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Review Article

Plant-Derived Phytochemicals as Potential Therapeutic Agents Against ESKAPE Pathogens: Recent Advances

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The rapid emergence of antimicrobial resistance (AMR) has rendered conventional antibiotics increasingly ineffective, particularly against the ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* spp.). These multidrug-resistant organisms are among the leading causes of nosocomial infections worldwide, significantly elevating morbidity, mortality, and healthcare costs. The failure of existing treatment regimens underscores the urgent need for alternative antimicrobial strategies. Plant-derived phytochemicals, including alkaloids, flavonoids, terpenoids, phenolics, and saponins, have emerged as promising candidates due to their structural diversity, multi-target mechanisms, and lower propensity for resistance development. Recent studies highlight their ability to disrupt bacterial membranes, inhibit nucleic acid and protein synthesis, interfere with quorum sensing, and prevent biofilm formation. Additionally, phytochemicals such as resveratrol, curcumin, and diosgenin demonstrate synergistic interactions with conventional antibiotics, enhancing therapeutic efficacy and reducing required doses. Advances in nanotechnology-based formulations further improve solubility, bioavailability, and targeted delivery of these compounds, addressing key translational challenges. However, issues related to standardization, toxicity profiling, and clinical validation remain critical barriers to their integration into mainstream antimicrobial therapy. This review provides a comprehensive overview of phytochemicals with reported activity against ESKAPE pathogens, emphasizing their mechanisms of action, synergistic potential, and future prospects as adjuncts or alternatives to conventional antibiotics. Harnessing phytochemicals represents a sustainable and innovative approach in the global fight against AMR.

Keywords: Phytochemicals; ESKAPE pathogens; Antimicrobial resistance; Plant-derived antimicrobials; Synergy; Nanotechnology.

INTRODUCTION

Antimicrobial resistance (AMR) represents a growing global health concern, particularly due to the rise of the ESKAPE pathogens—*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species. These bacteria are notorious for causing hospital-acquired infections and exhibit high levels of multidrug resistance, leading to increased morbidity, mortality, and healthcare costs worldwide [1,2]. Their resistance is driven by sophisticated mechanisms such as efflux pump overexpression, biofilm formation, quorum sensing regulation, and enzymatic degradation of antibiotics, all of which contribute to persistent and difficult-to-treat infections [3–6]. These adaptive strategies enable bacteria to evade immune responses, reduce antibiotic penetration, and survive in hostile environments [4,7]. In response to the declining efficacy of conventional antibiotics, plant-derived phytochemicals have gained attention as promising alternatives. Compounds such as alkaloids, flavonoids, terpenoids, phenolics, and saponins have shown broad-spectrum antimicrobial activity and are often less prone to inducing resistance [8,9]. Their mechanisms of action include disrupting

bacterial cell membranes, inhibiting protein and nucleic acid synthesis, interfering with quorum sensing pathways, inhibiting biofilm formation, and modulating efflux pump activity [9,10]. These diverse targets make phytochemicals valuable candidates for addressing the current antibiotic resistance crisis. Moreover, several phytochemicals exhibit synergistic interactions with conventional antibiotics, which can lower the required therapeutic doses and potentially reduce drug-associated toxicity. For instance, curcumin in combination with meropenem has demonstrated synergistic activity against carbapenem-resistant *Klebsiella pneumoniae*, enhancing antimicrobial efficacy in vitro [11]. Similarly, trans-resveratrol and curcumin have shown the ability to inhibit key virulence factors in methicillin-resistant *Staphylococcus aureus* (MRSA), including biofilm formation and toxin production, thereby sensitizing the pathogen to antibiotics [12,13]. In another study, curcumin combined with colistin significantly reduced both the minimum inhibitory concentrations (MICs) and biofilm-forming capacity of *Pseudomonas aeruginosa* [14]. These findings highlight the therapeutic potential of phytochemical-antibiotic combinations in tackling multidrug-resistant infections.

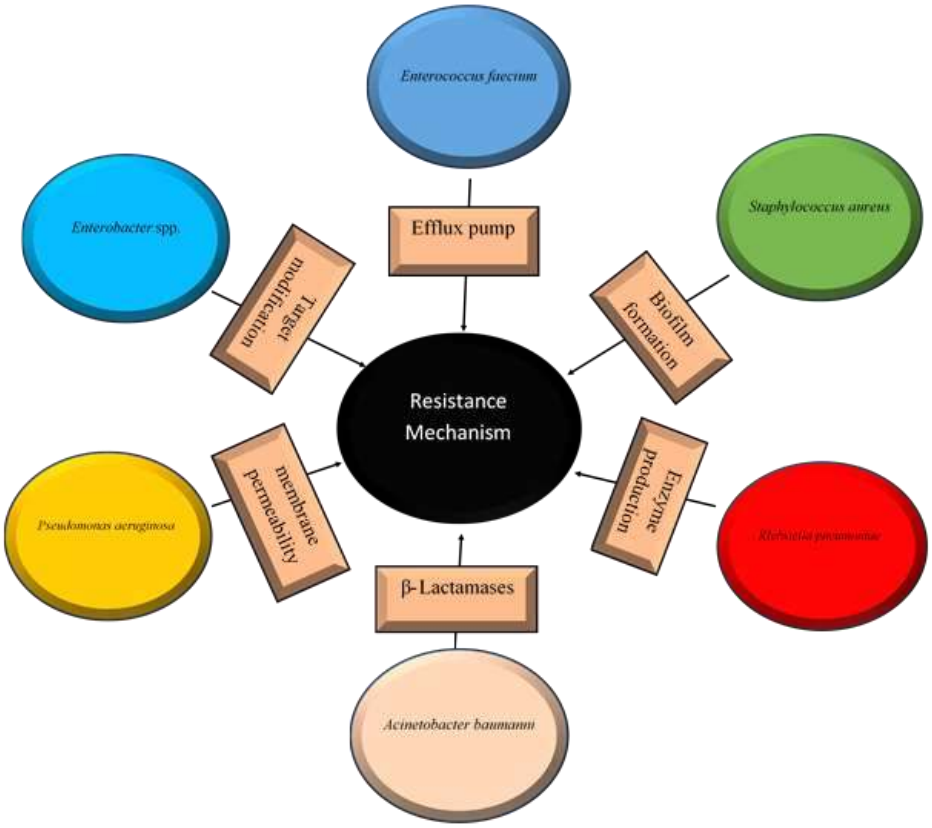

Figure 1: Overview of ESKAPE Pathogens and Their Resistance Mechanisms

Phytochemicals as Antimicrobial Agents

Phytochemicals are naturally occurring bioactive compounds produced by plants as part of their defence against herbivores, pathogens, and environmental challenges. These metabolites have recently garnered strong interest for their therapeutic potential, especially as antimicrobial agents effective against multidrug-resistant organisms. Unlike many conventional antibiotics that target a single molecular site, phytochemicals often act on multiple targets, which helps lower the risk of resistance development [15]. Classes such as alkaloids, flavonoids, terpenoids, tannins, and saponins have shown inhibition of a broad spectrum of microbes, including clinically important ESKAPE pathogens [16]. Their structural diversity enables a variety of antimicrobial mechanisms, ranging from disruption of microbial membranes to suppression of virulence factors and interference in regulatory systems [17]. Together, these traits support phytochemicals as promising candidates for alternative or adjunctive antimicrobial therapies.

Overview of Plant Secondary Metabolites

Plant secondary metabolites are broadly classified into alkaloids, phenolics (including flavonoids, tannins, and coumarins), terpenoids (mono-, sesqui-, and triterpenes), and glycosides. Although not essential for primary metabolism, these compounds play crucial ecological roles in plant defence and adaptation [18]. Alkaloids, such as berberine and quinine, exhibit strong antibacterial activity through mechanisms including DNA intercalation and inhibition of protein synthesis, while flavonoids like quercetin and apigenin disrupt bacterial cell walls, modulate efflux pumps, and inhibit biofilm formation. Terpenoids (e.g. thymol, carvacrol) destabilize microbial membranes and impair respiration, whereas tannins and phenolic acids act by precipitating proteins and inhibiting enzyme activity. This structural and functional diversity imparts a wide spectrum of antimicrobial effects, allowing many plant-derived compounds to selectively inhibit both Gram-positive and Gram-negative bacteria, including strains resistant to conventional antibiotics [19,20].

Mechanistic Basis of Antimicrobial Activity

The antimicrobial efficacy of phytochemicals often depends on their capacity to attack multiple cellular processes simultaneously, which helps reduce the likelihood of resistance. For example, terpenoids and saponins have been shown to compromise bacterial membranes and envelope integrity: saponins isolated from *Achyranthus aspara* inhibited *Staphylococcus aureus* growth in a dose-dependent manner, consistent with actions on cell envelopes [21]. Flavonoids such as quercetin interfere with quorum sensing pathways and inhibit biofilm formation; in *Pseudomonas aeruginosa* PAO1, quercetin significantly reduced expression of QS genes (lasI, lasR, rhlI, rhlR), virulence factors, and biofilm formation at sub-MIC concentrations [22]. Curcumin, especially when formulated (e.g. liposomes) or in combination with agents like honey, similarly disrupts QS-regulated phenotypes, including motility, enzyme production, and biofilm formation, without necessarily killing cells outright [23,24]. Conessine has been identified as an inhibitor of multidrug efflux pumps in *Pseudomonas aeruginosa*, which can restore antibiotic accumulation and effectiveness [25]. Polyphenols more broadly (resveratrol, curcumin, etc.) also exert antimicrobial effects via inhibition of critical microbial enzymes and by inducing oxidative stress, for example through generation of reactive oxygen species, contributing to cellular damage [26]. Altogether, these multifaceted mechanisms highlight the promise of phytochemicals as scaffolds for developing next-generation antimicrobials against multidrug-resistant ESKAPE pathogens.

Phytochemicals Active Against ESKAPE Pathogens

Alkaloids

Alkaloids are a structurally diverse class of nitrogen-containing secondary metabolites with well-documented antimicrobial activity. Representative compounds such as berberine, sanguinarine, and related isoquinoline alkaloids exhibit inhibitory effects by binding to nucleic acids (DNA intercalation) and suppressing topoisomerase activity, thereby interfering with replication and transcription [21,22]. These compounds also disrupt cell division; for example, berberine inhibits bacterial FtsZ, a key protein in septum formation[14]. In addition, certain alkaloids function as efflux pump inhibitors (EPIs), enhancing intracellular accumulation of antibiotics and restoring drug effectiveness: resverpine (an indole alkaloid) enhances antibiotic susceptibility in multidrug-resistant *Acinetobacter baumannii* and *Stenotrophomonas maltophilia* by inhibiting efflux pumps [14]. Collectively, the capacity of alkaloids to target multiple cellular processes and virulence determinants underscores their promise in combatting multidrug-resistant ESKAPE pathogens.

Flavonoids

Flavonoids, including quercetin, apigenin, and catechin, show robust antimicrobial properties via multiple mechanisms, such as disrupting cell wall or membrane integrity, inhibiting nucleic acid synthesis, and attenuating quorum sensing [27]. Notably, quercetin has been demonstrated to strongly inhibit biofilm formation and virulence factor production in *Pseudomonas aeruginosa* — it reduces expression of QS genes (lasI, lasR, rhlI, rhlR), decreases pyocyanin, elastase, protease production, and suppresses biofilm

mass even at sub-MIC levels [28,29]. There is also emerging (though more limited) evidence of antibiofilm effects of quercetin against *Acinetobacter baumannii*, pointing toward its potential as a natural antibiofilm agent for multidrug-resistant ESKAPE pathogens.

Terpenoids

Terpenoids such as thymol, carvacrol, and lupeol exert antimicrobial effects by disrupting bacterial membranes, impairing respiration, and inducing oxidative stress [29,30]. These compounds are especially effective against Gram-positive pathogens including *Enterococcus faecium* and *Staphylococcus aureus*, while also demonstrating inhibitory activity against Gram-negative ESKAPE pathogens such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* [30]. Their multifaceted mechanisms contribute to membrane depolarization, biofilm reduction, and interference with bacterial energy metabolism, highlighting their potential as broad-spectrum antimicrobial agents.

Phenolics and Polyphenols

Phenolic compounds, including gallic acid, tannins, and curcumin, exert antimicrobial effects through protein precipitation, inhibition of essential microbial enzymes, and scavenging of free radicals that support bacterial survival [18]. In addition to these primary effects, polyphenols such as resveratrol and curcumin have been shown to suppress bacterial virulence factors and interfere with efflux pump activity, thereby increasing the susceptibility of pathogens like *Escherichia coli* and *Enterobacter* species to conventional antibiotics [26,30]. These mechanisms highlight the potential of phenolics as effective adjuncts in the treatment of infections caused by multidrug-resistant organisms.

Saponins

Alkaloids represent a diverse group of nitrogen-containing secondary metabolites with broad antimicrobial activity. Compounds such as berberine, quinine, and sanguinarine have been shown to act against *Staphylococcus aureus* and *Klebsiella pneumoniae* by intercalating into DNA, inhibiting topoisomerases, and disrupting cell division [15,16]. Their ability to modulate efflux pumps and impair bacterial virulence factors makes them particularly effective against multidrug-resistant strains of ESKAPE pathogens [18,23,25].

Other Bioactive Compounds

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have been shown to inhibit bacterial DNA gyrase, while essential oils rich in eugenol and cinnamaldehyde interfere with quorum sensing and biofilm development. Such compounds highlight the untapped reservoir of structurally diverse phytochemicals that can be harnessed as alternative or adjunct therapeutics in combating antimicrobial resistance.

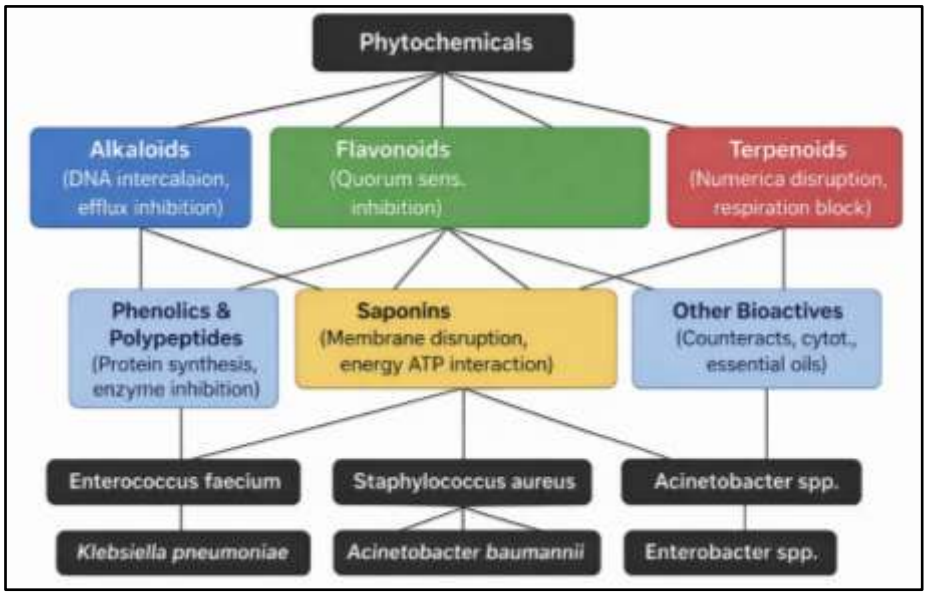

Figure 2: Pathway-style infographic of phytochemicals, mechanisms, and their targets among ESKAPE pathogens

Mechanisms of Action of Plant-Derived Compounds

Plant-derived compounds exert their biological effects through diverse mechanisms, targeting multiple cellular and molecular pathways:

Table 1: Mechanisms of Action of Plant-Derived Compounds

Mechanism of Action	Phytochemicals Involved	Description / Effect	Example
Cell Wall & Membrane Disruption	Terpenoids, Saponins, Essential Oils	Integrate into lipid bilayers, increase permeability, cause leakage and cell lysis	Terpenoids disrupting bacterial membranes
Enzyme Inhibition	Alkaloids, Flavonoids, Phenolics	Inhibit key microbial or host enzymes, affecting DNA/protein synthesis and metabolism	Flavonoids inhibiting DNA gyrase
DNA/RNA Interference	Alkaloids (Berberine, Quinoline)	Intercalate into nucleic acids, preventing transcription and replication	Berberine blocking bacterial DNA replication
Oxidative Stress Induction	Polyphenols, Quinones	Generate reactive oxygen species (ROS), causing damage to lipids, proteins, nucleic acids	ROS-induced apoptosis in cancer cells
Anti-Quorum Sensing & Biofilm Disruption	Flavonoids, Terpenoids, Phenolics	Inhibit bacterial communication, reduce biofilm formation and virulence	Flavonoids reducing biofilm in Pseudomonas
Immunomodulatory Effects	Polysaccharides, Flavonoids	Enhance host defence via cytokine modulation, phagocytosis, or NK cell activity	Polysaccharides from Fabaceae stimulating macrophages

Synergistic Potential with Conventional Antibiotics

Plant-derived compounds exhibit remarkable synergistic potential when combined with conventional antibiotics, offering an effective strategy to combat antimicrobial resistance. Such synergy is achieved through diverse mechanisms, including inhibition of bacterial efflux pumps, increased membrane permeability, disruption of biofilms, and

inhibition of resistance enzymes such as β-lactamases. By facilitating antibiotic entry, restoring sensitivity, and weakening microbial defence systems, phytochemicals like flavonoids, alkaloids, terpenoids, and phenolics significantly enhance antibiotic efficacy. This interaction not only reduces the required dosage of antibiotics but also minimizes adverse effects and delays the emergence of resistant strains, highlighting the therapeutic relevance of combining natural products with existing antimicrobial agents.

Advances in Phytochemical Delivery Systems

Despite their therapeutic promise, many phytochemicals are hindered by poor solubility, instability, and low bioavailability, which restrict their clinical translation. Advances in nanotechnology-based delivery systems have addressed these limitations by improving stability and pharmacokinetics. Liposomes, polymeric nanoparticles, and solid lipid nanoparticles have been shown to enhance solubility and protect bioactive compounds from degradation (7,9). Nano emulsions and micelles further increase dispersibility and intestinal absorption of hydrophobic phytochemicals, thereby improving systemic availability [16,18]. Biopolymer-based carriers such as chitosan and alginate provide biocompatibility and controlled release, making them suitable for safe therapeutic applications [19]. Moreover, ligand-functionalized nanocarriers allow site-specific targeting, minimizing systemic toxicity while maximizing therapeutic efficiency [20,23]. Collectively, these strategies significantly enhance the efficacy and safety of phytochemicals, bridging the gap between experimental findings and clinical application.

Delivery System	Description / Advantage	Examples of Phytochemicals	Reference
Liposomes	Biocompatible lipid vesicles; enhance solubility, stability, and targeted delivery	Curcumin, Quercetin	Patra et al., 2018
Polymeric Nanoparticles	Provide controlled release, protect against degradation, improve bioavailability	Resveratrol, Epigallocatechin gallate (EGCG)	Sharma et al., 2019
Solid Lipid Nanoparticles (SLNs)	Stable carriers with high drug loading capacity; prolonged release	Curcumin, Genistein	Ansari et al., 2021
Dendrimers	Highly branched nanostructures; improve solubility and allow surface modifications	Quercetin, Naringenin	Mousa & Bharali, 2019
Nanoemulsions	Improve dispersibility of hydrophobic compounds; rapid absorption	Curcumin, Thymol	Patra et al., 2018
Micelles	Amphiphilic carriers that solubilize poorly water-soluble compounds	Resveratrol, Kaempferol	Ansari et al., 2021
Biopolymer-based Systems	Biodegradable, safe carriers using chitosan, alginate, or starch; enhance mucoadhesion	Curcumin, Catechins	Ansari et al., 2021
Ligand-functionalized Nanoparticles	Provide targeted delivery, reduce systemic toxicity	Curcumin, Paclitaxel (plant-derived alkaloid)	Mousa & Bharali, 2019

Phytochemicals and Resistance Modulation

Phytochemicals play a crucial role in modulating antimicrobial resistance by targeting multiple resistance mechanisms in pathogenic microorganisms. Secondary metabolites such as alkaloids, flavonoids, terpenoids, and phenolics can act as efflux pump inhibitors, thereby preventing the extrusion of antibiotics and restoring drug sensitivity [18,23,25]. In addition, several compounds disrupt biofilm formation and quorum sensing, reducing bacterial virulence and enhancing the efficacy of conventional antibiotics [9,22,24]. Certain phytochemicals also inhibit resistance enzymes, including β-lactamases, thus protecting antibiotics from degradation [6,15]. Furthermore, by enhancing membrane permeability, phytochemicals facilitate antibiotic uptake and potentiate antimicrobial activity

[16,19]. Collectively, these mechanisms highlight the potential of plant-derived compounds as resistance-modifying agents, offering a promising adjunct strategy to counter multidrug resistance.

Preclinical and Clinical Investigations

Preclinical and clinical studies provide essential insights into the therapeutic potential of phytochemicals, bridging the gap between laboratory research and clinical application. Preclinical investigations, including *in vitro* assays and *in vivo* animal models, have demonstrated antimicrobial, anticancer, antioxidant, and anti-inflammatory properties of numerous plant-derived compounds [19]. These studies help establish pharmacokinetics, toxicity profiles, and mechanisms of action, which are crucial for further clinical evaluation. Clinical trials have validated the safety and efficacy of several phytochemicals, such as curcumin, resveratrol, and quercetin, in managing infections, metabolic disorders, and inflammatory diseases [7,20]. However, challenges such as low bioavailability, variability in plant extracts, and limited large-scale clinical data restrict their widespread therapeutic use. Advances in delivery systems and standardization techniques are expected to overcome these hurdles, paving the way for integration of phytochemicals into mainstream medicine.

Challenges and Future Perspectives

Despite their immense therapeutic promise, the translation of phytochemicals into mainstream medicine faces several challenges that must be addressed for successful clinical application.

Standardization and Quality Control of Plant Extracts

One of the major limitations is the variability in phytochemical content due to differences in plant species, growing conditions, harvesting methods, and extraction techniques. Lack of standardized protocols often leads to inconsistent efficacy and safety profiles, highlighting the need for robust quality control measures and validated analytical techniques.

Regulatory and Translational Hurdles

Unlike synthetic drugs, phytochemicals and herbal formulations face complex regulatory pathways, which vary across countries. Issues related to patentability, large-scale production, reproducibility of clinical outcomes, and insufficient toxicological data further hinder their translation into approved therapeutics.

Integrating Phytochemicals into Antimicrobial Stewardship

With rising antimicrobial resistance, phytochemicals hold potential as antibiotic adjuvants. However, their integration into antimicrobial stewardship programs requires evidence-based clinical guidelines, multidisciplinary collaboration, and awareness among healthcare providers. Bridging this gap will demand rigorous clinical trials, advanced delivery systems, and stronger regulatory frameworks.

CONCLUSION

Summary of Current Evidence

Phytochemicals have emerged as promising alternatives and adjuncts in the fight against antimicrobial resistance, particularly against the multidrug-resistant ESKAPE pathogens. Evidence from in vitro, in vivo, and early clinical studies highlights their diverse mechanisms of action, including disruption of microbial membranes, inhibition of resistance enzymes, efflux pump suppression, and biofilm interference. Advances in nanotechnology-driven delivery systems have further improved their solubility, stability, and targeted activity, addressing major limitations of conventional plant extracts. Moreover, synergistic interactions between phytochemicals and antibiotics demonstrate their potential in restoring antibiotic efficacy and reducing resistance development.

Outlook for Phytochemicals in Combating ESKAPE Pathogens

Looking forward, phytochemicals represent a valuable resource for next-generation antimicrobial strategies. Their ability to modulate resistance mechanisms and enhance host immunity positions them as strong candidates for integration into antimicrobial stewardship programs. However,

challenges related to standardization, bioavailability, regulatory approval, and large-scale clinical validation must be addressed to enable their widespread application. Future research should focus on systematic preclinical and clinical evaluations, development of advanced delivery systems, and translational frameworks. With continued innovation and multidisciplinary collaboration, phytochemicals hold significant promise as effective therapeutic tools in combating ESKAPE pathogens and mitigating the global antimicrobial resistance crisis.

REFERENCES

1. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic resistant bacteria and tuberculosis. Lancet Infectious Diseases. 2018 Mar;18(3):318 27.
2. Santajit S, Indrawattana N. Mechanisms of Antimicrobial Resistance in ESKAPE Pathogens. BioMed Research International. 2016; 2016:2475067.
3. Dawan J, Li Y, Lu F, He X, Ahn J. Role of Efflux Pump Mediated Antibiotic Resistance in Quorum Sensing Regulated Biofilm Formation by Salmonella Typhimurium. Pathogens. 2022;11(2):147.
4. "The burden of ESKAPE pathogen related hospital acquired infections: clinical and financial perspective from a systematic review." Journal name / PubMed. 2023. [It reports that resistant ESKAPE HAIs nearly double risk of death, lengthen hospital stays, and raise costs.]5
5. Biofilm inhibition based on controlling the transmembrane transport and extracellular accumulation of quorum sensing signals: study of astragaloside IV, eugenol, baicalin against Pseudomonas aeruginosa. Elsevier. 2023.
6. Bacterial resistance to antibiotics: enzymatic degradation and modification. Clinical Microbiology Reviews. 2005;18(1):3 27.
7. Nanobiotics against antimicrobial resistance: harnessing the power of nanoscale materials and technologies. Journal of Nanobiotechnology. 2022; 20:428.
8. Clinical and economic impact of antibiotic resistance in developing countries: a systematic review and meta-analysis. PLoS ONE. 2017;12(12):e0189621.
9. Plant Based Phytochemicals as Possible Alternative to Antibiotics in Combating Bacterial Drug Resistance. Antibiotics (Basel). 2020;9(8):480.
10. Flavonoids as Antimicrobial Agents: A Comprehensive Review of Mechanisms and Therapeutic Potential. [Journal (Flavonoids Review)]. 2023; details as per article.
11. Gülen D, Şafak B, Erdal B, Günaydın B. Curcumin-meropenem synergy in carbapenem resistant Klebsiella pneumoniae. Iran J Microbiol. 2022;14(4):265–72.
12. Alqahtani M, Almukainzi M, Alghoribi MF, et al. Antivirulence effects of trans-resveratrol and curcumin on methicillin-resistant Staphylococcus aureus from Saudi Arabia. Life (Basel). 2024;14(4):491.
13. El-Mahdy AM, Alqahtani M, Almukainzi M, Alghoribi MF, Abdel-Rhman SH. Effect of resveratrol and curcumin on gene expression of methicillin-resistant Staphylococcus aureus (MRSA) toxins. J Microbiol Biotechnol. 2023;34(1):141–8.
14. Basu A, Maity AR, Chakraborti S, et al. Curcumin and colistin are synergistic in inhibiting the growth and biofilm formation of Pseudomonas aeruginosa isolated from environmental sample. Gavin J Pharmacol Ther. 2021;4(1):1–9.
15. Cushnie TPT, Cushnie B, Lamb AJ. Alkaloids: an overview of their antibacterial, antibiotic enhancing and antivirulence activities. Int J Antimicrob Agents. 2014;44(5):377 86
16. Gyawali R, Ibrahim SA. Natural products as antimicrobial agents. Food Control. 2014; 46:412 29
17. Cushnie TPT, Lamb AJ. Recent advances in understanding the antibacterial properties of flavonoids. Int J Antimicrob Agents. 2011;38(2):99 107
18. Upadhyay A, Upadhyaya I, Kollanoor Johny A, Venkitanarayanan K. Combating Pathogenic Microorganisms Using Plant Derived Antimicrobials: A Minireview of the Mechanistic Basis. Biomed Res Int. 2014; 2014:761741.
19. Bassey K, Mabowe M. Phytoconstituent Detection, Antioxidant, and Antimicrobial

Potentials of Moringa oleifera Lam. Hexane Extract Against Selected WHO ESKAPE Pathogens. Horticulturae. 2025;11(8):869.
20. Plant Flavonoids with Antimicrobial Activity against Methicillin Resistant Staphylococcus aureus (MRSA). ACS Infect Dis. 2024;10(9):3086 3097.
21. Sharma S, Shrivastava P, Saxena RC. Antimicrobial Activity of Saponins Isolated from Achyranthus aspara Against Staphylococcus aureus. Asian J Chem. 2010;18(4):2766–70.
22. Ouyang J, Sun F, Feng W, Sun Y, Qiu X, Xiong L, et al. Quercetin is an effective inhibitor of quorum sensing, biofilm formation and virulence factors in Pseudomonas aeruginosa. J Appl Microbiol. 2016;120(4):966 74.
23. Chadha N, Kumar A, Kulshrestha S, et al. Repurposing phytochemicals as anti-virulent agents to attenuate quorum sensing regulated virulence factors and biofilm formation in Pseudomonas aeruginosa. Microbial Biotechnology. 2022;15(9):2722 2739.
24. Jadaun V, Prateeksha, Singh BR, Paliya BS, Upreti DK, Rao ChV, et al. Honey enhances the anti-quorum sensing activity and anti-biofilm potential of curcumin. RSC Adv. 2015; 5:71060 71070.
25. Thien Trung P, Vu Giang N, Quach TP, et al. Conessine as a novel inhibitor of multidrug efflux pump systems in Pseudomonas aeruginosa. Antimicrob Agents Chemother. 2017;61(7): e01228 17.
26. Santos A, Lima L, Franco R, Pinto M. Exploring phenolic compounds as quorum sensing inhibitors in foodborne bacteria. Int J Food Microbiol. 2021; 353:109377.
27. Antimicrobial Activity of Quercetin: An Approach to Its Mechanistic Principle. Molecules. 2022;27(8):2494. (This review covers mechanisms of flavonoids including membrane disruption, nucleic acid effects, QS interference, etc.)
28. Ouyang J, Sun F, Feng W, Sun Y, Qiu X, Xiong L, et al. Quercetin is an effective inhibitor of quorum sensing, biofilm formation and virulence factors in Pseudomonas aeruginosa. J Appl Microbiol. 2016;120(4):966 74.
29. Quercetin Exhibits Broad Spectrum Antibiofilm and Antiquorum Sensing Activities Against Gram Negative Bacteria: In Vitro and In Silico Investigation Targeting Antimicrobial Therapy. Can J Infect Dis Med Microbiol. 2025; [Date?]. (Demonstrates antibiofilm/anti QS activities of quercetin vs P. aeruginosa and others)
30. Marchese A, Orhan IE, Daglia M, Barbieri R, Di Lorenzo A, Nabavi SF, et al. Antibacterial and antifungal activities of thymol: A brief review of the literature. Food Chem. 2016; 210:402 14.
31. Ghosh I, Khanra M, Banerjee T, Sar S, Chakraverty R, Halder AK, Chaki R, Ghosh N. Phytochemicals as Therapeutic Agents for ESKAPE Pathogens. Current Indian Science. 2025 Jan;3(1): e2210299X354280.
32. Shin J, Prabhakaran VS, Kim KS. The multi-faceted potential of plant-derived metabolites as antimicrobial agents against multidrug-resistant pathogens. Microbial pathogenesis. 2018 Mar 1; 116:209-14.
33. Pattnaik S, Mishra M, Naik PK. Phytochemicals as Potential Antibacterial Agents Against ESKAPE Pathogens. InESKAPE Pathogens: Detection, Mechanisms and Treatment Strategies 2024 Mar 30 (pp. 379-419). Singapore: Springer Nature Singapore.
34. AlSheikh HM, Sultan I, Kumar V, Rather IA, Al-Sheikh H, Tasleem Jan A, Haq QM. Plant-based phytochemicals as possible alternative to antibiotics in combating bacterial drug resistance. Antibiotics. 2020 Aug 4;9(8):480.
35. Bhatia P, Sharma A, George AJ, Anvitha D, Kumar P, Dwivedi VP, Chandra NS. Antibacterial activity of medicinal plants against ESKAPE: An update. Heliyon. 2021 Feb 1;7(2).
36. Woo S, Marquez L, Crandall WJ, Risener CJ, Quave CL. Recent advances in the discovery of plant-derived antimicrobial natural products to combat antimicrobial resistant pathogens: insights from 2018–2022. Natural product reports. 2023;40(7):1271-90.
37. Rafeeq A, Arshad S, Abid MA, Sajjad MA, Shahzad M, Qadir ML, Safdar Z, Majid B. Potential of Plant-Derived Phytochemicals in Combating Antimicrobial Resistance: A Comprehensive Review. Journal of Health, Wellness and Community Research. 2025 Oct 7:e762-.
38. Chowdhury SK, Misra D, Mandal V. Medicinal plant-derived antimicrobials' fight against

multidrug-resistant pathogens. InMedicinal and aromatic plants: healthcare and industrial applications 2021 Mar 28 (pp. 391-427). Cham: Springer International Publishing.

39. Al-Arnoot S, Abdullah QY, Al-Maqtari MA, Ibrahim HM, Al-Shamahy HA, Salah EM, Al-Thobhani A, Al-Bana MN, Al-Akhali B. Multitarget antimicrobial mechanisms of plant extracts: A review of harnessing phytochemicals against drug-resistant pathogens. Sana'a University Journal of Medicine and Health Sciences. 2025 Aug 31;19(4):292-309.
40. Shanmugam Y, raj Gopinath G, christopher Moses A, Thanikachalam P, MS P, Bharathy P. Plant-Based phytochemicals as antibiotic alternatives for gangrene: A sustainable approach to infection management. Sustainable Chemistry for Climate Action. 2025 Jun 1; 6:100089.
41. Panda SK, Buroni S, Swain SS, Bonacorsi A, da Fonseca Amorim EA, Kulshrestha M, Da Silva LC, Tiwari V. Recent advances to combat ESKAPE pathogens with special reference to essential oils. Frontiers in Microbiology. 2022 Dec 6; 13:1029098.
42. Suganya T, Packiavathy IA, Aseervatham GS, Carmona A, Rashmi V, Mariappan S, Devi NR, Ananth DA. Tackling multiple-drug-resistant bacteria with conventional and complex phytochemicals. Frontiers in Cellular and Infection Microbiology. 2022 Jun 30; 12:883839.
43. Ghosh S, Basu S, Anbarasu A, Ramaiah S. A comprehensive review of antimicrobial agents against clinically important bacterial pathogens: prospects for phytochemicals. Phytotherapy Research. 2025 Jan;39(1):138-61.
44. Ashraf MV, Pant S, Khan MH, Shah AA, Siddiqui S, Jeridi M, Alhamdi HW, Ahmad S. Phytochemicals as antimicrobials: prospecting Himalayan medicinal plants as source of alternate medicine to combat antimicrobial resistance. Pharmaceuticals. 2023 Jun 15;16(6):881.
45. Gupta A, Verma A, Katiyar K. Phytochemical-based drug designing against efflux-pump of ESKAPE pathogen to combat multidrug-resistant: an in-silico study. Journal of Biomolecular Structure and Dynamics. 2025 Feb 25:1-21.

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