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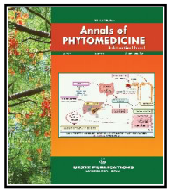

Invited Commentary : Open Access

The role of phytomedicine in combating antimicrobial resistance

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Abstract

Antimicrobial resistance (AMR) is a critical global health threat, necessitating alternative and complementary therapies to conventional antibiotics. Phytomedicine, utilizing plant-derived compounds, offers promising solutions due to its diverse mechanisms of action. This commentary explores the potential of phytomedicine in combating AMR by disrupting bacterial cell walls, inhibiting biofilm formation, interfering with quorum sensing, and modulating host immune responses. Key advantages include a lower likelihood of resistance development, synergistic effects with antibiotics, broad-spectrum activity, and minimal side effects. However, challenges in standardizing and regulating phytomedicines, as well as the need for rigorous clinical trials, must be addressed. Future directions emphasize interdisciplinary research, standardized regulatory frameworks, and integration into mainstream healthcare. By leveraging the strengths of both traditional and modern medicine, phytomedicine can significantly contribute to global efforts against AMR, offering hope for sustainable and effective healthcare solutions.

1. Introduction

Antimicrobial resistance (AMR) is a pressing global health issue characterized by the ability of microorganisms. Bacteria, viruses, fungi, and parasites to resist the effects of medications previously effective for treating infections. This phenomenon significantly undermines the efficacy of antibiotics, antivirals, antifungals, and antiparasitics, leading to prolonged illnesses, increased healthcare costs, and higher mortality rates. According to the World Health Organization (WHO), AMR is projected to cause 10 million deaths annually by 2050 if left unaddressed, surpassing the mortality rates of cancer and diabetes combined.

Phytomedicine, the practice of using plant-based compounds for medicinal purposes, has a long history in traditional medicine systems across various cultures. For centuries, plants have been a cornerstone in the treatment of infections, leveraging their bioactive compounds to combat pathogens. Historical records indicate the use of herbal remedies dating back to ancient civilizations, with modern science progressively validating these traditional practices through rigorous research and clinical studies (Newman and Cragg, 2022).

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1.1 Current state of antimicrobial resistance

Antimicrobial resistance (AMR) represents one of the most formidable challenges to global public health today. According to the Centers for Disease Control and Prevention (CDC), more than 2.8 million antibiotic-resistant infections occur in the United States each year, leading to over 35,000 deaths.

One of the most alarming examples of AMR is the emergence of multidrug-resistant (MDR) bacteria such as Methicillin-resistant Staphylococcus aureus (MRSA), which causes severe infections that are difficult to treat with standard antibiotics. Similarly, carbapenem-resistant Enterobacteriaceae (CRE) and extended-spectrum beta-lactamase (ESBL)-producing bacteria pose significant threats due to their resistance to multiple antibiotics, including last-resort treatments (Tamma *et al*., 2022).

Developing new antibiotics to counteract AMR has proven to be a challenging endeavor. The process of antibiotic discovery and development is time-consuming, expensive, and often yields limited success. The pharmaceutical pipeline for new antibiotics is alarmingly sparse, with many large pharmaceutical companies scaling back or abandoning their antibiotic research efforts due to low financial returns and high development risks (Renwick *et al*., 2016). Additionally, the rapid pace at which bacteria develop resistance to new drugs exacerbates the problem, often rendering new antibiotics ineffective shortly after their introduction to the market.

2. Phytomedicine: A promising alternative

Phytomedicine, the use of plant-derived compounds for therapeutic purposes, encompasses a wide array of natural substances, including plant extracts, essential oils, and isolated compounds. These bioactive components possess diverse chemical structures and mechanisms of action, making them a rich resource for combating antimicrobial resistance (AMR). Plant extracts often contain complex mixtures of secondary metabolites such as alkaloids, flavonoids, tannins, terpenoids, and glycosides, which contribute to their antimicrobial properties. Essential oils, aromatic volatile compounds extracted from plants, are known for their potent antibacterial, antifungal, and antiviral activities. Additionally, isolated compounds from plants, such as berberine, curcumin, and eugenol, have been extensively studied for their antimicrobial efficacy (Savoia, 2012).

In many cultures, herbal remedies have been passed down through generations, providing a rich repository of ethnopharmacological knowledge. The use of garlic (*Allium sativum* L.) for its antibacterial properties, tea tree oil (*Melaleuca alternifolia* Maiden & Betche)

Cheel) for its antimicrobial effects, and neem (*Azadirachta indica* A. Juss.) for its wide range of medicinal applications are just a few examples of how traditional practices have harnessed the power of plants to treat infections. Modern scientific research has increasingly validated the antimicrobial efficacy of these traditional remedies. Studies have demonstrated that phytomedicines not only possess direct antimicrobial activity but also have the potential to disrupt biofilms, enhance the immune response, and work synergistically with conventional antibiotics (Khare *et al*., 2021).

2.1 Mechanisms of action

Phytomedicines exert their antimicrobial effects through multiple mechanisms, each contributing to their potential in combating antimicrobial resistance (AMR). These mechanisms include the disruption of bacterial cell walls and membranes, inhibition of biofilm formation, interference with bacterial communication (quorum sensing), and modulation of host immune responses.

One of the primary mechanisms by which phytomedicines exert antimicrobial effects is through the disruption of bacterial cell walls and membranes. Essential oils and plant extracts often contain compounds like terpenoids and phenolic acids that can compromise the integrity of microbial cell structures. For example, eugenol, a phenolic compound found in clove oil (*Syzygium aromaticum* (L.) Merr. & L.M.Perry), disrupts the cell membrane of bacteria, leading to cell lysis and death (Nazzaro *et al*., 2017). Similarly, tea tree oil (*M. alternifolia*) contains terpinen-4-ol, which has been shown to penetrate and disrupt bacterial cell walls (Brun *et al*., 2019).

Biofilms protect bacteria from antibiotics and the immune system, making infections harder to treat. Phytomedicines can inhibit the formation of biofilms or disrupt existing ones. For instance, garlic (*A. sativum*) contains allicin, which has been demonstrated to prevent biofilm formation in various bacterial species, including *Pseudomonas aeruginosa* and *Staphylococcus aureus* (Shahid *et al*., 2021). Quorum sensing is a process by which bacteria communicate and coordinate group behaviors, including biofilm formation and virulence factor production. Phytochemicals can interfere with quorum sensing, thereby reducing bacterial pathogenicity (Subramani and Jayaprakashvel, 2019; Ghosh *et al*., 2022).

Phytomedicines can also enhance the host immune response, helping the body to combat infections more effectively. Echinacea [*Echinacea purpurea* (L.) Moench] is well-known for its immune-modulating properties, stimulating the activity of macrophages and the production of cytokines, which are critical for an effective immune response (Hudson, 2012). Likewise, curcumin from turmeric (*Curcuma longa* L,) has anti-inflammatory properties and modulates the immune system by influencing the activity of various immune cells and cytokine production (Khare *et al*., 2021).

3. Advantages of phytomedicine

Phytomedicine offers several advantages over synthetic antibiotics, making it a promising alternative in the fight against antimicrobial resistance (AMR). One significant advantage of phytomedicines is their lower likelihood of inducing resistance compared to synthetic antibiotics. The complex mixtures of bioactive compounds in plant extracts act on multiple microbial targets simultaneously, making it more challenging for pathogens to develop resistance. This polypharmacological approach reduces the selection pressure for resistant strains, unlike single-target synthetic antibiotics, which bacteria can more easily overcome through specific genetic mutations (Khare *et al*., 2021). Phytomedicines can enhance the efficacy of conventional antibiotics through synergistic interactions. When used in combination, plant-derived compounds can increase bacterial susceptibility to antibiotics, lower the required doses, and reduce adverse effects (Onyancha *et al*., 2021). Such synergistic effects can help in overcoming resistance and extending the lifespan of existing antibiotics.

Phytomedicines often exhibit broad-spectrum antimicrobial activity, capable of targeting a wide range of pathogens, including bacteria, fungi, and viruses. This broad-spectrum efficacy is attributed to the diverse bioactive compounds present in plant extracts (Sarkar *et al*., 2021). This versatility makes phytomedicines valuable in treating mixed infections and reducing the need for multiple antibiotics. Phytomedicines generally have lower side effects compared to synthetic antibiotics, leading to better patient compliance. The natural origin of plant-based compounds often results in fewer adverse reactions, as they are more biocompatible and less likely to disrupt the body's natural microbiota (Pancu *et al*., 2021). Improved tolerability and acceptance by patients can enhance treatment outcomes and adherence to therapy regimens.

4. Challenges and future directions

One of the primary challenges in utilizing phytomedicine to combat antimicrobial resistance (AMR) is the standardization and regulation of plant-based therapies. The variability in the phytochemical content of plant extracts, influenced by factors such as plant species, geographical location, and extraction methods, poses significant hurdles. Ensuring consistency in the composition and potency of phytomedicines is crucial for their reliable use in healthcare. Moreover, regulatory frameworks for phytomedicines differ globally, with varying degrees of scrutiny and approval processes, complicating their acceptance and integration into mainstream medicine. While *in vitro* and *in vivo* studies have demonstrated the potential of phytomedicines, rigorous clinical trials are essential to establish their efficacy and safety in humans. The lack of large-scale, well-designed clinical trials limits the evidence base needed for the acceptance of phytomedicines by the medical community. Ensuring that these trials are conducted with standardized preparations and robust methodologies will help validate the therapeutic claims and ensure patient safety.

Integrating phytomedicine into mainstream healthcare systems requires a multifaceted approach. This includes educating healthcare professionals about the benefits and limitations of plant-based therapies and incorporating phytomedicines into treatment guidelines where evidence supports their use. Collaboration between traditional practitioners and modern healthcare providers can facilitate a more holistic approach to treatment, leveraging the strengths of both systems. Moreover, the development of phytomedicine-specific regulatory frameworks can help ensure quality and safety, fostering greater acceptance and use.

4.1 Future research and policy initiatives

To fully harness the potential of phytomedicine in combating AMR, future research should focus on the following areas:

- **Phytochemical standardization:** Developing standardized methods for the extraction, characterization, and quantification of bioactive compounds in plant extracts.
- **Mechanistic studies:** Investigating the molecular mechanisms of action of phytochemicals to better understand how they combat microbial infections and resist resistance development.
- **Clinical trials:** Conducting large-scale, randomized controlled trials to establish the safety and efficacy of phytomedicines in human populations.
- **Regulatory harmonization:** Establishing harmonized regulatory standards across countries to ensure the quality and safety of phytomedicines.
- **Policy support:** Encouraging policy initiatives that support the integration of phytomedicine into national healthcare systems, including funding for research and development and incentives for clinical trials.

Conclusion

Phytomedicine holds significant promise in the battle against antimicrobial resistance (AMR), offering numerous benefits such as lower likelihood of resistance development, synergistic effects with conventional antibiotics, broad-spectrum antimicrobial activity, and fewer side effects leading to better patient compliance. These advantages make plant-based therapies a valuable addition to the existing arsenal against resistant pathogens. However, realizing the full potential of phytomedicine requires ongoing research and a concerted effort to bridge the gap between traditional and modern medical practices. Rigorous scientific studies, including standardized clinical trials, are essential to validate the efficacy and safety of phytomedicines. Additionally, fostering collaboration between traditional practitioners and contemporary healthcare providers can facilitate a more integrated and holistic approach to treatment, leveraging the strengths of both systems. As we move forward, the future of phytomedicine in addressing global health challenges looks promising. By embracing interdisciplinary research, establishing standardized regulatory frameworks, and promoting educational initiatives, we can harness the power of plant-based therapies to combat AMR and other emerging health threats. This integrated approach not only enhances treatment options but also contributes to the sustainability and resilience of healthcare systems worldwide. In conclusion, phytomedicine represents a valuable and innovative frontier in the ongoing fight against AMR, offering hope for more effective and sustainable healthcare solutions.

I firmly believe that **'Annals of Phytomedicine: An International Journal'** continues to play a crucial role in advancing the field of phytomedicine. By consistently publishing high-quality research and innovative findings, the journal has become an indispensable resource for scientists and researchers. The dedicated editorial team's commitment to excellence ensures that each issue provides valuable insights and contributes significantly to the scientific community. As the journal progresses, it will undoubtedly remain a beacon of knowledge and inspiration, driving forward the frontiers of phytomedicine and promoting the integration of traditional and modern medical practices. I extend my best wishes for its continued success and many future accomplishments.

Conflict of interest

The author declares no conflicts of interest relevant to this article.

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Biography

Dr. Juber Akhtar is currently serving as Professor and Head in the Department of Pharmacy, Integral University, Lucknow, Uttar Pradesh. Professor Juber Akhtar's illustrious career in the field of pharmaceutical sciences has been marked by significant contributions to academia, research, and industry. His academic journey began with a strong foundational education, obtaining a B.Sc. from A.M.U., Aligarh in 2001, followed by B. Pharm. from Hamdard University, New Delhi in 2005, and M. Pharm. from Manipal University, Karnataka in 2007. He achieved his Ph.D. from Integral University, Lucknow in 2014, demonstrating his deep commitment to advancing his knowledge and expertise.

Professor Akhtar's professional career has been equally impressive. He began his academic tenure at Integral University, Lucknow, where he held multiple roles ranging from Lecturer to Professor and Head of the Faculty of Pharmacy. His international experience includes a notable tenure as a Professor at Buraydah College of Pharmacy, Al-Qassim, Saudi Arabia, enhancing his global perspective and exposure.

In his role as an educator, Professor Akhtar has been deeply involved in teaching a variety of subjects such as Industrial Management, Pharmaceutical Marketing, Biopharmaceutics and Pharmacokinetics, and more. His approach to education is not only about imparting knowledge but also motivating and inspiring students, which is evident from his ability to handle classes effectively and his capacity as a team facilitator.

Professor Akhtar's research portfolio is particularly distinguished. His doctoral research focused on developing a novel oral nanoemulsion-based drug delivery system for antidiabetic drugs, showcasing his expertise in nanoformulation, a field in which he has considerable skills. His research has been impactful, with numerous publications in high-impact journals and significant contributions to conferences and seminars worldwide. Noteworthy among his research endeavors are his studies on nanoemulsion for improved delivery systems, and his contributions to the development of niosomal gel for wound healing.

Moreover, Professor Akhtar holds patents that further exemplify his innovative approach. One such patent is for an emulsion for cardiac protection, reflecting his focus on creating therapeutic solutions with practical applications. His ability to translate research into patentable innovations underscores his role as a leader in pharmaceutical sciences.

His professional memberships and roles as a reviewer for several international journals demonstrate his standing in the global scientific community. He has been a member of the Australian Diabetes Society and served as an editor and member of the editorial boards for various scientific journals, further highlighting his commitment to advancing pharmaceutical sciences.

Beyond his professional and research achievements, Professor Akhtar has also made significant contributions to the administrative and leadership aspects of academia. He has served as the head of various committees and boards, significantly influencing curriculum development, research direction, and academic standards at Integral University.

Professor Akhtar's career is also marked by his commitment to continuous learning and professional development. He has completed several value-added courses and certificates, including those in clinical research and intellectual property rights, which have enriched his knowledge and expertise in critical areas of pharmaceutical sciences.