
NATURAL ANTIMICROBIAL COMPOUNDS OF PLANT ORIGIN: MECHANISMS OF ACTION AND PROSPECTS FOR APPLICATION AGAINST BACTERIAL INFECTION AGENTS

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INTRODUCTION

The increasing prevalence of antimicrobial resistance among bacterial pathogens has become one of the most urgent challenges in modern medicine. The excessive and inappropriate use of synthetic antibiotics has accelerated the emergence of multidrug-resistant strains, creating a need to develop new antimicrobial agents. Natural plant-derived products have a long history of use in traditional medical systems worldwide, and modern research increasingly confirms their pharmacological efficacy.¹ From a fundamental biological perspective, plant secondary metabolites evolved primarily as chemical defences against competing microorganisms, making the biodiversity of medicinal flora a valuable bioresource studied at the intersection of applied biology and ecology. Investigating their biological functions advances our understanding of plant–microbe interactions in the environment. It aligns with the «One Health» concept, which recognises the interconnection between human, animal, and environmental health. Such an ecologically grounded approach reinforces the relevance of this research to fundamental and applied studies in biology and ecology. So, phytochemicals are attracting considerable attention as potential antimicrobial agents.

Secondary metabolites of medicinal plants represent a vast library of chemically diverse compounds with proven antimicrobial, anti-inflammatory, and antioxidant properties. Among them, phenolic compounds, flavonoids, terpenoids, and alkaloids constitute the predominant classes of biologically active substances. Phenols and their derivatives, including flavonoids and phenolic acids, form one of the largest groups of plant secondary metabolites and are

¹ Newman D. J., Cragg G. M. Natural products as sources of new drugs from 1981 to 2019. *Journal of Natural Products*. 2020. Vol. 83, No 3. P. 770–803. DOI: 10.1021/acs.jnatprod.9b01285

present in virtually all species of medicinal plants.² Flavonoids, a subclass of phenolic compounds, exhibit diverse structural variations and possess multiple mechanisms of antimicrobial action.³ Terpenoids and their derivatives are found predominantly in essential oils⁴ and have well-documented antibacterial properties. Alkaloids, nitrogen-containing compounds with complex structures, represent another class of secondary metabolites with antimicrobial potential.⁵ The chemical diversity and multiplicity of mechanisms of action of all these compounds make them attractive candidates for combating antibiotic-resistant bacteria.

However, comparative studies of mechanisms across several classes of compounds and bacterial species remain limited. Understanding the mechanisms by which these plant compounds exert their antimicrobial effects is essential for rational drug development and the optimisation of therapeutic applications. Unlike single-target antibiotics, plant metabolites demonstrate polypharmacological activity, which may reduce the likelihood of resistance development. In addition, the use of plant compounds in topical applications, such as dermatology and wound treatment, offers clear advantages, including reduced systemic toxicity and improved tolerability.⁶

This study aims to investigate and compare the mechanisms of antimicrobial action of flavonoids, terpenoids, phenols, and alkaloids derived from medicinal plants against three clinically significant bacterial species: *S. aureus*, *E. coli*, and *C. acnes*. This study seeks to elucidate patterns of antimicrobial activity specific to individual compounds and mechanisms, characterise differential susceptibility among bacterial species, and provide scientific evidence supporting the therapeutic potential of these plant compounds as alternatives or adjuncts to conventional antimicrobial agents.

1. Main Antibacterial Mechanisms of Action of Phytochemicals

1.1. Studied pathogenic bacteria and biologically active compounds

Staphylococcus aureus is a facultatively anaerobic Gram-positive coccid bacterium and one of the most important bacterial pathogens in humans. It

² Taguri T., Tanaka T., Kouno I. Antimicrobial activity of 10 different plant polyphenolic compounds against bacteria associated with periodontal disease in vitro. *Journal of Periodontal Research*. 2024. Vol. 59, No 3. P. 457–469. DOI: 10.1248/bpb.27.1965

³ Cushnie T. P., Lamb A. B. Antimicrobial activity of flavonoids. *International Journal of Antimicrobial Agents*. 2021. Vol. 26, No 5. P. 343–356. DOI: 10.1016/j.ijantimicag.2005.09.002

⁴ Tian F., Woo S. Y., Lee S. Y., Park S. B., Zheng Y., Chun H. S. Antifungal activity of essential oil and plant-derived natural compounds against *Aspergillus flavus*. *Antibiotics*. 2022. Vol. 11, No 12. Art. 1727. DOI: 10.3390/antibiotics11121727

⁵ Zhang X. Z. et al. Natural alkaloids as antimicrobial agents: mechanisms, potentials and challenges. *Molecules*. 2026. Vol. 31, No 7. Art. 1204. DOI: 10.3390/molecules31071204

⁶ Fais A., Era B. Phytochemical composition and biological activity. *Plants*. 2024. Vol. 13, No 3. Art. 331. DOI: 10.3390/plants13030331

colonises the skin and the anterior nasal cavity in many healthy individuals. However, when the body's barrier functions are impaired, this can lead to a wide range of diseases, including impetigo, abscesses, cellulitis, osteomyelitis, endocarditis, and pneumonia.⁷

The clinical significance of *S. aureus* is greatly increased by its ability to acquire antibiotic resistance. Methicillin-resistant *Staphylococcus aureus* (MRSA) strains are resistant to most β -lactam antibiotics and are associated with various infections.⁸ *S. aureus* can also form biofilms on the surfaces of wounds, catheters, and other medical devices. Bacteria within biofilms exhibit reduced susceptibility to antibiotics and immune defence mechanisms, which complicate the eradication of infection.⁹ Plant phytochemical compounds, such as flavonoids, terpenoids, phenolic compounds, and alkaloids,⁵ are actively being investigated as potential agents against *S. aureus*.

Escherichia coli is a Gram-negative, facultatively anaerobic bacterium that normally inhabits the intestines. Many strains are harmless commensals, but pathogenic variants can cause urinary tract infections, gastrointestinal infections, and sepsis, with an increasing prevalence of strains producing extended-spectrum β -lactamases and carbapenem-resistant strains. Important pathogenic groups include enterotoxigenic, enterohemorrhagic, enteropathogenic, enteroaggregative, uropathogenic, and enteroinvasive *E. coli*.¹⁰ Unlike Gram-positive bacteria, *E. coli* has an outer membrane with lipopolysaccharide, limiting the penetration of hydrophobic and large molecules. The periplasmic space contains enzymes such as β -lactamases, while the inner membrane harbours efflux systems that export toxic compounds.¹⁰ These features often make *E. coli* less susceptible to many plant extracts than *S. aureus*.

Cutibacterium acnes – formerly known as *Propionibacterium acnes*, although both names are found in the literature – is a slow-growing, anaerobic Gram-positive bacterium of the normal microbiota of sebaceous areas of the skin.¹¹ *C. acnes* is primarily associated with acne vulgaris, a highly prevalent dermatological disease affecting millions of people worldwide. Some strains are more strongly associated with acne than others, indicating that pathogenicity

⁷ Sutton J. A. F. et al. *Staphylococcus aureus* cell wall structure and dynamics during host-pathogen interaction. *PLoS Pathogens*. 2021. Vol. 17, No 3. Art. e1009468. DOI: 10.1371/journal.ppat.1009468

⁸ Chalmers S. J., Wylam M. E. Methicillin-resistant *Staphylococcus aureus* infection and treatment options. *Methods in Molecular Biology*. 2020. Vol. 2069. P. 229–251. DOI: 10.1007/978-1-4939-9849-4_16

⁹ Peng Q. et al. A review of biofilm formation of *Staphylococcus aureus* and its regulation mechanism. *Antibiotics*. 2023. Vol. 12, No 1. Art. 12. DOI: 10.3390/antibiotics12010012

¹⁰ Naidoo N., Zishiri O.T. Presence, Pathogenicity, Antibiotic Resistance, and Virulence Factors of *Escherichia coli*: A Review. *Bacteria*. 2025. Vol. 4, No 1. Art. 16. DOI: 10.3390/bacteria4010016

¹¹ Cogen A. L., Nizet V., Gallo R. L. Skin microbiota: A source of disease or defence? *British Journal of Dermatology*. 2023. Vol. 189, No 3. P. 299–309. DOI: 10.1111/j.1365-2133.2008.08437.x

depends on strain-level differences rather than the mere presence or absence of the microorganism.¹² *C. acnes* also forms biofilms, contributing to follicular persistence and reducing susceptibility to antimicrobial agents. The potential effect of medicinal compounds in acne may be twofold. First, they may directly inhibit the growth of *C. acnes*. Second, many phytochemicals possess anti-inflammatory, antioxidant, or skin-modulating properties.

Structural differences between Gram-positive and Gram-negative bacteria, associated with differences in cell wall architecture and outer membrane composition, create distinct barriers to the penetration of antimicrobial agents, making these bacteria suitable models for evaluating compound efficacy. In addition, *C. acnes* presents unique challenges related to biofilm formation and anaerobic metabolism, which are increasingly recognised as important virulence factors.

The paper considers antibacterial effects for 4 classes of phytochemicals.

Flavonoids are distributed in fruits, vegetables, and other plant materials. They usually contain a C6-C3-C6 carbon skeleton consisting of two aromatic rings connected by a three-carbon bridge. Flavonoids are divided into several structural subclasses, such as flavonols, flavones, flavanones, isoflavonoids, catechins, anthocyanins, etc.^{13,14} Examples of antibacterial flavonoids include quercetin, kaempferol, apigenin, luteolin, baicalin, naringenin, EGCG, catechin, and rutin.

Terpenoids, also known as isoprenoids, are one of the largest groups of plant secondary metabolites. They are derived from isoprene units and include monoterpenes, sesquiterpenes, diterpenes, triterpenes, and related compounds. Many terpenoids are major constituents of essential oils obtained from aromatic medicinal herbs.¹⁵ Examples of antibacterial terpenoids include thymol, carvacrol, menthol, linalool, terpinen-4-ol, α -pinene, 1,8-cineole, borneol, geraniol, and citral.

Phenols and polyphenols. The term «phenolic compounds» refers to plant metabolites containing one or more hydroxyl groups attached to aromatic rings. This broad category partially overlaps with flavonoids but also includes simple phenols, phenolic acids, tannins, stilbenes, lignans, and other polyphenols.

¹² Mayslich C., Grange P. A., Dupin N. *Cutibacterium acnes* as an opportunistic pathogen: an update of its virulence-associated factors. *Microorganisms*. 2021. Vol. 9, No 2. Art. 303. DOI: 10.3390/microorganisms9020303

¹³ Farhadi F. et al. Antibacterial activity of flavonoids and their structure–activity relationship: an update review. *Phytotherapy Research*. 2019. Vol. 33, No 1. P. 13–40. DOI: 10.1002/ptr.6208

¹⁴ Górniak I., Bartoszewski R., Króliczewski J. Comprehensive review of antimicrobial activities of plant flavonoids. *Phytochemistry Reviews*. 2019. Vol. 18, No 1. P. 241–272. DOI: 10.1007/s11101-018-9591-z

¹⁵ Yamaguchi T. Antibacterial effect of the combination of terpenoids. *Archives of Microbiology*. 2022. Vol. 204. Art. 520. DOI: 10.1007/s00203-022-03142-y

In the context of medicinal herbs, phenols and polyphenols contribute to antimicrobial, antioxidant, anti-inflammatory, and astringent effects.^{16,17} Examples of antibacterial phenolic compounds include eugenol, gallic acid, caffeic acid, rosmarinic acid, ferulic acid, chlorogenic acid, curcumin, tannic acid, ellagic acid, and resveratrol.

Alkaloids are nitrogen-containing secondary metabolites that exhibit considerable structural diversity. Many alkaloids exhibit strong biological activity, and some are used in drug development.¹⁸ Examples of antibacterial alkaloids include berberine, palmatine, sanguinarine, chelerythrine, piperine, harmine, tetrandrine, etc.

Plant-derived antibacterial compounds usually act simultaneously on multiple cellular targets, distinguishing them from synthetic antibiotics, which have a single-target mechanism of action. This polypharmacological activity makes phytochemicals promising sources of new antibacterial agents, antibiotic adjuvants, and antivirulence compounds.¹⁹ Ten major mechanisms of antibacterial action of phytochemicals were grouped into four functional categories (Table 1). They all affect *S. aureus*, *E. coli*, and *C. acnes*, but their effectiveness varies depending on the bacterial cell envelope structure, metabolic state, growth conditions, and biofilm-forming capacity.

Table 1

Classification of antibacterial mechanisms of phytochemical compounds

Group	Mechanism	Main target
I. Structural	Membrane damage; disruption of the cell envelope	Cell integrity
II. Metabolic	Inhibition of DNA/RNA synthesis; inhibition of protein synthesis; energy dysfunction; oxidative stress	Intracellular processes
III. Regulatory	Efflux inhibition; suppression of quorum sensing; antibiofilm activity	Adaptation and virulence
IV. Synergistic	Potentialiation of antibiotics	Enhancement of therapy

¹⁶ De Rossi L., Rocchetti G., Lucini L., Rebecchi A. Antimicrobial potential of polyphenols: mechanisms of action and microbial responses – a narrative review. *Antioxidants*. 2025. Vol. 14, No 2. Art. 200. DOI: 10.3390/antiox14020200

¹⁷ De Rossi L., Rocchetti G., Lucini L., Rebecchi A. Antimicrobial potential of polyphenols: mechanisms of action and microbial responses – a narrative review. *Antioxidants*. 2025. Vol. 14, No 2. Art. 200. DOI: 10.3390/antiox14020200

¹⁸ Faisal S. et al. Alkaloids as potential antivirals: a comprehensive review. *Natural Products and Bioprospecting*. 2023. Vol. 13. Art. 4. DOI: 10.1007/s13659-022-00366-9

¹⁹ Ghosh S. et al. A comprehensive review of antimicrobial agents against clinically important bacterial pathogens: prospects for phytochemicals. *Phytotherapy Research*. 2025. Vol. 39. P. 138–161. DOI: 10.1002/ptr.8365

1.2. Structural Group: Two Active Mechanisms

Damage to membrane integrity is the most common mechanism of action for terpenoids and phenols. Hydrophobic phytochemical compounds integrate into the lipid bilayer, disrupt lipid organisation, and cause leakage of potassium ions, ATP, and nucleic acids.²⁰ The Gram-positive bacteria *S. aureus* and *C. acnes* are more susceptible to this mechanism because they lack an outer membrane. *E. coli* is protected by a lipopolysaccharide barrier, which limits the penetration of hydrophobic compounds.²¹

Disruption of the cell envelope is an effect exhibited by certain flavonoids (e.g. baicalein and apigenin) and alkaloids (berberine), which affect peptidoglycan biosynthesis.^{22,23} Curcumin inhibits the polymerisation of the FtsZ protein, thereby disrupting bacterial cytokinesis.²⁴ Compounds that weaken the cell wall can increase susceptibility to β -lactam antibiotics.²⁵

1.3. Metabolic Group: Four Active Mechanisms

Inhibition of nucleic acid synthesis. Flavonoids and alkaloids can inhibit DNA gyrase, topoisomerase IV, and replication.²⁶ The planar aromatic structure of berberine, palmatine, and sanguinarine promotes DNA intercalation. Curcumin may affect the organisation of the bacterial nucleoid.²⁷ In Gram-negative bacteria, the effectiveness of this mechanism is limited by efflux pumps.

Inhibition of enzymes and protein synthesis. Phytochemical compounds can inhibit enzymes involved in energy metabolism, fatty acid synthesis, and

²⁰ Kumar G., Engle K. Natural products acting against *S. aureus* through membrane and cell wall disruption. *Natural Product Reports*. 2023. Vol. 40, No 10. P. 1608–1646. DOI: 10.1039/D2NP00084A

²¹ Lou Z. et al. The antibacterial mechanism and cell damage mechanism of natural antibacterial agents from different sources and their applications in food. *Journal of Food Measurement and Characterization*. 2026. Vol. 20. P. 1362–1386. DOI: 10.1007/s11694-025-03794-6

²² Mu L. et al. The antibacterial activity, action mechanisms and prospects of baicalein as an antibacterial adjuvant. *World Journal of Microbiology and Biotechnology*. 2025. Vol. 41. Art. 304. DOI: 10.1007/s11274-025-04508-2

²³ Boberek J. M., Stach J., Good L. Genetic evidence for inhibition of bacterial division protein FtsZ by berberine. *PLoS One*. 2010. Vol. 5, No 10. Art. e13745. DOI: 10.1371/journal.pone.0013745

²⁴ Rai D. et al. Curcumin inhibits FtsZ assembly: an attractive mechanism for its antibacterial activity. *Biochemical Journal*. 2008. Vol. 410, No 1. P. 147–155. DOI: 10.1042/BJ20070891

²⁵ Xu S. et al. Plant flavonoids with antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA). *ACS Infectious Diseases*. 2024. Vol. 10, No 9. P. 3086–3097. DOI: 10.1021/acsinfecdis.4c00292

²⁶ Allison D. G., Lambert P. A. Modes of action of antibacterial agents. *Molecular Medical Microbiology* / ed. by Y. W. Tang et al. 3rd ed. Academic Press, 2024. P. 597–614. DOI: 10.1016/B978-0-12-818619-0.00133-7

²⁷ Davidova S., Galabov A. S., Satchanska G. Antibacterial, antifungal, antiviral activity, and mechanisms of action of plant polyphenols. *Microorganisms*. 2024. Vol. 12, No 12. Art. 2502. DOI: 10.3390/microorganisms12122502

virulence factor production.²⁸ Flavonoids interact with enzyme active sites through hydrogen bonds and hydrophobic interactions.²⁹ Tannins precipitate surface proteins, while eugenol and phenolic acids denature proteins and affect redox balance.³⁰ For *C. acnes*, inhibition of lipases is particularly important, since these enzymes hydrolyse sebum triglycerides into pro-inflammatory free fatty acids.

Disruption of energy metabolism. Membrane-active terpenoids, such as carvacrol and thymol, collapse the proton gradient, reduce ATP synthesis, and impair nutrient transport.¹⁶ Flavonoids can inhibit respiratory-chain enzymes and ATP synthase. This mechanism is relevant to all three pathogens.

Induction of oxidative stress. Under certain conditions, phenolic compounds can generate reactive oxygen species (ROS) or disrupt bacterial antioxidant systems.^{31,32} Flavonoids and phenolic acids chelate metal ions and, in the presence of transition metals, promote ROS formation. This mechanism may enhance the effectiveness of antibiotics and immune defence mechanisms.

1.4. Regulatory Group: Three Active Mechanisms

Inhibition of efflux pumps. Efflux pumps, such as NorA in *S. aureus* and AcrAB–TolC in *E. coli*, export antibiotics and toxic compounds from the cell. Some plant compounds inhibit their activity, increasing the intracellular concentration of antimicrobial agents.^{33,34} It is especially important for MRSA and biofilm populations.

Suppression of quorum sensing. Quorum sensing coordinates the expression of virulence factors, motility, and biofilm formation. Phenolic

²⁸ de Souza Nascimento A. M. et al. Antibacterial action mechanisms and mode of trypsin inhibitors: a systematic review. *Journal of Enzyme Inhibition and Medicinal Chemistry*. 2022. Vol. 37, No 1. P. 749–759. DOI: 10.1080/14756366.2022.2039918

²⁹ Liu Y. et al. Flavonoids as promising natural compounds for combating bacterial infections. *International Journal of Molecular Sciences*. 2025. Vol. 26, No 6. Art. 2455. DOI: 10.3390/ijms26062455

³⁰ Bae J. Y., Seo Y. H., Oh S. W. Antibacterial activities of polyphenols against foodborne pathogens and their application as antibacterial agents. *Food Science and Biotechnology*. 2022. Vol. 31, No 8. P. 985–997. DOI: 10.1007/s10068-022-01058-3

³¹ Bellanti F. et al. Redox imbalance in inflammation: the interplay of oxidative and reductive stress. *Antioxidants*. 2025. Vol. 14, No 6. Art. 656. DOI: 10.3390/antiox14060656

³² Bhattacharya S. et al. Mitigating ROS signalling pathway-mediated defence mechanism: a novel approach to counteract bacterial resistance using natural antioxidant-based antibiotics. *Phytochemistry Reviews*. 2025. DOI: 10.1007/s11101-025-10179-6

³³ Ramalingam S. et al. Plant-based natural products as inhibitors for efflux pumps to reverse multidrug resistance in *Staphylococcus aureus*: a mini review. *Mini-Reviews in Medicinal Chemistry*. 2024. Vol. 24, No 3. P. 272–288. DOI: 10.2174/1389557523666230406092128

³⁴ Zhang L. et al. Bacterial efflux pump inhibitors reduce antibiotic resistance. *Pharmaceutics*. 2024. Vol. 16, No 2. Art. 170. DOI: 10.3390/pharmaceutics16020170

compounds, flavonoids, and terpenoids can inhibit the synthesis of signalling molecules, block their receptors, or alter gene expression.³⁵ In *S. aureus*, the *agr* system – the accessory gene regulator – is particularly important, as it controls toxin synthesis. In *E. coli*, quorum sensing affects biofilms and motility. In *C. acnes*, these mechanisms have been studied less extensively, but antibiofilm activity remains clinically important.

Antibiofilm activity. Biofilms confer increased tolerance to antibiotics and enhanced immune defence mechanisms. Phytochemicals prevent bacterial adhesion, inhibit matrix synthesis, disrupt quorum sensing, and improve antibiotic penetration.^{36,37} Antibiofilm activity is essential in chronic wounds caused by *S. aureus*, catheter-associated infections with *E. coli*, and follicular persistence of *C. acnes*.

1.5. Synergistic Group: One Active Mechanism

Synergy with antibiotics. Phytochemical compounds can restore the susceptibility of resistant bacteria or reduce the required antibiotic doses by increasing membrane permeability, inhibiting efflux pumps, and suppressing resistance enzymes.^{38,39} Examples include the enhancement of β -lactam and fluoroquinolone activity against *S. aureus* by flavonoids, as well as the increased effectiveness of berberine in combination with efflux pump inhibitors.

2. Specific Mechanisms of Action of Individual Phytochemical Classes

2.1. Flavonoids: Mechanisms and Antibacterial Significance

Flavonoids exert antibacterial effects through several mechanisms. These include disruption of bacterial membranes, inhibition of DNA gyrase and topoisomerases, inhibition of energy metabolism, interference with cell envelope synthesis, suppression of virulence factors, and prevention of

³⁵ Bouyahya A. et al. Mechanisms, anti-quorum-sensing actions, and clinical trials of medicinal plant bioactive compounds against bacteria: a comprehensive review. *Molecules*. 2022. Vol. 27, No 5. Art. 1484. DOI: 10.3390/molecules27051484

³⁶ Zhang M. et al. Recent advances on the regulation of bacterial biofilm formation by herbal medicines. *Frontiers in Microbiology*. 2022. Vol. 13. Art. 1039297. DOI: 10.3389/fmicb.2022.1039297

³⁷ Liu Y. et al. Eradicating biofilms: decoding persistent mechanisms and combating therapeutic strategies. *Advanced Healthcare Materials*. 2026. Vol. 15, No 6. Art. e02707. DOI: 10.1002/adhm.202502707

³⁸ Alam M. et al. Synergistic role of plant extracts and essential oils against multidrug resistance and gram-negative bacterial strains producing extended-spectrum β -lactamases. *Antibiotics*. 2022. Vol. 11, No 7. Art. 855. DOI: 10.3390/antibiotics11070855

³⁹ Dai C., Liu Y., Lv F., Cheng P., Qu S. An alternative approach to combat multidrug-resistant bacteria: new insights into traditional Chinese medicine monomers combined with antibiotics. *Advanced Biotechnology*. 2025. Vol. 3. Art. 6. DOI: 10.1007/s44307-025-00059-7

biofilm formation.^{40,41} Some flavonoids also inhibit bacterial efflux pumps, thereby increasing the intracellular accumulation of antibiotics or other toxic compounds.

The antibacterial activity of flavonoids depends strongly on their chemical structure. Aglycones are generally more active than glycosides because of their higher lipophilicity. Hydroxyl groups enhance binding to molecular targets, while structural planarity facilitates DNA intercalation. Galloylation, as seen in EGCG, increases membrane activity. In *S. aureus*, inhibition of DNA gyrase may contribute to growth suppression. In *E. coli*, the penetration of flavonoids is limited by the outer membrane; however, once inside the cell, DNA gyrase remains a potential intracellular target. In *C. acnes*, gyrase inhibition is also relevant, although additional organism-specific studies are needed. Flavonoids can also affect bacterial energy metabolism by altering membrane potential, electron transport, and ATP synthesis. Some flavonoids inhibit ATP synthase or enzymes involved in respiratory metabolism. It may reduce bacterial growth, motility, and active transport.

Efflux pumps are membrane transport proteins that export various substances from the bacterial cell. Inhibition of efflux pumps is one of the main resistance-modifying mechanisms of flavonoids. By suppressing efflux activity, flavonoids increase the intracellular concentration of antibiotics and restore bacterial susceptibility. Flavonoids may reduce bacterial virulence without necessarily producing strong bactericidal activity. They can inhibit adhesion, toxin production, motility, quorum sensing, and biofilm development. Therefore, flavonoids are particularly important not only as direct antibacterial compounds but also as antivirulence and antibiotic-adjuvant agents.

2.2. Terpenoids: Mechanisms and antibacterial significance

The antibacterial effects of terpenoids are closely associated with their hydrophobicity. Many terpenoids are volatile, hydrophobic, and membrane-active compounds. The dominant antibacterial mechanism of terpenoids is the disruption of membrane permeability.

Due to their hydrophobic nature, terpenoids partition into lipid bilayers and disturb membrane structure. They penetrate bacterial membranes, disrupt lipid packing, increase membrane fluidity and permeability, and cause leakage of ions, ATP, and other intracellular components.¹⁵ They may also collapse the proton motive force, reduce ATP synthesis, and interfere with membrane-associated enzymes.

⁴⁰ Ullah S. et al. Important flavonoids and their role as a therapeutic agent. *Molecules*. 2020. Vol. 25, No 22. Art. 5243. DOI: 10.3390/molecules25225243

⁴¹ Dias M. C., Pinto D. C. G. A., Silva A. M. S. Plant flavonoids: chemical characteristics and biological activity. *Molecules*. 2021. Vol. 26, No 17. Art. 5377. DOI: 10.3390/molecules26175377

Terpenoids are usually more active against Gram-positive bacteria than Gram-negative bacteria because the outer membrane of Gram-negative bacteria restricts access to the cytoplasmic membrane. Therefore, *S. aureus* and *C. acnes* are generally more susceptible to terpenoid-mediated membrane damage than *E. coli*. However, small hydrophobic terpenoids may still affect Gram-negative bacteria, especially when combined with other agents that destabilise the outer membrane.

Examples of membrane-active terpenoids include thymol, carvacrol, menthol, linalool, terpinen-4-ol, α -pinene, borneol, etc. Thymol and carvacrol are particularly well known for their ability to disrupt membrane integrity and energy metabolism. Their rapid membrane-targeting activity makes them promising candidates for topical antimicrobial formulations and for combination therapy with conventional antibiotics.

2.3. Phenols and Polyphenols: Mechanisms and antibacterial significance

Phenols and polyphenols are numerous and chemically diverse compounds. Important antibacterial phenolic compounds include eugenol, gallic acid, caffeic acid, ferulic acid, rosmarinic acid, chlorogenic acid, curcumin, tannic acid, ellagic acid, and resveratrol. Flavonoids are technically polyphenols, but they are discussed separately here because they represent a distinct structural class.

Phenolic compounds are relevant to all three target bacteria and may act through several mechanisms. They disrupt bacterial membranes, inhibit extracellular microbial enzymes, bind metal ions required for bacterial metabolism, damage cell walls, interfere with nucleic acid synthesis, modulate oxidative stress, and inhibit biofilm formation.^{2,27} Compounds that combine antibacterial and anti-inflammatory effects are particularly useful, especially if inflammation plays a central role. More hydrophobic phenolic acids generally enter bacterial membranes more easily.

Phenolic compounds can interact with proteins through hydrogen bonding, hydrophobic interactions, and covalent reactions after oxidation to quinones. Tannins are especially known for their ability to precipitate proteins. It inhibits microbial adhesins, enzymes, transport proteins, and cell envelope proteins. Many phenols can also damage bacterial membranes, particularly when they are sufficiently lipophilic.

Eugenol, for example, can disrupt membrane integrity and denature proteins. Curcumin may interfere with bacterial cell division by inhibiting FtsZ polymerisation and by affecting nucleoid organisation. Resveratrol and phenolic acids can influence oxidative balance, enzyme activity, and biofilm formation. In *C. acnes*, phenolic compounds are of special interest because they may combine direct antibacterial activity with anti-inflammatory and antioxidant effects relevant to acne pathogenesis.

2.4. Alkaloids: Mechanisms and antibacterial significance

Alkaloids are nitrogen-containing compounds with diverse structures and biological activities. Some alkaloids possess strong antimicrobial properties, although toxicity may limit their application. Alkaloids can act through several mechanisms. Some intercalate into DNA or inhibit nucleic acid synthesis. Others interfere with cell division, inhibit enzymes, disrupt membranes, or suppress efflux pumps.⁴²

Many alkaloids have planar aromatic structures and positive charges, allowing them to interact with DNA and potentially interfere with replication and transcription. Berberine, palmatine, and sanguinarine are examples of alkaloids that interact with nucleic acids. Berberine is also known for its ability to affect bacterial membranes, inhibit efflux systems, and enhance the activity of other antimicrobial agents.

Regarding the target microorganisms, alkaloids are particularly interesting for *S. aureus*, as they exhibit activity against Gram-positive bacteria and may modify resistance mechanisms. For *E. coli*, the effectiveness of alkaloids is often limited by the outer membrane and efflux systems, but combination strategies may help overcome these barriers. For *C. acnes*, alkaloid-rich extracts require further research; compounds that combine antibacterial and anti-inflammatory properties appear promising.

Some medicinal plants contain combinations of antibacterial compounds and agents that modify resistance. Thus, alkaloids may be more effective in combination therapy than as isolated single agents. Their ability to interact with DNA, inhibit efflux pumps, and potentiate antibiotics makes them valuable candidates for further research, especially as adjuvants in the treatment of resistant bacterial infections.

3. Pathogen-Specific Manifestations of Antibacterial Activity

Although flavonoids, terpenoids, phenols, and alkaloids exhibit broad-spectrum antibacterial activity, their activity differs substantially against *S. aureus*, *E. coli*, and *C. acnes*. Variations in cell envelope architecture, oxygen tolerance, metabolism, virulence systems, and biofilm ecology explain these differences. In general, phytochemicals that disrupt membranes, inhibit efflux pumps, or suppress virulence tend to show stronger activity against Gram-positive organisms such as *S. aureus* and *C. acnes* than against Gram-negative *E. coli*, whose outer membrane limits the penetration of many hydrophobic compounds.⁴³

⁴² Rajput A., Sharma R., Bharti R. Pharmacological activities and toxicities of alkaloids on human health. *Materials Today: Proceedings*. 2022. Vol. 48, pt. 5. P. 1407–1415. DOI: 10.1016/j.matpr.2021.09.189

⁴³ Villanueva X. et al. Effect of chemical modifications of tannins on their antimicrobial and antibiofilm effect against Gram-negative and Gram-positive bacteria. *Frontiers in Microbiology*. 2023. Vol. 13. Art. 987164. DOI: 10.3389/fmicb.2022.987164

3.1. Activity against *Staphylococcus aureus*

Staphylococcus aureus is the causative agent of a wide range of infections. Its cell envelope consists of a thick peptidoglycan layer containing teichoic and lipoteichoic acids, but it lacks the outer membrane characteristic of Gram-negative bacteria. It makes *S. aureus* relatively accessible to hydrophobic phytochemicals, such as terpenoids and phenolic compounds in essential oils.

Methicillin-resistant *S. aureus* strains are of particular concern. Their resistance is mainly associated with the altered penicillin-binding protein PBP2a, encoded by the *mecA* gene. This protein allows cell wall synthesis to continue even in the presence of β -lactam antibiotics. In addition, *S. aureus* possesses efflux pumps, oxidative stress defence systems, virulence factors, adhesins, and a strong biofilm-forming ability. Promising plant-derived compounds should act not only by directly inhibiting bacterial growth or killing cells, but also by weakening virulence factors, suppressing biofilm formation and maturation, and modifying mechanisms of antibiotic resistance.

Flavonoids have been studied for their antistaphylococcal activity.^{13,14} Their mechanisms include membrane disruption, inhibition of nucleic acid-related enzymes, suppression of efflux pumps, interference with cell wall synthesis, and reduction of toxin production. Some flavonoids may attenuate bacterial adhesion and biofilm development, which is especially important in persistent *S. aureus* infections.

Terpenoids are particularly active against *S. aureus* because the Gram-positive envelope provides less protection against hydrophobic molecules. Their main action is to disrupt the cytoplasmic membrane, increasing permeability and causing the leakage of potassium ions, ATP, and other intracellular components. The collapse of the proton motive force reduces ATP synthesis and impairs nutrient transport. Terpenoids may also decrease biofilm formation through several overlapping effects: reduced cell viability, impaired surface adhesion, altered bacterial surface hydrophobicity, and interference with quorum-sensing pathways. When terpenoids are in mixtures, additive or synergistic interactions are possible. Minor components may influence solubility, membrane partitioning, volatility, and overall antimicrobial potency.

Phenolic compounds are also important against *S. aureus*,²² as they can damage membranes, bind proteins, inhibit enzymes, and affect virulence factors. For example, phenolic compounds may reduce toxin secretion, interfere with adhesins, and impair the integrity of the bacterial envelope. Tannins can precipitate proteins and inhibit enzymes required for colonisation and persistence.

Alkaloids have demonstrated activity against *S. aureus*,⁴⁴ especially when combined with efflux pump inhibitors or antibiotics. Compounds such as berberine and sanguinarine may interfere with DNA, inhibit efflux systems, and enhance the intracellular accumulation of antibacterial agents.

Biofilm formation is a key factor in the persistence of *S. aureus* infections. Biofilms protect bacteria from antibiotics, host immune responses, and adverse environmental conditions. Many phytochemicals inhibit the formation and development of *S. aureus* biofilms by preventing initial bacterial adhesion, suppressing extracellular polysaccharide synthesis, disrupting mature biofilm architecture, inhibiting quorum-sensing systems, and improving antibiotic penetration into biofilm.

The *agr* quorum-sensing system is especially important for *S. aureus* virulence because it regulates toxin production, enzyme secretion, and biofilm dispersal. Some phytochemicals can suppress *agr*-mediated expression of virulence factors, including α -hemolysin and other secreted proteins. Such antivirulence activity reduces bacterial pathogenicity without necessarily requiring complete bacterial eradication.

3.2. Activity against *Escherichia coli*

E. coli includes many harmless commensal strains, but pathogenic lineages can cause urinary tract infections, sepsis, neonatal meningitis, gastroenteritis, and intra-abdominal infections. The antibacterial response of *E. coli* differs substantially from that of *S. aureus* because *E. coli* possesses a complex Gram-negative outer membrane.

This outer membrane contains LPS, porins that restrict the entry of compounds according to size and polarity, a periplasmic space containing enzymes such as β -lactamases, a thin peptidoglycan layer, an inner cytoplasmic membrane, and multiple efflux systems, especially AcrAB–TolC. The outer membrane limits the penetration of many hydrophobic terpenoids and phenols. Thus, *E. coli* is often less susceptible to essential oils and lipophilic phytochemicals than Gram-positive organisms.⁴⁴

Flavonoids inhibit *E. coli*, but their potency depends on structure, polarity, and ability to cross the outer membrane, which limits intracellular accumulation.¹³ More hydrophilic flavonoid glycosides pass through porins more easily than hydrophobic aglycones, but glycosides bind less strongly to intracellular targets. In contrast, hydrophobic aglycones interact more effectively with bacterial membranes and molecular targets, but they enter Gram-negative

⁴⁴ Huang P. Y., Hsu C. K., Tang H. J., Lai C. C. Eravacycline: a comprehensive review of in vitro activity, clinical efficacy, and real-world applications. *Expert Review of Anti-infective Therapy*. 2024. Vol. 22, No 6. P. 387–398. DOI: 10.1080/14787210.2024.2351552

cells less efficiently. So, antibacterial activity depends on the balance between permeability and intrinsic target affinity.

Terpenoids may act against *E. coli* by damaging surface-associated cells and disturbing membrane integrity. However, the outer membrane is the major barrier to their activity. Their effects are often enhanced when other compounds or antibiotics destabilise the outer membrane. It makes terpenoids especially relevant in combination strategies rather than as isolated agents against Gram-negative bacteria.

Phenolic compounds show mixed activity against *E. coli*. Small phenols with sufficient hydrophobicity can damage membranes, while more polar phenolic acids may act through enzyme inhibition, metal chelation, oxidative stress modulation, or interference with biofilm formation. However, their effectiveness is still limited by permeability barriers and efflux mechanisms.

The contribution of alkaloids against *E. coli* is often considered more relevant as a bioavailability enhancer and a resistance-modifying mechanism than as a strong direct antibacterial agent. Alkaloids inhibit efflux systems, increasing susceptibility to antibiotics and other phytochemicals. It is important for multidrug-resistant strains, including extended-spectrum β -lactamase-producing and carbapenem-resistant *E. coli*.

Biofilms of *E. coli* play an important role in urinary tract infections, catheter-associated infections, intestinal colonisation, and long-term bacterial persistence in the environment. Inhibition of *E. coli* biofilm formation may occur through suppression of initial adhesion, reduction of cell motility, disruption of quorum-sensing systems, inhibition of extracellular matrix synthesis, and enhancement of oxidative or membrane stress. At the same time, eradicating mature *E. coli* biofilms remains difficult. Most phytochemicals are much more effective at preventing biofilm formation than at destroying already established biofilm structures. It is due to the protective function of the extracellular matrix and the activation of adaptive mechanisms that increase bacterial tolerance to antimicrobial agents.

3.3. Activity against *Cutibacterium acnes*

Cutibacterium acnes contributes to the development of acne vulgaris through follicular colonisation, biofilm formation, lipase production, inflammation, and activation of innate immune pathways. Unlike *S. aureus*, *C. acnes* grows slowly and is adapted to lipid-rich, low-oxygen environments. It produces lipases that hydrolyse sebum triglycerides, releasing free fatty acids that contribute to follicular irritation and inflammation. It also stimulates keratinocytes and immune cells to produce inflammatory mediators, including IL-1 β , IL-8, TNF- α , and other cytokines.

Phytochemicals from medicinal plants may exert a dual action against *C. acnes*, namely (i) direct antibacterial inhibition of follicular *C. acnes*, and (ii) reduction of inflammation, oxidative stress, and biofilm-associated bacterial persistence.

Because acne is an inflammatory disease rather than a simple infection, compounds with both antibacterial and anti-inflammatory activity are especially attractive.⁴⁵ Disease severity is determined not only by bacterial load but also by the intensity of the host inflammatory response. Therefore, phytochemicals may be useful in acne through direct inhibition of *C. acnes* growth, reduction of bacterial lipase activity, suppression of biofilm formation, decreased sebum oxidation, inhibition of NF- κ B and MAPK signalling pathways, antioxidant protection, reduced neutrophil recruitment, and decreased production of pro-inflammatory cytokines.

Flavonoids may help control *C. acnes* through antibacterial, anti-inflammatory, and antioxidant effects. They can inhibit bacterial growth, reduce oxidative stress, and modulate inflammatory signalling pathways involved in acne pathogenesis. Their ability to suppress cytokine production and protect against oxidative damage makes them particularly relevant for inflammatory skin conditions.

Terpenoids are highly relevant to *C. acnes* because many of them are lipophilic and may accumulate in the sebaceous environment. Essential oils used in dermatology often owe their activity to monoterpenes and related compounds. Since *C. acnes* is Gram-positive and lacks an outer membrane, it is relatively vulnerable to membrane-active terpenoids. These compounds may disrupt bacterial membranes, reduce metabolic activity, and interfere with biofilm formation within follicles.

Phenolic compounds may directly affect *C. acnes* while simultaneously reducing inflammatory responses. Eugenol, curcumin, resveratrol, gallic acid, and others may combine antibacterial, antioxidant, and anti-inflammatory properties. This dual activity is valuable in acne, where inflammation and bacterial persistence are closely linked.

Alkaloids or their extracts require further research against *C. acnes*. Compounds that combine antibacterial activity with anti-inflammatory or resistance-modifying effects are potentially useful. However, their safety profile is especially important for dermatological use, since topical irritation and cytotoxicity may limit application.

The main limitations of phytochemicals against *C. acnes* include potential skin irritation, poor solubility, chemical instability, and limited penetration into

⁴⁵ Pannakal S. T. et al. Acnocure, a synergistic antimicrobial and anti-inflammatory combination of thymol and Curcuma turmerones, formulation and time-kill studies against *C. acnes*. *Cosmetics*. 2025. Vol. 12, No 2. Art. 37. DOI: 10.3390/cosmetics12020037

pilosebaceous follicles. These challenges may be addressed through topical delivery systems such as gels, nanoparticles, liposomes, nanoemulsions, or other formulations designed to improve stability, follicular penetration, and local bioavailability.

4. Discussion

The antibacterial properties of medicinal plants depend on several factors. First, results obtained *in vitro* do not always correlate with clinical efficacy.⁴⁶ Many compounds exert antibacterial effects at concentrations that are difficult to achieve safely in humans, especially in systemic infections. Topical applications, such as anti-acne preparations, may achieve higher local concentrations. Second, the composition of herbal extracts varies depending on plant species, cultivar, growth and storage conditions, harvesting time, and extraction method.⁴⁷ Third, antibacterial activity may result from synergy among different compounds.⁴⁸ A crude extract may be more active than its isolated constituents. Such synergy is relevant both for plant-based preparations themselves and for their combinations with conventional antibiotics. Finally, safety must be considered because natural origin does not guarantee low toxicity.⁴⁹ Some natural substances may irritate the skin or mucous membranes and may exhibit cytotoxicity. Thus, antibacterial activity must be balanced against toxicity, pharmacokinetics, formulation stability, and the intended route of administration.

4.1. Dominant Antibacterial Mechanisms

Analysis of the literature indicates that the effects of phytochemicals on pathogenic bacteria can be described through ten distinct pathogen–compound interaction mechanisms. These mechanisms can be further grouped into four major categories according to the level at which they affect the bacterial cell.

Additional qualitative information can be obtained by ranking individual mechanisms according to their relative importance, assigning each a score from 10 (strongest contribution) to 1 (weakest contribution), based on the literature. In this approach, the scores form an ordinal scale; that is, the

⁴⁶ Peng Z., Wang X., Huang J., Li B. Pathogenic *Escherichia coli*. *Molecular Medical Microbiology* / ed. by Y. W. Tang et al. 3rd ed. Academic Press, 2024. P. 1065–1096. DOI: 10.1016/B978-0-12-818619-0.00069-1

⁴⁷ Li Y., Zidorn C. Seasonal variations of natural products in European herbs. *Phytochemistry Reviews*. 2022. Vol. 21. P. 1549–1575. DOI: 10.1007/s11101-021-09797-7

⁴⁸ Chaachouay N. Synergy, additive effects, and antagonism of drugs with plant bioactive compounds. *Drugs and Drug Candidates*. 2025. Vol. 4, No 1. Art. 4. DOI: 10.3390/ddc4010004

⁴⁹ Balkrishna A. et al. Exploring the safety, efficacy, and bioactivity of herbal medicines: bridging traditional wisdom and modern science in healthcare. *Future Integrative Medicine*. 2024. Vol. 3, No 1. P. 35–49. DOI: 10.14218/FIM.2023.00086

distance between neighbouring values is not constant, but the scale allows mechanisms to be ordered according to their probable importance within each phytochemical class.

The individual mechanisms can be grouped into four major categories according to the level of phytochemical action on the bacterial cell: structural, metabolic, regulatory, and synergistic. The first group, the structural group, includes mechanisms that disrupt bacterial cell structures: membrane damage, disruption of the cell envelope, and interference with cell wall synthesis. The second group, the metabolic group, includes mechanisms that inhibit intracellular processes: inhibition of nucleic acid synthesis, inhibition of bacterial enzymes and protein synthesis, and disruption of energy metabolism. The third group, the regulatory group, includes antivirulence and anti-adaptive mechanisms: induction or modulation of oxidative stress, inhibition of efflux pumps, suppression of quorum sensing, and antibiofilm activity. The fourth group, the synergistic group, refers to the enhancement of antimicrobial therapy through synergy with conventional antibiotics. The results of the assessment of each mechanism's contribution and each phytochemical are presented in Figure 1.

The most important mechanisms of flavonoids are inhibition of nucleic acid synthesis, observed for quercetin, catechins, and related flavonoids, as well as inhibition of efflux pumps and antibiofilm activity. Thus, flavonoids should primarily be regarded as multitarget regulatory and intracellular inhibitors.

For phenols and polyphenols, the dominant mechanisms are membrane damage, as demonstrated for eugenol and phenolic acids, and inhibition of proteins and enzymes, particularly with tannins. Many phenols contain hydroxyl groups that enable hydrogen bonding with proteins and membranes. Antibiofilm activity is also important, as shown for curcumin, because phenols can interfere with bacterial adhesion, matrix production, and survival of surface-associated bacteria. So, phenols should be considered membrane-active and protein-reactive antibacterial agents.

Terpenoids are the class most closely associated with membrane disruption. Compounds such as thymol, carvacrol, terpinen-4-ol, citral, and linalool are hydrophobic and can penetrate bacterial lipid bilayers. It disrupts membrane packing, increases permeability, and causes leakage of potassium ions, ATP, proteins, and other intracellular contents. Since bacterial energy production depends strongly on membrane integrity, terpenoid-induced membrane damage leads to collapse of the proton motive force, reduced ATP synthesis, and impaired nutrient transport. Therefore, disruption of energy metabolism ranks second among terpenoid-associated mechanisms, although it is often a consequence of membrane damage. Terpenoids may also improve antibiotic penetration into bacteria, especially Gram-negative microorganisms such as *E. coli*, where the

outer membrane limits compound entry. Thus, terpenoids are best considered membrane-disrupting permeability enhancers.

Alkaloids often form strong interactions with intracellular macromolecules. Several planar alkaloids, such as berberine- and sanguinarine-type compounds, can interact with DNA or interfere with DNA-associated processes. Thus, interference with nucleic acid metabolism is one of their most important mechanisms. Alkaloids such as berberine may also directly inhibit efflux pumps or act synergistically with other compounds. In addition, alkaloids can inhibit proteins involved in cell division, particularly FtsZ, and interfere with bacterial enzymes. Alkaloids are therefore best regarded as inhibitors of intracellular targets and resistance-modifying agents.

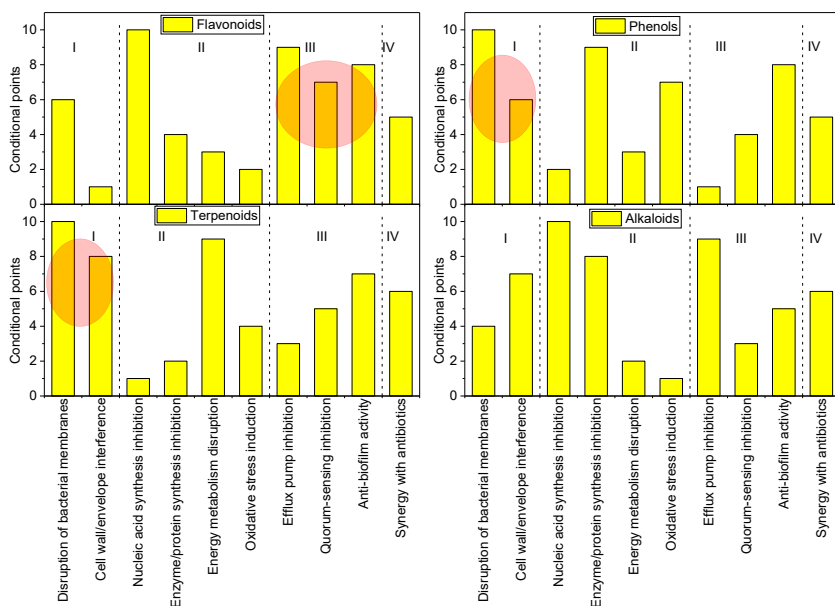


Fig. 1. Contribution of antibacterial mechanisms, scored from 1 to 10, to the effectiveness of four phytochemical classes. Mechanism groups:

I – structural; II – metabolic; III – regulatory; IV – synergistic.

Dominant mechanisms for each class are highlighted in pink

Additional information can be obtained by analysing mean scores across the four mechanism groups for each phytochemical class (Figure 2). The most balanced distribution among mechanism groups is characteristic of

alkaloids, with mean scores ranging between 5 and 6. Flavonoids show a clear predominance of regulatory mechanisms, with an average score of 8, compared with structural mechanisms, which average 3.5. For phenols and terpenoids, structural factors are more important, with scores of 8 and 9, respectively, than regulatory mechanisms, which score 4–5.

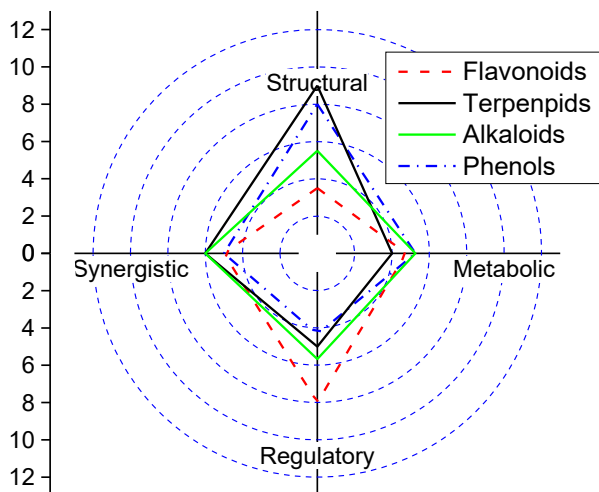


Fig. 2. Relative contribution, expressed as scores, of the four mechanism groups for flavonoids, phenols, terpenoids, and alkaloids

4.2. Key Pathogen-Specific Effects

The previous section assessed the effectiveness of antibacterial mechanisms across different phytochemical classes without considering specific pathogens. However, phytochemicals from medicinal plants exhibit different effects depending on the pathogen. Against *S. aureus*, the most relevant effects include membrane disruption, antibiofilm activity, efflux pump inhibition, and antibiotic potentiation. Flavonoids such as EGCG and baicalin are especially important as modulators of MRSA resistance. Against *E. coli*, activity is limited by the Gram-negative outer membrane and efflux systems. Effective approaches require compounds that increase permeability, inhibit efflux, or are delivered using improved formulations. Against *C. acnes*, phytochemicals combine antibacterial, antibiofilm, antioxidant, and anti-inflammatory properties. Compounds that can simultaneously reduce bacterial load and inflammatory signalling are particularly important.

Overall, the most promising therapeutic direction is not necessarily the replacement of antibiotics with isolated phytochemicals. However, the use of plant-derived preparations as multitarget adjuvants that weaken bacterial defences, reduce virulence, inhibit biofilms, and increase antibiotic susceptibility.

Analysis of the literature enables a qualitative 5-point rating of pathogen-specific activity. A score of 5 out of 5 stars corresponds to excellent, well-documented activity; 4 stars means good and consistent activity; 3 stars – moderate or variable activity; 2 stars – limited, weak, or inconsistent activity; and 1 star indicates low, rarely effective, or insufficiently studied activity. The results of this analysis, including dominant mechanisms for each phytochemical class and pathogen, are summarised in Table 2.

Table 2

Dominant antibacterial mechanisms with qualitative assessment of activity by pathogen and phytochemical class

Pathogen	Dominant antibacterial mechanisms with activity rating by a 5-star scale
Flavonoids	
<i>S. aureus</i>	Inhibition of quorum sensing, especially the <i>agr</i> system; inhibition of efflux pumps, particularly NorA – 4★
<i>E. coli</i>	Inhibition of efflux pumps, especially AcrAB–TolC; inhibition of DNA gyrase – 3★
<i>C. acnes</i>	Inhibition of lipases/enzymes; antibiofilm activity; inhibition of DNA gyrase – 4★
Phenols/polyphenols	
<i>S. aureus</i>	Membrane disruption; binding to proteins/enzymes; antibiofilm activity 5★
<i>E. coli</i>	Membrane disruption; disturbance of the cell wall/cell envelope – 4★
<i>C. acnes</i>	Membrane disruption; inhibition of sebum-associated enzymes; antibiofilm activity – 4★
Terpenoids	
<i>S. aureus</i>	Membrane disruption → ATP leakage → cell death – 5★
<i>E. coli</i>	Membrane disruption; increased outer membrane permeability; synergy with antibiotics – 4★
<i>C. acnes</i>	Membrane disruption; modulation of inflammatory signalling 0 5★
Alkaloids	
<i>S. aureus</i>	Inhibition of FtsZ and cell division; DNA interaction; involvement in efflux-related mechanisms – 4★
<i>E. coli</i>	Interaction with DNA/topoisomerases; involvement in efflux-related mechanisms – 3★
<i>C. acnes</i>	Enzyme inhibition; antibiofilm activity, although data remain moderate – 3★

The absence of an outer membrane in *S. aureus* makes this bacterium more susceptible to both membrane-active and intracellularly acting compounds.

Flavonoids received a high rating against this pathogen because *S. aureus* virulence strongly depends on quorum sensing, while efflux pump-mediated resistance is clinically relevant. Phenols and terpenoids received the highest ratings. Phenolic compounds can damage membranes, bind proteins, inhibit enzymes, and influence virulence factors. The absence of an outer membrane allows terpenoids to act rapidly and effectively against *S. aureus*. Alkaloids also received a high rating because FtsZ and DNA are accessible targets in *S. aureus*, and efflux-mediated resistance is common.

For *E. coli*, flavonoids received a moderate rating because the outer membrane and efflux systems significantly reduce flavonoid entry and effectiveness. Their activity increases significantly when combined with compounds that enhance outer membrane permeability. Phenols and polyphenols received a good rating because phenolic compounds with multiple hydroxyl groups can partially overcome the outer membrane barrier, especially tannins and gallic acid derivatives. Terpenoids also received a good rating because they are among the few phytochemical classes capable of substantially disturbing the outer membrane of Gram-negative bacteria. Their activity is somewhat lower than against *S. aureus* because of the structural complexity of the outer membrane, but their synergistic potential is considerable. Alkaloids received a moderate rating because the outer membrane barrier and efficient efflux systems strongly restrict their bioavailability and intrinsic activity against *E. coli*.

C. acnes is a Gram-positive, anaerobic/aerotolerant, slow-growing commensal that becomes pathogenic in sebaceous follicles. It contributes to acne vulgaris by promoting follicular colonisation, biofilm formation, lipase production, inflammation, and activation of innate immune pathways.

Flavonoids received a high rating because many target the virulence cascade of *C. acnes* rather than merely inhibiting growth. Phenols and polyphenols also received a high rating because anti-inflammatory mechanisms are clinically as important as direct antibacterial activity in acne pathogenesis. Terpenoids received the highest rating because they combine direct bactericidal activity, antibiofilm effects, anti-inflammatory properties, and pharmacokinetic suitability, as their lipophilicity is compatible with the sebaceous follicular environment. Alkaloids received a moderate rating because specific mechanistic data for *C. acnes* are less extensive than for other bacteria. Alkaloids do not appear to affect the lipase/porphyrin/sebum axis as effectively as flavonoids, and the available evidence remains limited.

In summary, the key patterns of pathogen-specific activity are as follows:

1. The barrier function of the outer membrane is the dominant factor reducing the susceptibility of *E. coli* to all phytochemical classes.

2. Target accessibility is greater in Gram-positive bacteria; thus, *S. aureus* and *C. acnes* demonstrate higher susceptibility because they lack an outer membrane.

3. Pathogen-specific virulence targets include the *agr* quorum-sensing system, NorA efflux pumps, biofilm-associated *icaADBC* genes (all for *S. aureus*); Lip1/Lip2 lipases, porphyrin metabolism, 5 α -reductase-associated pathways (all for *C. acnes*); AcrAB–TolC efflux system and the outer membrane (all for *E. coli*).

4. Synergistic combinations outperform monotherapy for all three pathogens.

4.3. Comparative Susceptibility of the Three Pathogens to Phytochemicals

Influence of Gram-positive and Gram-negative Cell Envelopes. The most consistent pattern across numerous studies is the greater susceptibility of Gram-positive bacteria to hydrophobic phytochemicals than Gram-negative bacteria. *S. aureus* and *C. acnes* lack an outer membrane; therefore, phytochemicals can more easily reach the cytoplasmic membrane. In contrast, *E. coli* possesses an LPS-rich outer membrane that prevents the penetration of many hydrophobic molecules. Their entry into the cell depends on porin channels, disruption of outer membrane integrity, or the use of formulations that improve active compound penetration. In addition, efflux pumps reduce intracellular accumulation of these substances.

Therefore, the approximate susceptibility ranking for membrane-active phytochemicals is: *C. acnes* $\approx$ *S. aureus* > *E. coli*.

This ranking is conditional and may vary depending on the bacterial strain, compound polarity, formulation, and experimental conditions.

Biofilm Context. Bacterial susceptibility within biofilms differs substantially from the susceptibility of planktonic cells. In planktonic culture studies, many essential oils and phenolic compounds demonstrate strong antibacterial activity. In biofilms, bacteria are embedded in an extracellular matrix, grow more slowly, and activate stress-response mechanisms. All these reduce susceptibility to antimicrobial agents. Several general patterns can be identified:

- prevention of biofilm formation is more effective and easier than the destruction of already established biofilms;
- terpenoids and phenols are useful for damaging biofilm-associated cells;
- tannins and flavonoids are effective in inhibiting bacterial adhesion and processes associated with extracellular matrix formation and maintenance;
- alkaloids and efflux pump inhibitors may increase intracellular stress in biofilm-associated bacteria.

Modification of Antibiotic Resistance by Phytochemicals. Phytochemicals are of interest as modifiers of antibiotic resistance. Due to their multitarget

mechanisms of action, they make it more difficult for bacteria to develop resistance, because a single mutation is usually insufficient to overcome their effects.

For *E. coli*, modifying antibiotic resistance is more challenging because the outer membrane and the AcrAB–TolC efflux system provide effective protection against many antimicrobial agents. Nevertheless, the combined use of phytochemicals with membrane-permeabilising agents, nanoparticles, or antibiotics may partially overcome this barrier and increase the effectiveness of antimicrobial therapy.

4.4. From Laboratory Data to Clinical Application

Despite strong *in vitro* antibacterial potential, translation into clinical practice remains limited. Laboratory conditions do not fully reproduce the environment of human tissues, including wounds, biofilms, and anaerobic follicles.

For example, *S. aureus* in wounds may be embedded in pus, necrotic tissue, or a biofilm matrix. *E. coli* in urinary or intestinal infections encounters immune factors and pH fluctuations. *C. acnes* grows slowly in anaerobic, lipid-rich follicles, which are difficult to reproduce in standard laboratory assays.

Chemical variability in plant extracts and essential oils is a major challenge. The composition of medicinal plant extracts depends on many factors, including plant species, geographical origin, soil and climate, harvesting season, plant part used, solvent, drying conditions, and storage conditions. Without strict chemical standardisation, antibacterial results are difficult to compare across studies.

Isolated Compounds versus Whole Extracts. Some studies test purified compounds, while others examine crude extracts. These results are not equivalent. Crude extracts may demonstrate: additive or synergistic effects; antagonistic effects; improved solubility of active components; reduced toxicity due to balancing among components; weaker activity due to dilution of active substances.

Bioavailability and Solubility Problems. Many antibacterial phytochemicals have low water solubility or limited bioavailability. These limitations are especially relevant for systemic infections. For topical infections, such as acne, achieving high local concentrations is more feasible, making topical administration more realistic.

Safety, Toxicity, and Irritation. «Natural» is not synonymous with «safe.» Some phytochemicals may cause irritation, allergy, cytotoxicity, or drug interactions. Therefore, safety studies are essential, especially for repeated topical application or systemic administration.

Limited Clinical Evidence. For many phytochemicals, clinical evidence remains limited, and additional clinical studies are required before therapeutic

use. These studies should include standardised composition, appropriate manufacturing control points, defined bacterial endpoints, and monitoring of toxicity and irritation.

4.5. Future Research Directions

Standardised Phytochemical Profiling. Future studies should use chemically well-characterised extracts. Modern analytical methods, including different combinations of chromatography, mass spectrometry, and NMR spectroscopy, should be used to identify and quantify active components. It would improve reproducibility and facilitate comparison among studies.

Improved Delivery Systems. Since many phytochemicals are poorly soluble or unstable, pharmaceutical formulation is a key research direction. For *C. acnes*, lipid-compatible topical formulations may improve penetration into sebaceous follicles. Phytochemical-loaded hydrogels or dressings may help target *S. aureus* biofilms; formulations that enhance outer membrane penetration may be valuable for *E. coli*.

Combination Therapy with Antibiotics. One of the most promising applications of phytochemicals is their use as adjuvant agents in antibiotic therapy. Combined use of phytochemicals and antibiotics may help reduce therapeutic antibiotic doses, restore susceptibility in resistant strains, and decrease selective pressure on microorganisms. However, synergistic interactions must be confirmed by microbial time-kill kinetics and *in vivo* experimental studies.

Antivirulence Strategies and Microbiome Preservation. Not all effective antibacterial therapeutic strategies need to kill bacteria directly. Some phytochemicals reduce microbial pathogenicity by inhibiting toxin production, quorum sensing, adhesion, motility, biofilm formation, inflammatory stimulation, and lipase activity. It is particularly important in *C. acnes* acne, because it is not only a potential pathogen but also a normal member of the resident skin microbiota. Complete eradication of this microorganism may disrupt the skin microbiome's balance. Therapeutic approaches aimed at reducing inflammation, virulence, and biofilm-associated persistence may be more appropriate than strategies focused solely on bacterial elimination.

CONCLUSIONS

Phytochemicals from medicinal herbs exhibit antibacterial activity against *S. aureus*, *E. coli*, and *C. acnes* via multiple mechanisms. These include membrane disruption, interference with the cell wall, inhibition of DNA replication, inhibition of enzymes, collapse of energy metabolism, inhibition of efflux pumps, antibiofilm activity, and suppression of virulence.

The strongest activity is generally observed against Gram-positive bacteria, such as *S. aureus* and *C. acnes*, because they lack the protective outer membrane of Gram-negative bacteria, such as *E. coli*. Terpenoids and phenolic compounds are particularly effective membrane-disrupting agents. Flavonoids act through enzyme inhibition, membrane effects, anti-inflammatory activity, and antibiotic potentiation. Alkaloids show promise, especially in combination with efflux pump inhibitors.

Against *S. aureus*, phytochemicals are particularly valuable as antibiofilm agents, efflux pump inhibitors, and modulators of MRSA resistance. Against *E. coli*, the main challenge is overcoming the Gram-negative outer membrane and the multidrug efflux system. In the treatment of *C. acnes*, phytochemicals that combine antibacterial and anti-inflammatory effects are particularly attractive, as they are highly relevant to acne pathogenesis.

Overall, phytochemicals derived from medicinal herbs should not be viewed simply as direct replacements for antibiotics. The greatest potential lies in their use as multitarget adjuvant agents that weaken bacterial defences, reduce virulence, disrupt biofilms, increase susceptibility to antibiotics, and support topical or localised therapy.

SUMMARY

The increasing prevalence of antibiotic-resistant pathogens underscores the need to discover new plant-derived antimicrobial agents. This study analyses the mechanisms of antibacterial action of flavonoids, terpenoids, phenols, and alkaloids against clinically significant pathogens: *Staphylococcus aureus*, *Escherichia coli*, and *Cutibacterium acnes*. Ten major ways of action of phytochemicals were identified and grouped into structural, metabolic, regulatory, and synergistic mechanisms. Terpenoids and phenols mainly exert antibacterial activity by damaging bacterial membranes and cell envelopes. Flavonoids exhibit pronounced regulatory effects. Alkaloids demonstrate the most balanced spectrum of activity. The sensitivity of bacteria to phytochemical compounds depends on the structure of the cell envelope: Gram-positive *S. aureus* and *C. acnes* are more vulnerable to membrane-active substances than Gram-negative *E. coli*. For *S. aureus*, compounds with antibiofilm activity that inhibit quorum sensing and efflux pumps are the most promising, particularly for combating MRSA. Substances that combine antibacterial and anti-inflammatory effects are particularly important for *C. acnes*. For *E. coli*, the effectiveness of phytochemicals requires increased outer membrane permeability or the use of advanced delivery systems. Phytochemicals should be considered not as direct substitutes for antibiotics, but as multifunctional adjuvant agents

capable of reducing bacterial virulence, inhibiting biofilms, and enhancing the effectiveness of antibiotic therapy. Further research should focus on standardised phytochemical profiling of extracts, active compound delivery systems, and synergy with conventional drugs.

Bibliography

1. Newman D. J., Cragg G. M. Natural products as sources of new drugs from 1981 to 2019. *Journal of Natural Products*. 2020. Vol. 83, No 3. P. 770–803. DOI: 10.1021/acs.jnatprod.9b01285
2. Taguri T., Tanaka T., Kouno I. Antimicrobial activity of 10 different plant polyphenolic compounds against bacteria associated with periodontal disease in vitro. *Journal of Periodontal Research*. 2024. Vol. 59, No 3. P. 457–469. DOI: 10.1248/bpb.27.1965
3. Cushnie T. P., Lamb A. B. Antimicrobial activity of flavonoids. *International Journal of Antimicrobial Agents*. 2021. Vol. 26, No 5. P. 343–356. DOI: 10.1016/j.ijantimicag.2005.09.002
4. Tian F. et al. Antifungal activity of essential oil and plant-derived natural compounds against *Aspergillus flavus*. *Antibiotics*. 2022. Vol. 11, No 12. Art. 1727. DOI: 10.3390/antibiotics11121727
5. Zhang X.Z. et al. Natural alkaloids as antimicrobial agents: mechanisms, potentials and challenges. *Molecules*. 2026. Vol. 31, No 7. Art. 1204. DOI: 10.3390/molecules31071204
6. Fais A., Era B. Phytochemical composition and biological activity. *Plants*. 2024. Vol. 13, No 3. Art. 331. DOI: 10.3390/plants13030331
7. Sutton J. A. F. et al. Staphylococcus aureus cell wall structure and dynamics during host-pathogen interaction. *PLoS Pathogens*. 2021. Vol. 17, No 3. Art. e1009468. DOI: 10.1371/journal.ppat.1009468
8. Chalmers S. J., Wylam M. E. Methicillin-resistant Staphylococcus aureus infection and treatment options. *Methods in Molecular Biology*. 2020. Vol. 2069. P. 229–251. DOI: 10.1007/978-1-4939-9849-4_16
9. Peng Q. et al. A review of biofilm formation of Staphylococcus aureus and its regulation mechanism. *Antibiotics*. 2023. Vol. 12, No 1. Art. 12. DOI: 10.3390/antibiotics12010012
10. Naidoo N., Zishiri O. T. Presence, Pathogenicity, Antibiotic Resistance, and Virulence Factors of Escherichia coli: A Review. *Bacteria*. 2025. Vol. 4, No 1. Art. 16. DOI: 10.3390/bacteria4010016
11. Cogen A. L., Nizet V., Gallo R. L. Skin microbiota: A source of disease or defence? *British Journal of Dermatology*. 2023. Vol. 189, No 3. P. 299–309. DOI: 10.1111/j.1365-2133.2008.08437.x

12. Mayslich C., Grange P.A., Dupin N. Cutibacterium acnes as an opportunistic pathogen: an update of its virulence-associated factors. *Microorganisms*. 2021. Vol. 9, No 2. Art. 303. DOI: 10.3390/microorganisms9020303
13. Farhadi F. et al. Antibacterial activity of flavonoids and their structure–activity relationship: an update review. *Phytotherapy Res.* 2019. Vol. 33, No 1. P. 13–40. DOI:10.1002/ptr.6208
14. Górniak I., Bartoszewski R., Króliczewski J. Comprehensive review of antimicrobial activities of plant flavonoids. *Phytochemistry Reviews*. 2019. Vol. 18, No 1. P. 241–272. DOI: 10.1007/s11101-018-9591-z
15. Yamaguchi T. Antibacterial effect of the combination of terpenoids. *Archives of Microbiology*. 2022. Vol. 204. Art. 520. DOI: 10.1007/s00203-022-03142-y
16. De Rossi L., Rocchetti G., Lucini L., Rebecchi A. Antimicrobial potential of polyphenols: mechanisms of action and microbial responses – a narrative review. *Antioxidants*. 2025. Vol. 14, No 2. Art. 200. DOI: 10.3390/antiox14020200
17. Li G.Q. et al. Plant polyphenols: antibacterial activity and structural insights. *Fitoterapia*. 2025. Vol. 185. Art. 106763. DOI: 10.1016/j.fitote.2025.106763
18. Faisal S. et al. Alkaloids as potential antivirals: a comprehensive review. *Natural Products and Bioprospecting*. 2023. Vol. 13. Art. 4. DOI: 10.1007/s13659-022-00366-9
19. Ghosh S. et al. A comprehensive review of antimicrobial agents against clinically important bacterial pathogens: prospects for phytochemicals. *Phytotherapy Research*. 2025. Vol. 39. P. 138–161. DOI: 10.1002/ptr.8365
20. Kumar G., Engle K. Natural products acting against *S. aureus* through membrane and cell wall disruption. *Natural Product Reports*. 2023. Vol. 40, No 10. P. 1608–1646. DOI: 10.1039/D2NP00084A
21. Lou Z. et al. The antibacterial mechanism and cell damage mechanism of natural antibacterial agents from different sources and their applications in food. *Journal of Food Measurement & Characterization*. 2026. Vol. 20. P. 1362–1386. DOI: 10.1007/s11694-025-03794-6
22. Mu L. et al. The antibacterial activity, action mechanisms and prospects of baicalein as an antibacterial adjuvant. *World Journal of Microbiology and Biotechnology*. 2025. Vol. 41. Art. 304. DOI: 10.1007/s11274-025-04508-2
23. Boberek J. M., Stach J., Good L. Genetic evidence for inhibition of bacterial division protein FtsZ by berberine. *PLoS One*. 2010. Vol. 5, No 10. Art. e13745. DOI: 10.1371/journal.pone.0013745

24. Rai D. et al. Curcumin inhibits FtsZ assembly: an attractive mechanism for its antibacterial activity. *Biochemical Journal*. 2008. Vol. 410, No 1. P. 147–155. DOI: 10.1042/BJ20070891
25. Xu S. et al. Plant flavonoids with antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA). *ACS Infectious Diseases*. 2024. Vol. 10, No 9. P. 3086–3097. DOI: 10.1021/acsinfecdis.4c00292
26. Allison D. G., Lambert P. A. Modes of action of antibacterial agents. *Molecular Medical Microbiology* / ed. by Y. W. Tang et al. 3rd ed. Academic Press, 2024. P. 597–614. DOI: 10.1016/B978-0-12-818619-0.00133-7
27. Davidova S., Galabov A. S., Satchanska G. Antibacterial, antifungal, antiviral activity, and mechanisms of action of plant polyphenols. *Microorganisms*. 2024. Vol. 12, No 12. Art. 2502. DOI: 10.3390/microorganisms12122502
28. de Souza Nascimento A. M. et al. Antibacterial action mechanisms and mode of trypsin inhibitors: a systematic review. *Journal of Enzyme Inhibition and Medicinal Chemistry*. 2022. Vol. 37, No 1. P. 749–759. DOI: 10.1080/14756366.2022.2039918
29. Liu Y. et al. Flavonoids as promising natural compounds for combating bacterial infections. *International Journal of Molecular Sciences*. 2025. Vol. 26, No 6. Art. 2455. DOI: 10.3390/ijms26062455
30. Bae J. Y., Seo Y. H., Oh S. W. Antibacterial activities of polyphenols against foodborne pathogens and their application as antibacterial agents. *Food Science and Biotechnology*. 2022. Vol. 31, No 8. P. 985–997. DOI: 10.1007/s10068-022-01058-3
31. Bellanti F. et al. Redox imbalance in inflammation: the interplay of oxidative and reductive stress. *Antioxidants*. 2025. Vol. 14, No 6. Art. 656. DOI: 10.3390/antiox14060656
32. Bhattacharya S. et al. Mitigating ROS signalling pathway-mediated defence mechanism: a novel approach to counteract bacterial resistance using natural antioxidant-based antibiotics. *Phytochemistry Reviews*. 2025. DOI: 10.1007/s11101-025-10179-6
33. Ramalingam S. et al. Plant-based natural products as inhibitors for efflux pumps to reverse multidrug resistance in *Staphylococcus aureus*: a mini review. *Mini-Reviews in Medicinal Chemistry*. 2024. Vol. 24, No 3. P. 272–288. DOI: 10.2174/1389557523666230406092128
34. Zhang L. et al. Bacterial efflux pump inhibitors reduce antibiotic resistance. *Pharmaceutics*. 2024. Vol. 16, No 2. Art. 170. DOI: 10.3390/pharmaceutics16020170
35. Bouyahya A. et al. Mechanisms, anti-quorum-sensing actions, and clinical trials of medicinal plant bioactive compounds against bacteria:

a comprehensive review. *Molecules*. 2022. Vol. 27, No 5. Art. 1484. DOI: 10.3390/molecules27051484

36. Zhang M. et al. Recent advances on the regulation of bacterial biofilm formation by herbal medicines. *Frontiers in Microbiology*. 2022. Vol. 13. Art. 1039297. DOI: 10.3389/fmicb.2022.1039297

37. Liu Y. et al. Eradicating biofilms: decoding persistent mechanisms and combating therapeutic strategies. *Advanced Healthcare Materials*. 2026. Vol. 15, No 6. Art. e02707. DOI: 10.1002/adhm.202502707

38. Alam M. et al. Synergistic role of plant extracts and essential oils against multidrug resistance and gram-negative bacterial strains producing extended-spectrum β -lactamases. *Antibiotics*. 2022. Vol. 11, No 7. Art. 855. DOI: 10.3390/antibiotics11070855

39. Dai C., Liu Y., Lv F., Cheng P., Qu S. An alternative approach to combat multidrug-resistant bacteria: new insights into traditional Chinese medicine monomers combined with antibiotics. *Advanced Biotechnology*. 2025. Vol. 3. Art. 6. DOI: 10.1007/s44307-025-00059-7

40. Ullah S. et al. Important flavonoids and their role as a therapeutic agent. *Molecules*. 2020. Vol. 25, No 22. Art. 5243. DOI: 10.3390/molecules25225243

41. Dias M. C., Pinto D. C. G. A., Silva A. M. S. Plant flavonoids: chemical characteristics and biological activity. *Molecules*. 2021. Vol. 26, No 17. Art. 5377. DOI: 10.3390/molecules26175377

42. Rajput A., Sharma R., Bharti R. Pharmacological activities and toxicities of alkaloids on human health. *Materials Today: Proceedings*. 2022. Vol. 48, pt. 5. P. 1407–1415. DOI: 10.1016/j.matpr.2021.09.189

43. Villanueva X. et al. Effect of chemical modifications of tannins on their antimicrobial and antibiofilm effect against Gram-negative and Gram-positive bacteria. *Frontiers in Microbiology*. 2023. Vol. 13. Art. 987164. DOI: 10.3389/fmicb.2022.987164

44. Huang P. Y., Hsu C. K., Tang H. J., Lai C. C. Eravacycline: a comprehensive review of in vitro activity, clinical efficacy, and real-world applications. *Expert Review of Anti-infective Therapy*. 2024. Vol. 22, No 6. P. 387–398. DOI: 10.1080/14787210.2024.2351552

45. Pannakal S. T. et al. Acnocure, a synergistic antimicrobial and anti-inflammatory combination of thymol and Curcuma turmerones, formulation and time-kill studies against *C. acnes*. *Cosmetics*. 2025. Vol. 12, No 2. Art. 37. DOI: 10.3390/cosmetics12020037

46. Peng Z., Wang X., Huang J., Li B. Pathogenic *Escherichia coli*. *Molecular Medical Microbiology* / ed. by Y. W. Tang et al. 3rd ed. Academic Press, 2024. P. 1065–1096. DOI: 10.1016/B978-0-12-818619-0.00069-1

47. Li Y., Zidorn C. Seasonal variations of natural products in European herbs. *Phytochemistry Reviews*. 2022. Vol. 21. P. 1549–1575. DOI: 10.1007/s11101-021-09797-7

48. Chaachouay N. Synergy, additive effects, and antagonism of drugs with plant bioactive compounds. *Drugs and Drug Candidates*. 2025. Vol. 4, No 1. Art. 4. DOI: 10.3390/ddc4010004

49. Balkrishna A. et al. Exploring the safety, efficacy, and bioactivity of herbal medicines: bridging traditional wisdom and modern science in healthcare. *Future Integrative Medicine*. 2024. Vol. 3, No 1. P. 35–49. DOI: 10.14218/FIM.2023.00086

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