like quercetin and other catechins need special modifications or delivery mechanisms to reach systemic targets without being quickly metabolised or ejected.[46–48]

8. Challenges & Limitations

8.1 Standardisation and Quality Control

A key difficulty is the intrinsic heterogeneity of plant extracts caused by environmental variables, which affects the consistency of active components such as monoterpenes and flavonoids.[47,49] Standardising these combinations is critical for treatment reliability, but it remains a major technological challenge.[50]

8.2 Toxicity and Regulatory Hurdles

High amounts of active metabolites, while commonly thought to be harmless, can cause haemolysis or cellular toxicity.[48] Furthermore, the regulatory environment for complex plant-derived combinations is demanding, as evidenced by the specific criteria in the WHO Global Antimicrobial Resistance Surveillance Report.[44,51]

9. Future Perspectives

9.1 AI-Driven Discovery and Metabolomics

Future techniques will focus on "Interaction Metabolomics" to identify precise combinations of natural substances that function in tandem with current antibiotics.[21] According to a recent 2024 study, using LC-MS/MS to detect the exact ratios of components like cinnamaldehyde and thymol can help build more effective formulations that restore the efficiency of traditional treatments against resistant strains.[36]

9.2 Addressing the Clinical Pipeline Gap

According to the Who is 2025 antibacterial clinical pipeline analysis, future efforts should prioritise the development of non-traditional antibacterials that target priority infections such as Acinetobacter baumannii.[16] According to systematic reviews (2025), the next generation of treatments will most likely include standardised natural product formulations that target virulence factors rather than growth inhibition, lowering selection pressure for resistance.[17]

10 Conclusion

To summarise, what we have seen indicates that we need a balanced approach to addressing these difficulties. Instead of looking for a single "magic" answer, it is evident that true success comes from blending several principles, such as remaining inventive while acting ethically. Looking forward to the development, which will largely depend on our ability to adjust before difficulties arise. We will unquestionably face challenges, but the lessons we have learned so far provide us with a good strategy for coping with whatever happens next. At the end, it is more than just crossing the finish line; it is about always improving and learning as we go. If we follow these principles, the work we are doing now will have a long-term impact. Consider this both a concluding reflection and a motivation to continue exploring what is possible.

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