

Review

Phytochemicals: A Promising Weapon in the Arsenal against Antibiotic-Resistant Bacteria

Bahman Khameneh ¹, N. A. Michael Eskin ², Milad Iranshahy ^{3,*} and Bibi Sedigheh Fazly Bazzaz ^{1,4,*}

¹ Department of Pharmaceutical Control, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad 9177948954, Iran; khamenehbagherib@mums.ac.ir

² Department of Food and Human Nutritional Sciences, Faculty of Agricultural and Food Sciences, University of Manitoba, Winnipeg, MB R3T 2N2, Canada; michael.eskin@umanitoba.ca

³ Department of Pharmacognosy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad 9177948954, Iran

⁴ Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad 9177948954, Iran

* Correspondence: IranshahiMI@mums.ac.ir (M.I.); Fazlis@mums.ac.ir (B.S.F.B.);

Tel.: +98-51-31801253 (M.I.); +98-51-31801130 (B.S.F.B.); Fax: +98-51-38823251 (M.I. & B.S.F.B.)

Abstract: The extensive usage of antibiotics and the rapid emergence of antimicrobial-resistant microbes (AMR) are becoming important global public health issues. Many solutions to these problems have been proposed, including developing alternative compounds with antimicrobial activities, managing existing antimicrobials, and rapidly detecting AMR pathogens. Among all of them, employing alternative compounds such as phytochemicals alone or in combination with other antibacterial agents appears to be both an effective and safe strategy for battling against these pathogens. The present review summarizes the scientific evidence on the biochemical, pharmacological, and clinical aspects of phytochemicals used to treat microbial pathogenesis. A wide range of commercial products are currently available on the market. Their well-documented clinical efficacy suggests that phytomedicines are valuable sources of new types of antimicrobial agents for future use. Innovative approaches and methodologies for identifying plant-derived products effective against AMR are also proposed in this review.

Keywords: phytochemicals; antibiotic resistance; complementary medicine; herbal medicine; clinical applications



Citation: Khameneh, B.; Eskin, N.A.M.; Iranshahy, M.; Fazly Bazzaz, B.S. Phytochemicals: A Promising Weapon in the Arsenal against Antibiotic-Resistant Bacteria.

Antibiotics **2021**, *10*, 1044. <https://doi.org/10.3390/antibiotics10091044>

Academic Editor: Filippo Maggi

Received: 20 July 2021

Accepted: 17 August 2021

Published: 26 August 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

According to various surveys, there is a direct relationship between the increased use of antibiotics and the creation of resistant bacteria. The appearance of resistant microorganisms to drugs leads to the currently available treatment regimes becoming less effective or totally ineffective [1–4]. As a result, this has become a prominent issue and a serious concern for global health agencies such as the World Health Organization, Centers for Disease Control, and regional health ministries. Additionally, it represents a challenging problem for the medical fraternity [5,6]. In addition, the effectiveness of antibiotics has been substantially reduced by the existence of different resistance mechanisms. Of these, the major reasons are antibiotic inactivation by enzyme production, alteration of drug targets, changes in cell permeability, the intrinsic expression of efflux pumps, and biofilm formation. The last one, in particular, acts as a defense against drugs and contributes to the sustained persistence of resistant bacteria.

The first antibiotic, penicillin, was discovered by Alexander Fleming in 1928. Since then, other β -lactam antibiotics identified include cephalosporins, carbapenems, and monobactams. They all contain a four-membered cyclic ring consisting of three carbon atoms and one nitrogen atom. The nitrogen atom is attached to the β -carbon relative to the carbonyl group, and hence the name β -lactam is used.

Fleming [7] reported that several bacteria in the colityphoid group were not inhibited by penicillin. Subsequent work by Abraham and Chain [8] identified an enzyme in Gram-negative *Escherichia coli*, penicillinase, capable of destroying penicillin. This enzyme, now referred to as β -lactamase, is responsible for destroying the β -lactam ring in penicillin and other β -lactam antibiotics. Initially, very few bacteria produced β -lactamase, but the overuse of antibiotics has resulted in its widespread production by Gram-negative bacteria rendering them resistant to many life-saving antibiotics. Among the many strategies being investigated to overcome these resistant bacteria is to inhibit the β -lactamase enzyme. Synthetic compounds have been developed for inhibiting β -lactamase. However, concerns regarding their toxicity have resulted in a concerted effort to find safer plant sources of inhibitors.

In addition, mobile genetic elements such as plasmids, insertion sequences, transposons, and integrative conjugative elements all play an important role in developing resistance against antibacterial agents [4].

Under these circumstances and to overcome this problem, identifying alternative or complementary approaches is urgently needed to prevent and treat microbial infections. One such approach employs naturally occurring compounds with potential antibacterial activities [3,9–13]. Herbal medicines are rich in various compounds, such as alkaloids, flavonoids, terpenoids, coumarins, tannins, antimicrobial peptides, and steroids, which can be used as an alternative or complement to conventional antibiotics [14–18]. These compounds exert their antimicrobial activities via different mechanisms, including (I) structural disruption of the bacterial cell and increase in cell permeability and leakage of cell constituents, (II) alterations in the bacterial cell wall and cell membrane, (III) losing ATP, (IV) inhibition of protein synthesis, (V) intracytoplasmic damage, pH disturbance, DNA damage and (VI) inhibition of quorum sensing among bacteria [10,19–21]. Plant-derived compounds are generally less expensive, safer to use in terms of side effects, and more readily available than their synthetic counterparts [21,22]. Therefore, the isolation and characterization of plant-derived substances with suitable antibacterial activities are integral for developing natural antibacterial agents.

Despite a significant increase in publications on this topic, mechanisms of action and their clinical use have remained elusive. This review describes different aspects of phytochemicals, such as identification, characterization, and evaluation of their biological activities. In the next step, we will explain the valuable findings of preclinical and clinical studies of some phytomedicine in the market worldwide.

We conducted a systematic review and searched different databases such as PubMed, Embase, Scopus, Web of Science, and Google Scholar without time limitations.

2. Isolation, Characterization, and Bioassays of Phytochemicals

As mentioned earlier, using naturally occurring compounds with potential antibacterial activities has been considered an alternative or complementary in treating infectious diseases. Therefore, identifying bioactive components and understanding their properties play a vital role in evaluating phytochemicals [23,24]. Conventional screening methods, including disk diffusion, TLC-direct bioautography, and broth microdilution antibiotic sensitivity test, have been used extensively to screen the antimicrobial activities of extracts and purely natural compounds. These methods have helped discover almost every antibiotic available in the market and the identification of drug susceptibility. Despite the advantages of well-established procedures, classical methods suffer from several limitations such as unsatisfactory test speed, high cost, and low reliability.

Moreover, these methods provide no information about the mechanism of action of the crude extract or pure natural product that leads to the rediscovery of the compounds with a similar mechanism of action. Thus, several studies tried to offer some solutions to overcome some of the drawbacks mentioned above. This section will discuss the recent advanced development of the methods used for antimicrobial screening of phytochemicals against antibiotic-resistant microorganisms.

2.1. Microfluidic Technology

Establishing a high-throughput screening platform with high resolution and speed has attracted natural products to discover antibacterial drugs. Although droplet-based microfluidic technology is nascent, it continues to show promise in many biomedical fields and has revolutionized our understanding of single-cell interactions [25].

Recent studies confirmed the capability of microfluidic technology to rapidly and precisely screen novel antibiotic candidates, specifically against antibacterial-resistant mutants.

Dhayakaran et al. [25] developed a 3D microfluidic device to assess the antibacterial activity of synthesized soy peptides PGTAVFK and IKAF-KEATKVDKVVVLWTA against *Pseudomonas aeruginosa* and *Listeria monocytogenes*. The bottom layer was a glass layer; 24 incubation chambers were in the middle polydimethylsiloxane layer, and in the final layer were concentration generating gradients. Using the device, the authors were able to determine the antimicrobial activity of the peptides based on their optical density at 600 nm easily without any need for prior serial dilution. These devices can be successfully employed to screen huge libraries of natural products or crude extracts and substantially reduce the time needed for high-throughput screening. While a considerable effort has been spent establishing microfluidic technology to screen natural products against cancer [26], there are very few studies on the antibacterial drug screening of natural products using this technology. Future studies are desperately needed in this field.

2.2. Host-Pathogen Co-Culture Assay

Co-culturing of human cell lines and pathogenic bacteria in the presence of a natural antimicrobial product or crude extract can simultaneously determine the efficacy and tolerability of the antibacterial candidates. Human cell lines are incubated with an antibacterial candidate and then infected with the desired pathogenic bacteria in this method. In this way, the minimal inhibitory concentration or dose and the selectivity index are determined precisely. This is beneficial for optimization and high-throughput screening because of time- and cost-efficiencies [27].

In this regard, Haque et al. [28] evaluated the antimicrobial activity of semisynthetic derivatives of betulin as a triterpenoid natural product. Two derivatives showed promising activity against Gram-positive bacteria in broth microdilution assays. However, in the host-pathogen co-culture assay, weak or no activity was observed for derivatives. Further studies in the presence of an increased albumin concentration showed that betulin derivatives could potentially bind to albumin present in human cell line culture media. Hence, the host-pathogen co-culture assay can predict a drug candidate's serum protein binding potential and guides the researcher through therapeutic potential and pharmacokinetics in the primary steps of antibiotic drug discovery from natural products.

2.3. Colorimetric Assay of pH

A high-throughput screening method that is sensitive and robust gives more detailed information than the minimum bactericidal concentration (MBC) and minimum inhibitory concentration (MIC) and is highly desirable for finding natural products with a novel mechanism of action. Such a method was proposed by Ymele-Lek et al. [29], who used thymol blue and bromothymol blue as pH-sensitive dyes. As fermentation can decrease the pH of the culture medium, using these dyes coupled with the colorimetric assay enabled the authors to screen 39,000 crude extracts and find suitable candidates to inhibit bacterial sugar fermentation. This simple colorimetric assay led to the identification of a broad-spectrum antimicrobial natural product, mirandamycin. Further studies revealed that mirandamycin is active against *E. coli*, *P. aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA), and *Mycobacterium tuberculosis*.

These studies indicate that the development of novel screening methods has the same importance and impact as screening novel sources of natural products on antibacterial drug discovery.

2.4. In Silico Screening

With over 300,000 entries in SciFinder that have never been tested for their antibacterial activity, natural products are valuable sources of compounds that can be harnessed for discovering future antibacterial drugs [30]. However, the rapid exploitation of such potential with conventional methods of screening seems impossible. Using the advantages of in silico, however, one can successfully screen a plethora of entries in a database to identify chemical structures that can inhibit critical enzymes in bacteria in a matter of a few days. This method has several advantages, including ease of access and saving time and money. However, there are some limitations, i.e., these screenings can only be performed on proteins and enzymes whose 3D protein crystal structure is available in the appropriate databases [31].

An example of such a successful approach was recently published by Skariyachan and co-workers [32]. They filtered 236 natural compounds from the Super Natural II database for the ADMET properties using the PreADMET and SwissADME websites. Six lead compounds were selected for further docking studies in the binding site of proteins that are significantly involved in antibiotic resistance in *Acinetobacter baumannii*, including orotate phosphoribosyltransferase (PyrE), Orotidine 5'-phosphate decarboxylase (PyrF), outer membrane protein 38 (Omp38), and Protein RecAm. Among the natural drug ligands, 16-epiestriol exhibited the best binding potential to all proteins, especially PyrE, with a -7.3 kcal/mol binding energy. In vitro studies revealed that 16-epiestriol at 200 $\mu\text{g}/\text{mL}$ could significantly inhibit clinically isolated multidrug-resistant *A. baumannii* [32]. 16-Epiestriol is considered a lead compound, and by chemical optimization, more potent compounds can be synthesized in the future to overcome the antibacterial resistance in *A. baumannii*. This study demonstrates that a rational design of in silico screening studies may be valuable in the possible post-antibiotic era.

3. Mechanistic Insights on Phytochemicals

Phytochemicals show promising results in overcoming the resistance development of resistance in bacterial pathogens and combating bacterial infections. These compounds can restore the clinical application of conventional antibiotics by increasing their potency and avoiding the development of resistance. The antibacterial properties of phytochemicals are related to chemically interference with the function or synthesis of vital components and circumventing the mechanism of antibacterial resistance. Different mechanisms have been mentioned in antibacterial actions that inhibit bacterial cell-wall biosynthesis and cell membrane destruction, inhibiting bacterial protein biosynthesis, DNA replication and repairing, and metabolic pathways [33,34]. In addition, different mechanisms are involved in bacterial resistance to an antibiotic, such as overexpression of the efflux pumps, destroying the antibacterial agents, structural modification of porins, and modification of antibiotics [33,35]. Therefore, inhibition of them is an integral part of combating antibiotic resistance [3]. Phytochemicals based on their chemical structures and properties could exhibit antibacterial actions via one or more of these mechanisms [4]. Based on structures, they are categorized into major groups of alkaloids, tannins, carbohydrates, and glycosides, terpenoids, flavonoids, steroids, and coumarins [36]. These compounds have particular clinical value because their bioactivity generally does not lead to resistance. Some important plant-derivative compounds with antibacterial activities and their mechanism of action are illustrated in Figure 1.

Polyphenols show antibacterial activity against a broad spectrum of bacteria. Among them, flavanols, flavonols, and phenolic acids exhibit the highest activities because of (I) inhibiting bacterial virulence factors including enzymes and toxins, (II) interacting with the cytoplasmic membrane or reducing the pH values, (III) suppressing biofilm formation, (IV) exerting synergistic effects with conventional antibiotics, and (V) reducing the extracellular polysaccharide (EP) activity and acting as EP inhibitors (EPIs) [37–39]. Phenolic compounds that are produced in relatively high concentrations show promising EPI activity against pathogenic bacteria. They could inhibit cell wall biosynthesis and

critical enzymes such as urease, sortase A and dihydrofolate reductase. The Fabaceae family has the most phenolic derivative compounds among botanical families [35].

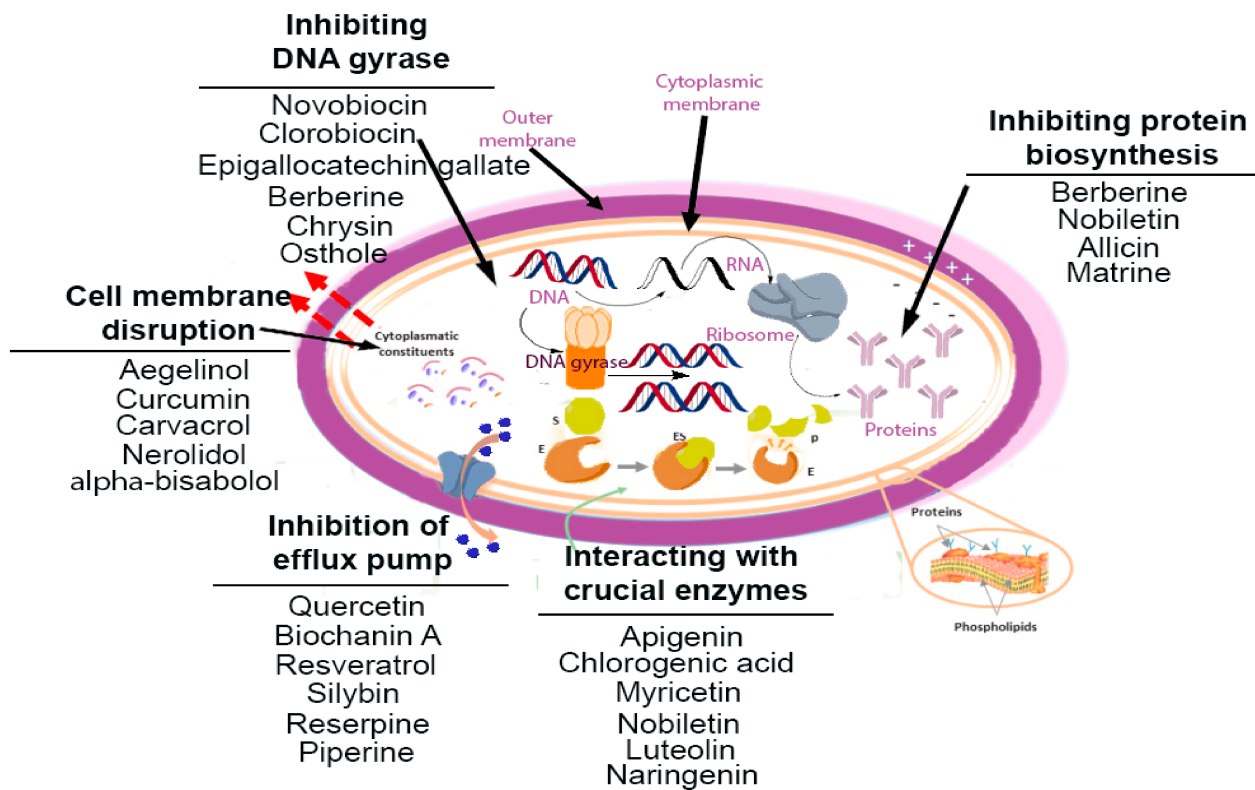


Figure 1. Antibacterial mechanism of action of plant-derivative compounds.

It should be noted that their activity is mainly weak and also non-specific. However, in some cases, target specificity among phytochemicals has been reported. For example, coumarins have high activity against *S. aureus*, while no activity against Gram-negative bacteria has been observed [40].

Zhao et al. [41] extracted, purified, and identified a specific β -lactamase inhibitor in green tea, epigallocatechin gallate (EGCG). They tested it on 21 clinical isolates of penicillinase-producing *S. aureus*. In addition to direct binding with peptidoglycan in the bacterial cell membrane, ECGG exhibited a dose-dependent inhibition of penicillinase activity with a 50% inhibition at a concentration of 10 $\mu\text{g}/\text{ml}$. A later study by Zhao et al. [42] reported restoring the antibacterial activity of β -lactams (cefotaxime and imipenem) in the presence of ECGG against a series of β -lactamase producing bacteria, including 21 *S. aureus*, 6 *E. coli*, 3 *Klebsiella pneumoniae*, and 8 *Serratia marcescens* strains. The in vitro studies showed the effectiveness of ECGG in β -lactamase activity inhibition and restoring the antibacterial activities of penicillin. However, in vivo studies exhibited less effectiveness due to the intracellular location of the enzymes and the protective permeability barrier of the cell walls and cell membranes [43].

An interesting flavonoid, galangin, was reported in the rhizomes of the perennial plant *Alpinia officinarum* by Eukeb et al. [44]. Galangin was effective in reversing the β -lactam antibiotic resistance of *S. aureus*. This led Sirlwong and co-workers [45] to examine the synergism between several other flavonoids, quercetin or kaempferol, in combination with amoxicillin for their ability to overcome amoxicillin-resistant *Staphylococcus epidermidis* (ARSE). The synergy between quercetin and amoxicillin proved to be very effective by inhibiting peptidoglycan synthesis in the bacterial cell membrane, inhibiting β -lactamase activity, increasing cell membrane permeability, and increasing protein amide I and II, and decreasing fatty acids in the bacterial cells. The authors pointed out the need to determine their safety and efficacy using animal and human subjects.

The increased resistance of *Streptococcus* spp. to antibiotics is one of the significant causes of mastitis. This condition is an inflammation of the mammary gland that results in major economic losses to the dairy industry [46]. To combat this problem, Maia and co-workers [47] isolated guttiferone-A and 7-epiclusianone from the fruits of *Garcinia brasiliensis*, a tree native to the Amazon and widely cultivated in Brazil. The pharmacological properties of these two bioactive compounds, particularly their antimicrobial properties against *S. aureus* and *Bacillus cereus* [48], suggested their possible prevention of metastasis. Synergistic effects were evident between 7-epiclusianone and guttiferone-A with ampicillin or gentamicin. At levels below their MIC values, both compounds reversed the antibiotic resistance of *Streptococcus agalactiae* and *Streptococcus uberis*. Neither compounds were cytotoxic, and their strong binding of β -lactamase could explain the reversal of ampicillin resistance. Their potential for the treatment of bovine mastitis appears promising.

A root canal infection such as apical periodontitis is a severe problem worldwide. The infection is primarily caused by the growth of *Prevotella* spp., *Porphyromonas* spp., *Fusobacterium* spp., *Enterococcus* spp., and *Candida* spp. While chemical irritants are used to eliminate these multidrug-resistant organisms, they generally fail, with the residual organisms causing tissue necrosis, gastritis, and local inflammation. To overcome this problem, Sriramkumar et al. [49] undertook the homology modeling of the β -lactamase protein from *Staphylococcus sciuri* and docking studies with 4-butanylanisole and 9-ocatadecene. These phytochemicals were extracted from *Garcinia imberti*, a flowering plant of the family Clusiaceae growing in India. Both compounds exhibited favorable inhibitory activity of β -lactamase by binding with the conserved amino acids glutamine, asparagine, lysine, and phenylalanine at their active site. Based on this information, antimicrobial compounds can be tailored for a specific organism, such as *S. sciuri*.

Resveratrol is another phenolic compound with potential antibacterial properties. It is active against multidrug-resistant (MDR) Gram-negative bacteria with MICs ranging from 32 $\mu\text{g}/\text{mL}$ to 128 $\mu\text{g}/\text{mL}$. The possible mechanism of action is related to the inhibition of the efflux pump activities [50,51].

Sophoraflavanone G is another potent antibacterial agent. This compound can inhibit the growth of MRSA via different mechanisms such as interacting with peptidoglycan and inhibiting cell wall biosynthesis [52,53].

Baicalein is an effective bactericide. The results of the study indicated that this compound had pronounced antibacterial activities on *S. aureus*. The mechanism could affect bacterial membrane penetrability, inhibit protein synthesis, and influence SDH, MDH, and DNA topoisomerase I and II activities to exert the antibacterial functions [54].

Quercetin and luteolin are other phenolic compounds with promising antibacterial activities. These compounds can increase cytoplasmic membrane permeability, caused irregular cell shape, peptidoglycan, and CM damage, and decrease nucleic acid content but increase proteins in bacterial cells. Luteolin and quercetin propose the potential to develop adjuncts to conventional antibiotics to treat infectious diseases [55].

Alkaloids are another important group of compounds that possess antibacterial properties. They are heterocyclic nitrogen compounds with highly variable chemical structures. Their antibacterial activities have been proven, and many studies have reported that they can play a significant role in treating infectious diseases. Their mechanism of action might be due to the enzymatic alterations affecting physiological processes, including inhibition of DNA synthesis and repair mechanisms by intercalating nucleic acids [9,56,57]. Isoquinolines, aporphines, quinolones, and phenanthrenes are the most critical alkaloid groups with suitable antibacterial activities [35].

It was shown that berberine had certain inhibitory effects on four common bacteria with MICs for *E. coli*, *B. subtilis*, *S. aureus*, and *Salmonella* were 2.40, 3.60, 3.30, and 3.95 mg/mL, respectively. Scanning electron microscopy showed that berberine damaged the morphology of the bacterial cells and ruptured the cells, leading to the leakage of intracellular substances. Consequently, the nucleic acid content in the bacterial suspension was increased remarkably. The polyacrylamide gel electrophoresis analysis indicated

that berberine could inhibit protein synthesis. Additionally, this compound could reduce the Na⁺/K⁺-ATPase activity of the cell membrane. Therefore, berberine inhibited the expression of bacterial proteins by destroying the cell membrane structures, which finally leads to the death of the cells so that it can exert good antibacterial effects and can be used as a valuable antibacterial agent [58].

Reserpine as an inhibitor of efflux pumps was shown to reduce the resistance of MRSA strains to conventional antibiotics [59].

Sanguinarine, a benzophenanthridin alkaloid, strongly induced filamentation in Gram-positive and -negative bacteria and prevented bacterial cell division by inhibiting cytokinesis. Sanguinarine inhibited bacterial division by perturbing FtsZ assembly dynamics in the Z ring. These observations support the hypothesis that the assembly and bundling of FtsZ play an important role in bacterial growth cytokinesis. Thus sanguinarine may be used as a lead compound to develop FtsZ-targeted antibacterial agents [60].

The investigations of the competitive binding of antibiotics and caffeine with DNA show that at physiological concentrations of antibiotic and caffeine (mM), the dominant mechanism influencing the affinity of the antibiotic with DNA is the displacement of bound antibiotic molecules from DNA due to caffeine-DNA complexation. These observations explain the protector actions of caffeine [61]. Sulfur-containing compounds are another critical group of phytochemicals with antibacterial and antifungal activities. They have exerted antibacterial activities against both Gram-positive and -negative bacteria. In addition, it has been shown that plants with high concentrations exert a broad spectrum of antimicrobial activities [62].

Allicin exhibited promising antifungal activities against different pathogens. The putative mechanisms of action are influencing DNA replication, mitochondrial translation, and chromatids cohesion. These processes play a critical role in yeast cells' cell cycle, growth, and viability [63].

Isothiocyanates derived from cruciferous plants reveal antibacterial activity. They showed antibacterial activities against *E. coli*, *K. pneumoniae*, *S. aureus*, *S. epidermidis*, *B. subtilis*, and *E. faecalis*. *E. coli* strains. They are effective against different pathogenic bacteria and act by at least two mechanisms depending on bacteria species. These compounds exert their antibacterial effects by acting on cell membranes and leakage of cellular metabolites [64,65].

The coumarins are heterocyclic compounds found in various plants. They exert a wide range of bioactive properties such as anticoagulant, antibacterial, antiviral, antioxidant, anti-inflammatory, antitumor, and enzyme inhibition. The antibacterial activity of coumarins is mainly due to inhibiting bacterial DNA gyrase, preventing supercoiling [66].

The dichloromethane extract of *Prangos hulusii* has yielded nine known and one new prenylated coumarins. The root extract and its prenylated coumarins exhibit antibacterial activities against nine standards and six clinically isolated strains at concentrations between 5 and 125 µg/mL [67].

Aegelinol and agasyllin showed antibacterial activities against nine ATCC and the same clinically isolated Gram-positive and -negative bacterial strains. At a concentration between 16 and 125 mg/mL, both coumarins showed remarkable antibacterial effects against Gram-negative and -positive bacteria [68].

Terpenes or isoprenoids are widely widespread in nature, have high biological activity. They show a broad spectrum of antibacterial activities via different mechanisms. Their mechanism is closely associated with their lipophilic features. Monoterpenes preferentially could impact the membrane structures and increase the fluidity and permeability, altering the topology of its proteins and making disturbances across the respiration chain [69]. In addition, they could change the membrane permeability without cell lysis.

Carvacrol is a monoterpenic phenol, biosynthesized from γ -terpinene through p-cymene. This compound occurs in aromatic plants and many essential oils of the Labiatae family. Carvacrol is reported to have a wide range of biological properties, including antibacterial activities. Compared to other volatile compounds present in essential oils, the

compound shows higher antibacterial power because of the phenol ring, which confers hydrophobicity and also the presence of the free hydroxyl group. Carvacrol is active against many Gram-positive and -negative human pathogenic bacteria. In particular, it is very effective in controlling foodborne pathogens, such as *E. coli*, *Salmonella*, and *B. cereus* [70,71].

Thymol is a carvacrol isomer also known as “hydroxy cymene”. The compound possesses antibacterial activities against a wide range of species, including biofilm-embedded microorganisms [72].

Table 1. The most prevalent natural antibacterial compounds with the related mechanism of action.

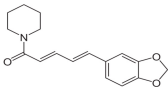
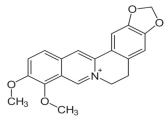
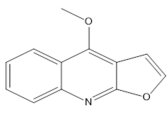
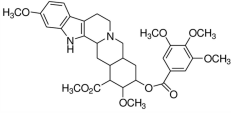
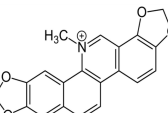
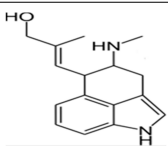
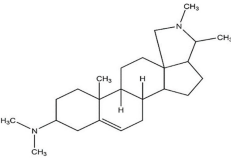
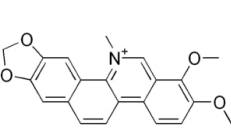
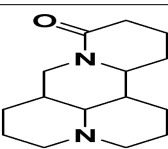
Compound	Chemical Structure	Active against (MIC/MBC Values)	Class of Phytochemicals	Mechanism of Action	Ref.
Piperine		<i>Staphylococcus aureus</i> and <i>Bacillus subtilis</i> (MIC values of 225 µg/mL)		Inhibition of efflux pump	[73,74]
Berberine		<i>Candida albicans</i> (MIC values ranging from 125 to 500 µg/ml)		DNA intercalation; inhibiting RNA polymerase, DNA gyrase, and topoisomerase IV, and IA; inhibiting protein biosynthesis, Inhibition of cell division	[75–77]
Dictamnine		<i>Saccharomyces cerevisiae</i> (MIC value of 64 µg/ml)		Inhibiting type II topoisomerase	[78,79]
Reserpine				Inhibition of efflux pump	[80]
Sanguinarine		carbapenem-resistant <i>Serratia marcescens</i> (MIC90 of 32 µg/ml)	Alkaloids	Inhibiting replication and transcription	[81,82]
Chanoclavine				Inhibition of efflux pump	[83]
Conessine		<i>Micrococcus luteus</i> ATCC 9341 (MIC value of 15.6 µg per disc)		Inhibition of efflux pump	[84,85]
Chelerythrine		MRSA (MIC values ranged from 2 to 4 µg/mL) and extended-spectrum β-lactamases <i>Escherichia coli</i> (MIC values varied from 16 to 256 µg/mL)		Damaging the bacterial cells	[86,87]
Matrine		<i>E. coli</i> and <i>Bacillus subtilis</i> (12.5 µg/mL)		Inhibiting the synthesis of proteins	[88,89]

Table 1. Cont.

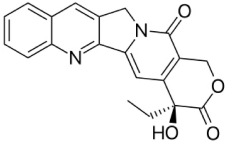
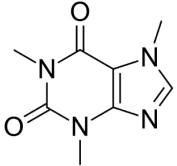
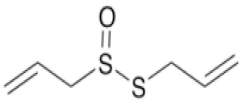
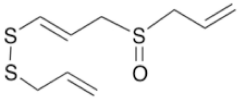
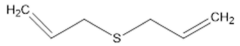
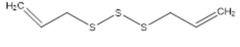
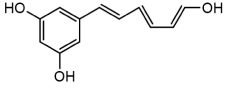
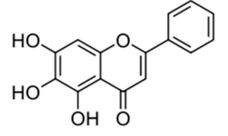
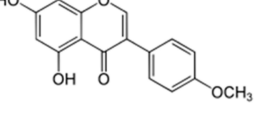
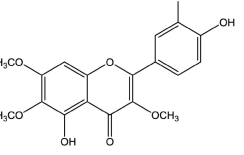
Compound	Chemical Structure	Active against (MIC/MBC Values)	Class of Phytochemicals	Mechanism of Action	Ref.
Camptothecin				Cleaving the intermediate complex of DNA topoisomerase I	[90]
Caffeine		<i>P. aeruginosa</i> (MIC value of 200 µg/mL)		Interaction with the quorum sensing proteins and inhibiting biofilm formation	[91,92]
Allicin		<i>C. albicans</i> (MIC value of 8 µg/ml)		Inhibiting sulfhydryl-dependent enzymes, inhibiting the DNA and protein synthesis	[93,94]
Ajoene		<i>Histoplasma capsulatum</i> (MIC values varied from 2.5 to 5 µg/mL)		Inhibiting sulfhydryl-dependent enzymes	[93,95]
Isothiocyanates	$R-N=C=S$		Organosulfur	Attacking the sulfhydryl groups of enzymes, damaging the cell wall integrity, and leakage of cellular metabolites	[96]
Diallyl Sulfides		<i>C. albicans</i> (MIC value of 500 µg/ml)		Inhibiting glutathione (GSH) S-transferase (GST) activity. Interaction with the quorum sensing proteins and inhibiting biofilm formation	[97,98]
Diallyl trisulfide (Allitridin)				Destructing the bacterial cell membrane. Decreasing the activity of the bacterial membrane transporter system.	[99]
Resveratrol		Multidrug resistant (MDR) Gram-negative (MICs ranging from 32 µg/mL to 128 µg/mL)		Inhibition of efflux pump	[50,51]
Baicalein		<i>S. typhimurium</i> (MIC value of 64 µg/ml)		Inhibition of efflux pump	[54,100]
Biochanin A		<i>S. aureus</i> (MIC values varied from 64 to 512 µg/mL)	Polyphenolic compounds	Inhibition of efflux pump	[100,101]
Chrysosplenol-D				Inhibition of efflux pump	[102]

Table 1. Cont.

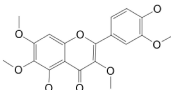
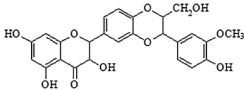
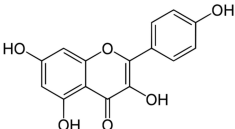
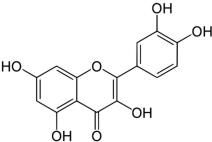
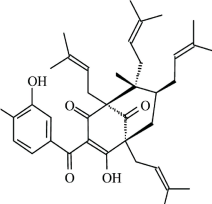
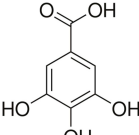
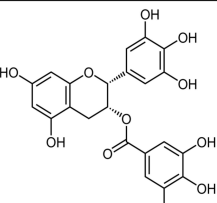
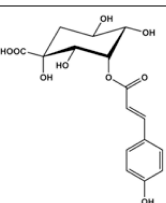
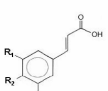
Compound	Chemical Structure	Active against (MIC/MBC Values)	Class of Phytochemicals	Mechanism of Action	Ref.
Chrysoplenetin				Inhibition of efflux pump	[102]
Silybin				Inhibition of efflux pump	[103]
Kaempferol				Inhibition of efflux pump	[104]
Quercetin		<i>Aspergillus fumigatus</i> (MIC values of 16–64 μM)		Inhibition of efflux pump, Interacting with some crucial enzymes such as β-lactamase, and cell membrane disruption	[45,105]
Guttiferone-A				β-lactamase inhibition	[48]
4-Butanylanisole				β-lactamase inhibition	[49]
Gallic acid				Cell membrane disruption, and Mg ²⁺ Chelation	[106]
Epigallocatechin gallate		<i>S. aureus</i> (MIC values of 7.81–62.5 μg/mL)		Inhibiting the B subunit of DNA gyrase, penicillinase, and β-lactamase	[41–43,107,108]
3-p-trans-Coumaroyl-2-hydroxyquinic acid				Damaging the cytoplasmic membrane	[109]
Hydroxycinnamic acids (p-Coumaric, Caffeic, and Ferulic acids)	 R ₂ = OH: p-Coumaric acid R ₂ = OH, R ₃ = OH: Caffeic acid R ₃ = OCH ₃ , R ₂ = OH: Ferulic acid R ₁ = OCH ₃ , R ₂ = OH, R ₃ = OCH ₃ : Sinapic acid			Interfering with membrane integrity	[110]

Table 1. Cont.

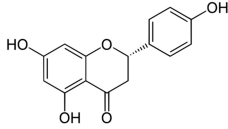
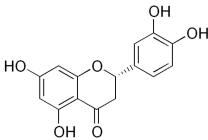
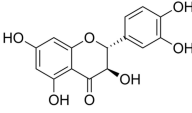
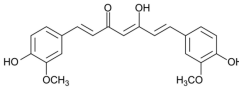
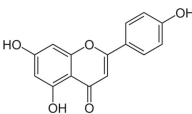
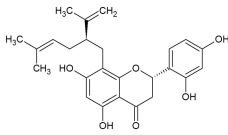
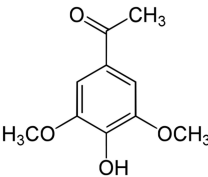
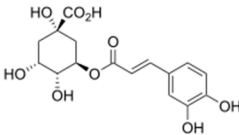
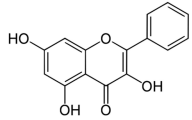
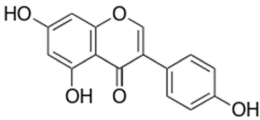
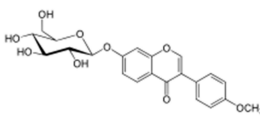
Compound	Chemical Structure	Active against (MIC/MBC Values)	Class of Phytochemicals	Mechanism of Action	Ref.
Naringenin				Interacting with some crucial enzymes	
Eriodictyol		<i>Streptococcus mutans</i> and <i>P. aeruginosa</i> (MIC values of 1 mg/mL)		Interacting with some crucial enzymes	[111–113]
Taxifolin		<i>Helicobacter pylori</i> (MIC = 625 µg/mL)		Interacting with some crucial enzymes	
Curcumin		<i>Shigella dysenteriae</i> and <i>Campylobacter jejuni</i> (MIC values of 256 µg/mL)		Damaging the cell membranes	[114,115]
Apigenin				Interacting with some crucial enzymes	[116]
Sophoraflavanone G		MRSA (MIC values of 0.5–8 µg/mL)		Interacting with peptidoglycan and inhibiting cell wall biosynthesis	[52,53]
Acetosyringone		<i>S. cerevisiae</i> (MIC = 24 mM)		Depolarization of the bacterial cell membrane	[117,118]
Chlorogenic acid		<i>Providencia alcalifaciens</i> , <i>Moraxella catarrhalis</i> , <i>S. aureus</i> , and <i>E. coli</i> (MIC values of 60 to 100 µM)		Interacting with some crucial enzymes	[119]
Galangin		<i>S. aureus</i> (MIC = 32 µg/mL)		Damaging of the cytoplasmic membrane and inhibition of β-lactamase	[44,120]
Genistein				Inhibition of efflux pump	[121]
Ononin					

Table 1. Cont.

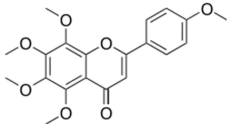
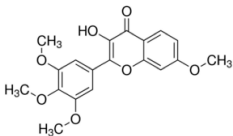
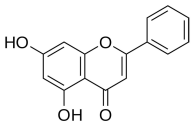
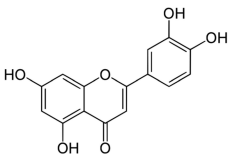
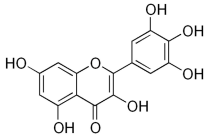
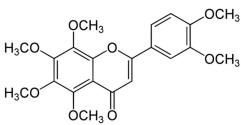
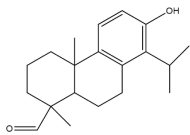
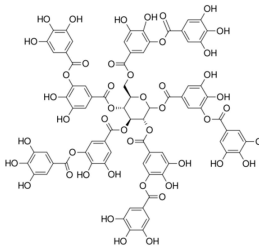
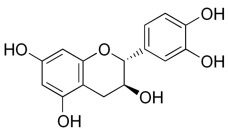
Compound	Chemical Structure	Active against (MIC/MBC Values)	Class of Phytochemicals	Mechanism of Action	Ref.
Tangeritin				Cell membrane disruption, DNA gyrase inhibition, Reduced protein synthesis, Interacting with some crucial enzymes	[122]
5,6,7,4'-Tetramethoxyflavone				Cell membrane disruption, DNA gyrase inhibition	
Chrysin		<i>H. pylori</i> (MIC = 6.25 µg/mL)		Cell membrane disruption, DNA gyrase inhibition	[123,124]
Luteolin		<i>S. aureus</i> (MIC = 16–32 µg/mL) and <i>Listeria monocytogenes</i> (MIC = 32–64 µg/mL)		Cell membrane disruption, DNA gyrase inhibition, Type III secretion inactivation, Interacting with some crucial enzymes	
Myricetin		<i>S. aureus</i> (MIC = 256 µg/mL)		DNA gyrase inhibition, Type III secretion inactivation, Interacting with some crucial enzymes	[125–127]
Nobiletin				Cell membrane disruption, DNA gyrase inhibition, Reduced protein synthesis, Interacting with some crucial enzymes	
Totaryl				Reduced expression of enterotoxins, multi-drug efflux pump inhibitor	[128]
Tannic acid		<i>S. aureus</i> (MIC = 512 µg/mL)		Ion binding	[129,130]
(+)-Catechin		MRSA (MIC = 78.1–156.2 µg/ml)		Inhibition of bacterial gene expression	[131,132]

Table 1. Cont.

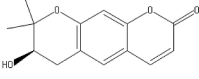
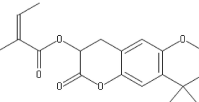
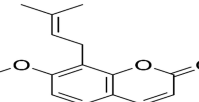
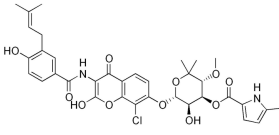
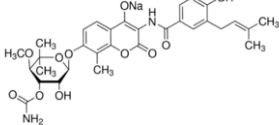
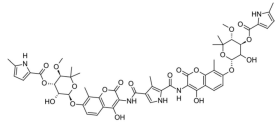
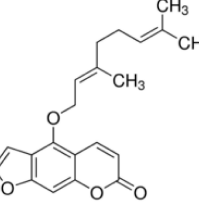
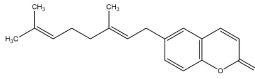
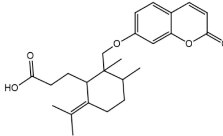
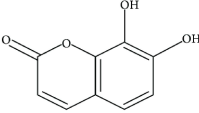
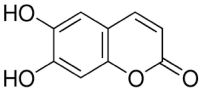
Compound	Chemical Structure	Active against (MIC/MBC Values)	Class of Phytochemicals	Mechanism of Action	Ref.
Aegelinol		<i>S. aureus</i> , <i>S. thypii</i> , <i>Enterobacter cloacae</i> and <i>E. carogenes</i> (MIC = 16 µg/mL)	Coumarins	Cell membrane Disruption	[68,133]
Agasyllin		<i>S. aureus</i> , <i>S. thypii</i> , <i>Enterobacter cloacae</i> and <i>E. carogenes</i> (MIC = 32 µg/mL)		Cell membrane Disruption	
Osthole				DNA gyrase inhibitor	[134]
Clorobiocin					
Novobiocin		<i>S. aureus</i> and <i>S. gallinarum</i> (MIC = 2 and 0.25 mg/L)		Inhibiting of DNA topoisomerase type II (DNA gyrase)	[135–137]
Coumermycin A1					
Bergamottin					
6-Geranyl coumarin				Inhibition of efflux pump	[138,139]
Gallbanic acid					
Daphnetin		<i>P. fluorescens</i> and <i>Shewanella putrefaciens</i> (MIC values were 0.16 and 0.08 mg/mL, respectively)		Cell membrane Disruption, Type III secretion inactivation	[140–142]
Esculetin		<i>Ralstonia pseudosolanacearum</i> (MIC = 125 mg/mL)			

Table 1. Cont.

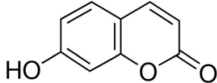
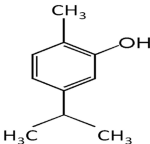
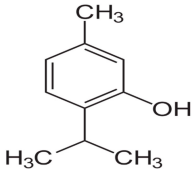
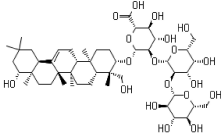
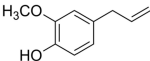
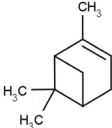
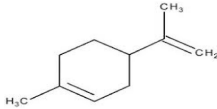
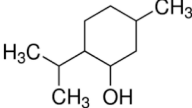
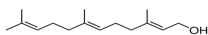
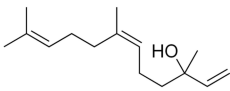
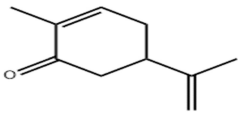
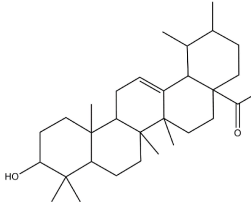
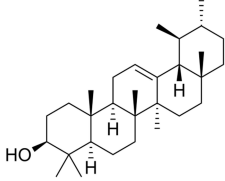
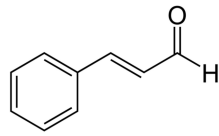
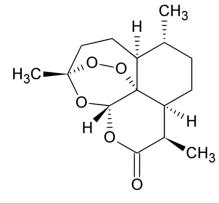
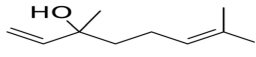
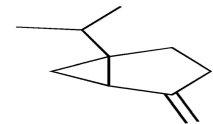
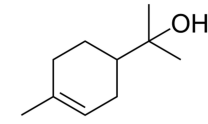
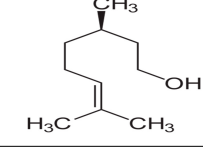
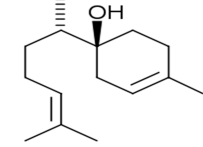
Compound	Chemical Structure	Active against (MIC/MBC Values)	Class of Phytochemicals	Mechanism of Action	Ref.
Umbelliferone		<i>R. pseudosolanacearum</i> (MIC = 325 mg/mL)			
Carvacrol		<i>Streptococcus pyogenes</i> (MIC = 125 µg/mL)		Disrupting cell membrane integrity, Inhibition of efflux pump	
Thymol		<i>B. cereus</i> (MIC = 0.625 mg/mL)			
Soyasaponin V					Inhibition of the New Dehli Metallo-β-lactamase 1
Eugenol		<i>E. coli</i> (MIC ranging from 0.0312 to 8 µg/mL)			
α-Pinene		<i>H. pylori</i> (MIC ranged from 275 to 1100 µg/mL)	Terpenes	Disrupting cell membrane integrity	
Limonene		Standard <i>S. aureus</i> (MIC = 256 µg/mL) and resistant <i>P. aeruginosa</i> (MIC = 512 µg/mL)			
Menthol		<i>C. albicans</i> (MIC 90 were 1.6 to 25 µg/mL)			
Farnesol		<i>Lactobacillus</i> spp. (MIC = 1500 µM)			
Nerolidol		<i>S. aureus</i> (MIC = 1 mg/mL), <i>S. mutans</i> (MIC = 4 mg/mL), <i>P. aeruginosa</i> (MIC = 0.5 mg/mL), and <i>K. pneumoniae</i> (MIC = 0.5 mg/mL).		Disrupting cell membrane integrity	[148–153]
Carvone				Inhibiting the transformation of cellular yeast to the filamentous	[154]

Table 1. Cont.

Compound	Chemical Structure	Active against (MIC/MBC Values)	Class of Phytochemicals	Mechanism of Action	Ref.
Ursolic acid		Carbapenem-resistant <i>E. cloacae</i> (MIC = 0.1 mg/mL)		Disrupting cell membrane integrity and inhibition of β -lactamase	[155,156]
α -Amyrin					[157]
Cinnamaldehyde		<i>E. coli</i> (MIC = 780 μ g/mL)		Disrupting cell membrane integrity, Decreasing membrane potential, and metabolic activity	[158,159]
Artemisinin				Free radicals formation	[160]
Linalool		<i>P. aeruginosa</i> (MIC = 431 μ g/mL)		Disrupting cell membrane integrity, changing in the nucleoid morphology, and interfering with cellular respiration	[161–163]
Sabinene		Multi drug-resistant strains (MIC \geq 1024 μ g/mL)		Disrupting cell membrane integrity and inhibiting DNA synthesis	[164,165]
α -Terpineol		<i>E. coli</i> (MIC \geq 0.78 μ g/mL)		Lossing membrane-bound autolytic enzymes, the cytoplasm leakage and inability to osmoregulate	[166,167]
Citronellol		<i>Trichophyton rubrum</i> (MIC values from 8 to 1024 μ g/mL)		Deteriorating membrane integrity	[168,169]
α -Bisabolol		<i>Propionibacterium acnes</i> and <i>S. epidermidis</i> (MIC = 75 and 37.5 μ g/mL)		Disrupting cell membrane integrity	[170,171]

Gram-positive bacteria are commonly more susceptible to terpenes than Gram-negative ones [172].

Catteau et al. [157] obtained a dichloromethane extract from the leaf of the shea butter tree (*Vitellaria paradoxa*) in which the triterpenic acids, ursolic acid (UA), and oleanolic acids (OA) were identified as major constituents. Both of these compounds, in the presence of β -lactams, restored the efficacy of the antibiotics against MRSA. UA proved more effective than OA with MIC values of 8–16 mg/L and 32–128 mg/L for UA and OA, respectively. Their ability to inhibit β -lactamase of living bacteria was observed among the different mechanisms, but this was not evident in bacteria lysates, suggesting an indirect mechanism was involved in the inhibition.

Horie et al. [144] reported the synergistic effects of soybean saponins on the antimicrobial activity of β -lactam antibiotics against *S. aureus* strains producing β -lactamases. In the presence of crude saponins, there was a significant decrease in the activities of β -lactamases, including the New Delhi Metallo- β -lactamase 1 (NDM-1). The latter had not been reported to be inhibited by any of the current β -lactamase inhibitors. The individual saponin components examined showed that the presence of 200 μ g/mL soysaponin V significantly ($p < 0.001$) inhibited NDM-1 compared to equivalent levels of either soysaponin I or soysaponin B. The combination of soy saponins and β -lactam antibiotics was proposed as a new therapeutic modality, particularly against bacteria encoding NDM-1. Table 1 shows the most prevalent natural antibacterial compounds with the related mechanism of action.

4. Preclinical and Clinical Studies on Antibacterial Effects of Phytochemicals

Many antimicrobial herbal medicines show antimicrobial activities that may serve as possible treatment alternatives to conventional antimicrobial regimens for infections sensitive to conventional antibacterial agents and resistant strains of microorganisms. As part of the efforts to broaden the employment of herbal medicines to treat infectious diseases, preclinical and clinical testing guidelines for phytochemicals should ensure consistency in formulation, efficacy, and safety. Finally, phytodrugs, original medications obtained from medicinal plants, have been preclinically tested and then licensed in a particular country through clinical trials. They are usually a complex of two or more biologically active constituents.

Considering the vast number of natural compounds that have been identified in the last two centuries, only a very small number of them have already been examined under clinical trials. Also, at the same time, hundreds of similar projects are being performed in preclinical evaluations in the clinical laboratory. Table 2 summarizes information about some of the important herbal-derived products as antibacterial agents in human health care.

4.1. Concentrated Herbal Extract Granules TRA

Urinary tract infections (UTIs) are among the most common infections and are a frequent reason for hospitalization and antimicrobial therapy. Increasing antimicrobial resistance has stimulated interest in the non-antibiotic prevention of UTIs [173]. The standardized concentrated herbal extract granules TRA were used in the “Tokoro Combination” and “Rehmannia and Akebia Formula” The product was prepared in small granules, including concentrated herbal extract granules of “Tokoro Combination”(50%) and “Rehmannia and Akebia Formula” (50%). The Ministry of Health and Welfare in Taiwan has already approved both medicines as ethical drugs. The major components in this product were diosgenin, yamogenin, betulin, oleanolic acid, hederagenin, akeboside, β -sitosterol, stigmasterol, inositol, catalpol, glycyrrhizin, etc. Clinical trials.gov identifier (NCT number) of this study is “NCT04272437”.

4.2. *Uva Ursi* Extract

Arctostaphylos uva-ursi (bearberry extract arbutin) has been traditionally used to treat UTI symptoms. Antiseptic and antimicrobial properties of uva-ursi have been proved, attributed to hydroquinones and tannins. *Uva-ursi* is concentrated in the urine and has shown to be effective against bacteria causing UTIs [173]. It is safe, and only mild adverse

events such as gastrointestinal complaints have been described previously. The detailed investigation did not reflect any toxicity related to the ingestion of *uva-ursi*. Limited clinical data from small studies suggest that *uva-ursi* effectively prevents UTIs in high-risk patients [174,175]. Using *uva-ursi* as a first-line treatment option is effective in resolving UTI symptoms and reducing antibiotic use. It also leads to favorable effects on resistance rates. Clinical trials.gov identifier (NCT number) of this study is “NCT03151603”.

Table 2. Examples of t herbal-derived products as antibacterial agents in clinical trials or markets.

Compound or Product	Sources or Ingredient	Indications
Concentrated herbal extract granules TRA	Traditional Chinese Medicine	Urinary tract infections
<i>Uva ursi</i> extract	<i>Uva ursi</i>	Urinary tract infections
Monoselect Macrocarpon	<i>Vaccinium</i> spp.	Urinary tract infections
Anthocran	<i>Vaccinium</i> spp.	Urinary tract infections
Cysticlean	<i>Vaccinium</i> spp.	Urinary tract infections
UVA-E	<i>Arctostaphylos uva-ursi</i> , <i>Taraxacum officinale</i>	Urinary tract infections
Pylorin	polyherbal formulation	<i>Helicobacter pylori</i> Infection
Sanguiritrin	<i>Macleaya cordata</i> and <i>Macleaya microcarpa</i>	Acute intestinal infections and wound infections
Eucalimin	Consisted of triterpene phenol aldehyde and triterpenoid that isolated from foliage and shoots of <i>Eucalyptus Viminalis</i> Labill	Pharyngitis, laryngitis, and sinusitis
<i>Scutellaria baicalensis</i> Georgi	<i>Scutellaria baicalensis</i> Georgi	Pathopyretic sores, ulcers or pustules
<i>Houttuynia cordata</i> Thunb		Pseudorabies herpesvirus
Berberine	<i>Berberis vulgaris</i>	Gastrointestinal infections
Mastic	<i>Pistacia lentiscus</i> resin	<i>H. pylori</i> Infection
GutGard	<i>Glycyrrhiza glabra</i> extract	<i>H. pylori</i> Infection
Listerine	eucalyptol, menthol, methyl salicylate, and thymol	Oral infections
Parodontax	<i>Commiphora myrrha</i> , <i>Echinacea purpurea</i> , <i>Krameria triandra</i> , and <i>Matricaria recutita</i> extracts; <i>Mentha arvensis</i> , <i>M. x Piperita</i> and <i>Salvia officinalis</i> essential oils	Oral infections
Myrtol	<i>Citrus limon</i> , <i>Citrus sinensis</i> , <i>Eucalyptus globulus</i> , and <i>Myrtus communis</i> essential oils	Chronic and acute bronchitis
Tea tree oil	TTO, <i>Melaleuca alternifolia</i> essential oil	Mild to moderate acne

4.3. *Vaccinium* spp.

Many researchers have suggested that cranberry, *Vaccinium macrocarpon*, is active against UTIs. The plant belongs to the *Ericaceae* family and can be potentially active against *E. coli*, the leading cause of bacteria-mediated UTIs, by reducing bacterial attaching to the bladder’s walls. The bacteria are then more likely to be washed out during urination [176]. It could also inhibit the binding of bacteria to gastrointestinal mucosa [177]. Cranberry contains proanthocyanidins that are stable phenolic compounds and contribute to the anti-adhesion activity against *E. coli*. Therefore, by its consumption, the biofilm formation of Gram-negative and Gram-positive uropathogens such as *S. aureus*, *P. aeruginosa*, *K. pneumoniae*, and *Proteus mirabilis* was reduced [178,179].

Cranberry also contains other biologically active constituents like anthocyanidin, catechin, flavanols, myricetin, quercetin, and phenolics, responsible for its activities [180].

Due to the health benefits of cranberry extract, different commercial formulations exist in the market, such as Monoselect Macrocarpon, Anthocran, and Cysticlean. In acute situations, 2–3 capsules/tablets should be taken two to four times per day, and for prevention, one capsule/tablet 2–3 times daily are recommended [181].

Blueberry, *Vaccinium myrtillus*, has also extensively been used to treat and prevent UTI. Blueberry extracts contain similar constituents as cranberry extracts, with the extracts possessing similar anti-adhesive activities against uropathogenic bacteria. The bacteria

are significantly less able to adhere to the bladder walls. Tannins are the most active constituents of blueberry extracts against UTI [182,183].

4.4. Sanguiritrin

Sanguiritrin is an original phytomedicine initially developed by scientists at the Institute of Medicinal and Aromatic Plants (VILAR, Russia). It has been made from the upper part of the plants *Macleaya cordata* and *Macleaya microcarpa* and has a different alkaloid composition. It mainly comprises the bisulfates of two benzophenanthridine alkaloids (sanguinarine and chelerythrine), isolated from the stems and leaves of these plants [184,185]. In vitro studies showed that sanguiritrin in concentrations 1–100 µg/mL could effectively suppress the growth of 130 laboratory strains of both Gram-positive and Gram-negative bacteria [40].

Additionally, sanguiritrin was effective against isolated strains resistant to one or more conventional antibiotics. Long-term exposure to this product and multiple passages of the bacterium in its presence did not lead to the development of phytodrug resistance [40]. The primary mechanism of antibacterial action of sanguiritrin is disruption of bacterial cell wall integrity and nucleotide structures and suppression of bacterial nuclease [186]. Treatment with sanguiritrin of *S. aureus* led to single or multiple perforations in the bacterial cell wall and fragmentation [184].

In conclusion, sanguiritrin and other phytodrugs containing benzophenanthridine alkaloids should be considered to treat infections caused by MDR bacteria.

4.5. Eucalimin

Eucalimin is a phytodrug constituent of triterpene phenol aldehyde and triterpenoid isolated from foliage and shoots of *Eucalyptus viminalis* Labill [187]. The coupling of phloroglucinol and sesquiterpene constituents is believed to be responsible for this and similar products [188,189]. This product is effective against the growth of Gram-positive bacteria, including clinical isolates of resistant bacteria. However, it was less effective against Gram-negative bacteria and fungi [40]. The antibacterial activities of this product were tested against both Gram-positive and Gram-negative bacteria, with the results showing higher antibacterial activities against Gram-positive bacteria. Gram-positive clinically isolates *Staphylococcus* (MIC 1.9–31.2 µg/mL), *Streptococcus* (*Streptococcus pneumoniae* and *Streptococcus viridans*, MIC 1.9–31.2 µg/mL, *Streptococcus faecalis*, MIC 0.5–1.9 µg/mL), and *Corynebacterium diphtheriae* (MIC 3.9–62.5 µg/mL). Gram-positive clinically isolates of *Staphylococcus* (MIC 1.9–31.2 µg/mL), *Streptococcus* (*Streptococcus pneumoniae* and *Streptococcus viridans*, MIC 1.9–31.2 µg/mL, *Streptococcus faecalis*, MIC 0.5–1.9 µg/mL), *Corynebacterium diphtheriae* (MIC 3.9–62.5 µg/mL). These results demonstrated the high sensitivity of Gram-positive bacteria to eucalimin. Only Gram-negative bacteria from families of *Acinetobacter* and *Enterobacteriaceae*, *Serratia* genus, were relatively sensitive to this product (MIC < 125 µg/mL) [40]. Clinical trials suggest that eucalimin is highly efficacious in treating various conditions, including pharyngitis, laryngitis, sinusitis, otitis, colpitis, and cervical erosion.

4.6. *Scutellaria baicalensis* Georgi

The radix of *Scutellaria baicalensis* Georgi (SB), is an important medicinal herb in Japanese and Chinese pharmacopeia. It is traditionally used for inflammatory and infectious diseases, including pathopyretic sores, ulcers, or pustules [190]. The antibacterial functions of SB are due to the active compound baicalein [191]. The mechanism could affect bacterial membrane penetrability, inhibit protein synthesis, and influence SDH, MDH, and DNA topoisomerase I and II to exert antibacterial activities [54,192]. This compound is effective against a wide range of pathogenic bacteria such as *S. aureus*, *Streptococcus mutans*, *S. pneumoniae*, *E. coli*, *P. aeruginosa*, *Salmonella enterica*, *S. epidermidis*, and *Propionibacterium acnes* [193,194]. A study demonstrated that baicalein exhibited synergistic activities against

some extended-spectrum β -lactamases positive *K. pneumoniae* strains, especially when combined with cefotaxime, inhibiting CTX-M-1 mRNA expression [195].

The mode of action in combination therapy showed that baicalein with antibiotics caused peptidoglycan and morphological damage, increasing cytoplasmic membrane permeability and protein concentrations and decreased cellular fatty acid and nucleic acid concentrations [196].

The results of another study demonstrated that baicalein could remarkably reverse the ciprofloxacin resistance of MRSA, possibly by inhibiting the NorA efflux pump activity. The inhibition of MRSA pyruvate kinase via baicalein could also lead to a deficiency of ATP, which might further contribute to the antibacterial properties of baicalein against MRSA [197].

Arweiler et al. [198] compared the effects of toothpaste with SB extract (0.5%) with placebo for treatment of gingivitis in 40 participants. The results showed that gingivitis symptoms in the treated group significantly improved compared to the control group.

A study showed that baicalein combined with antibiotics resulted in a higher survival rate in mice severely infected with *S. suis*. At the same time, baicalein can be combined with meropenem against MRSA [199].

Another study showed that baicalein has synergistic antibacterial effects with linezolid in the in vivo model against MRSA biofilms. Furthermore, the inhibitory effects were more pronounced when baicalein was combined with linezolid [200].

4.7. *Houttuynia Cordata* Thunb.

Houttuynia cordata Thunb. (HC) is used to treat various diseases such as purulent, supuration, sores, pustules, and respiratory infections in the Chinese pharmacopeia [40,201]. Houttuynin is the main antibacterial ingredient of HC. This compound and its derivatives are used alone or combined with conventional antibiotics to combat infectious diseases [202–204]. HC was found to exhibit anti-biofilm activities against MRSA by inhibiting interleukin-8 (IL-8) and C-C motif chemokine ligand 20 production in human keratinocytes [205]. Kim et al. [206] suggested the HC extract could effectively treat intracellular bacterial infections caused by *Salmonella*, *Brucella*, *Listeria*, *Bordetella*, and *Helicobacter*. The essential oils of this plant, such as methyl nonyl ketone, bornyl acetate, and β -myrcene, showed antibacterial properties [207]. Another study indicated that the flavonoids of HC had suitable antibacterial activities on *Bacillus subtilis*. The possible antibacterial mechanism is to disintegrate the cell wall, make the cell collapse, and cause content leakage [208].

HC injections were used to treat upper respiratory tract infections and pneumonia, and the results demonstrated that HC injections showed better antipyretic effects than antibiotics in adults [209].

An aqueous extract of HC exhibited virulence reduction activities in *Salmonella typhimurium*-infected BALB/c mice. After a lethal dose of *S. typhimurium*, the mortality rate in the untreated extract group was 100% on the 7th day. Still, at the doses of 25, 50, and 100 $\mu\text{g}/\text{mL}$ of extract, groups survived until 11, 17, and 23 days. These data suggest that HC aqueous extract is stable and beneficial in treating bacterial infection, including intracellular replicating pathogens [206].

4.8. *Berberine*

The emergence of antibacterial resistance highlights the need for new therapeutic approaches to ensure the continued effectiveness of conventional antibiotic therapy regimens. Berberine is an alkaloid that has been widely used as an anti-infective agent in traditional medicine. It possesses antibacterial activities against a wide range of microorganisms alone or in combination with antibiotics routinely [210–212].

It was shown that the effective concentration of berberine is above 64 $\mu\text{g}/\text{mL}$ because of the poor absorption in oral consumption retained in the intestine, reaching a high concentration with distinct benefits for treating intestinal infectious diseases and diarrhea [213]. The encapsulated form of berberine in the yeast cell of *Saccharomyces cerevisiae* has also

been shown to have higher stability and bioavailability due to the wall material acting as a barrier, increasing solubility, and sustained release of active material. Berberine-loaded microcapsules had improved MIC against *E. coli* and *S. aureus* compared to berberine alone [214,215]. Berberine has different forms, but the most important ones with proper antibacterial activities are hydrochloride, sulphate, and tannate [216]. Clinical studies showed that a single administration of berberine tannate and its combination with sulfadimidine and neomycin effectively treated acute infective diarrhea in experiments conducted with 55 and 127 children, respectively [217,218]. Compared with standard antibiotic therapy regimens, the recovery of children with acute diarrhea was faster when administering berberine tannate [219].

The hydrochloride form of berberine was found to be more effective than chloramphenicol in 356 and 264 individual cases of patients infected by cholera [35], and the combination of berberine with chloramphenicol and streptomycin exhibited better curative actions on 129 cases of acute diarrheal disorders such as gastroenteritis and bacillary dysentery [220,221].

Apart from the application of berberine in treating gastrointestinal infections, this compound could combat other infections such as urinary tract infections. The *in vivo* tests were conducted to assess the antibacterial activities of berberine on uropathogenic *E. coli* strains. *Galleria mellonella* as an infection model was used to confirm berberine's ability to reduce bacterial adhesion and invasion properties of *E. coli* on human bladder cells. The results indicated that increasing the surviving larvae infected with pathogens reduced circulating uropathogenic *E. coli* strains in larvae hemolymph [210].

In another study, the efficacy and safety of berberine hydrochloride, amoxicillin, and rabeprazole triple therapy versus bismuth-containing quadruple therapy (amoxicillin, clarithromycin, rabeprazole, and bismuth) in the first eradication treatment of *Helicobacter pylori* were assessed. It is hypothesized that berberine hydrochloride, amoxicillin, and rabeprazole triple therapy are non-inferior to bismuth-containing quadruple therapy. Clinical trials.gov identifier (NCT number) of this study is "NCT04697186".

4.9. Mastic

Mastic is a semi-translucent pastel yellow-to-white resin obtained from *Pistacia lentiscus*. It comprises polymer *cis*-1,4-poly- β -myrcene, triterpenoids, sterols, and simple phenolics [216]. It also contains about 2% of an essential oil composed mainly of α -pinene, producing weak antibacterial activities against *H. pylori*. However, α -terpineol and (E)-methyl isoeugenol, minor constituents of mastic essential oil, showed significant inhibitory effects against *H. pylori* strains [222,223]. In addition, mastic extract containing arabino-galactan proteins inhibited neutrophil activation and growth of *H. pylori*, suggesting its role in eliminating helicobacter infections [224].

This compound has been used in various dietary supplements and traditional medicines in different dosage forms such as capsules, oil extracts, and tablets for the protection and treatment of gastrointestinal health, gastric ulcers, healing peptic, relief of gastric and intestinal inflammation and also used as a natural treatment for *H. pylori* infections. In recent decades, several clinical trials were performed to evaluate the effect of mastic in *H. pylori* eradication. A double-blind clinical trial was carried out with 38 patients, and mastic was given orally (1 g daily). After two weeks of consumption, the results showed that relieving symptoms and healing duodenal ulcers were significantly more effective than placebo [225]. Additionally, administering 350 mg of mastic three times a day for 14 days to 52 patients demonstrated an effect on eradicating *H. pylori* [226]. The other study was performed with five *H. pylori*-infected patients and three healthy controls who received 1 g of mastic daily for two months. The results showed the inhibitory effects on *H. pylori* neutrophil-activating protein involved in *H. pylori*-related gastric pathologies [227].

4.10. GutGard

GutGard encapsulated standardized root extract of *Glycyrrhiza glabra* contains flavonoids (more than 10% *w/w*), mainly glabridin and glabrol, along with saponins (glycyrrhizin), and phenylpropanoids (eicosanyl caffeate and docosyl caffeate). GutGard exhibited in vitro anti-*H. Pylori* activities with MIC values ranging from 32 to 100 µg/mL. In addition, glabridin has MIC values of 12.5 µg/mL against various strains, including clarithromycin and amoxicillin-resistant [228,229]. Moreover, an aqueous extract of *G. glabra* significantly inhibited the adhesion of *H. pylori* to human stomach tissue. Its anti-adhesive properties were related to the polysaccharides, which did not have direct toxic effects against *H. pylori* [230].

This product could be used as an herbal supplement to combat *H. pylori* infections and their symptoms. It is claimed that GutGard can reduce abdominal fullness and pain, belching, bloating, dyspepsia, nausea, and *H. pylori* loading. It should be noted that different regulatory agencies such as the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) approve *G. glabra* root for the relief of digestive symptoms, such as burning sensation and dyspepsia. A randomized, double-blind placebo-controlled study with 107 *H. pylori*-infected patients received orally 150 mg of GutGard once daily for 60 days. The results revealed a significant decrease in the *H. pylori* gastric load compared to a placebo group, with the product safe and well-tolerated [231]. Other clinical experiments carried out with deglycyrrhizinised *G. glabra* extract clearly showed the product's effectiveness in treating and preventing gastric ulcers [232,233].

4.11. Listerine

Listerine Antiseptic Mouthwash is one of the highest-selling products in the United States and other markets. This product comprises essential oils from *Eucalyptus* spp., *Gaultheria* spp., *Mentha × piperita*, and *Thymus vulgaris*. It contains a mixture of their main constituents, eucalyptol and thymol, responsible for the antimicrobial activities, menthol and methyl salicylate, local anesthetic, and cleaning agent, respectively [234]. The long-term plaque- and gingivitis-reducing properties of this product have been confirmed in several clinical trials. For example, in a study by Sharma et al. [235], Listerine was remarkably more effective in controlling gingivitis and plaque formation than the control group. In another study, both Listerine and chlorhexidine mouthwashes significantly reduced plaque formation and gingivitis compared to the control [236]. The superiority of rinsing with Listerine in reducing plaque and gingivitis was demonstrated compared to rinsing with cetylpyridinium chloride or hydroalcoholic (control) solutions [237]. The ability of this product to reduce gingivitis- and plaque-reducing was also found in other similar studies [238,239].

4.12. Parodontax

Parodontax (GlaxoSmithKline, Brentford, UK) is a toothpaste (also available as a mouthwash) composed of the extracts of *Commiphora myrrha*, *Echinacea purpurea*, *Krameria triandra*, and *Matricaria recutita* together with the essential oils from *Mentha arvensis*, *M. x piperita*, and *Salvia officinalis*. *M. recutita* and *S. officinalis* have been used traditionally to treat minor ulcers and inflammations of the mouth and throat [216]. The in vitro antimicrobial activities of Parodontax and its herbal components, *S. officinalis* essential oil, were tested. The results showed a significant effect against *C. albicans* with MIC values ranging from 16 to 2780 µg/mL. The essential oil of another herbal ingredient, *M. arvensis*, also inhibited the growth of *Prophyromonas gingivalis* in both planktonic and biofilm forms with relatively high MBC values ranging from 6 and 26 mg/mL, respectively [240,241].

In a clinical study conducted with eight adult volunteers, this product significantly reduced dental plaque regrowth after four days and plaque vitality over a period of 24 h compared to a control group [242]. The efficacy of Parodontax on the reduction of plaque and gingivitis was also demonstrated in a randomized, double-blind controlled study, a 28-day trial performed with 48 volunteers with established gingivitis [243]. In another

study, the product showed antimicrobial activities against oral biofilms of different compositions (for example, of *Actinomyces naeslundii* and *Streptococcus oralis*) and maturational status [244].

4.13. Myrtol

Myrtol, a herbal medical product, is sold in gelatin capsule form and is recommended for reducing the risk of acute exacerbations from chronic bronchitis. A distillation procedure obtains it from various essential oils such as *Citrus limon*, *Citrus sinensis*, *E. globulus*, and *M. communis*. The monoterpenes D-limonene, eucalyptol, and α -pinene are the major biological active substances in this product [216]. The product shows a wide range of biological properties such as antimicrobial, mucociliary clearance, anti-inflammatory, and antioxidant [245]. HMPC approves *E. globulus* leaves and essential oil as a traditional herbal medicinal product used to relieve cough associated with cold. The product has proven to effectively treat acute and chronic respiratory infections in both adults and children in several clinical trials [246–248]. Myrtol was compared to prescription drugs cefuroxime and ambroxol in the double-blind, placebo-controlled study with 681 patients suffering acute bronchitis. The results showed it was superior to the control group and comparable to the prescribed drugs for faster and more complete recovery [248].

4.14. Tea Tree Oil

One of the best-known examples of topical herbal antiseptics is tea tree oil (TTO). It is composed of essential oil from *M. alternifolia* leaves. It is commonly sold in a pure form and is part of cosmetic products, including antiseptic wipes, balms, body lotions, creams, deodorants, gels, shampoos, and ointments [216]. HMPC approved TTO to treat small boils (furuncles and mild acne), minor superficial wounds, and insect bites to relieve itching and irritation. Several clinical trials demonstrated the antimicrobial properties of TTO against various important bacterial skin infections, dermatophytes, and dandruff [249–251]. Two clinical trials confirmed TTO activity against acne. 124 patients were randomly divided into groups in the first trial and treated with 5% TTO and 5% benzoyl peroxide. Both treatments had significant effects on reducing the number of lesions [249]. In another clinical trial with 60 patients, the effect of 5% TTO gel was compared with the placebo group. The TTO group was significantly more effective in reducing lesion count after 45 days, whereas the adverse effects were tolerable and similar to those of the placebo [250]. TTO 10% cream, 5% body wash, chlorhexidine 4%, and silver sulfadiazine 1% were used for MRSA decolonization of superficial skin sites and skin lesions. This study indicated that the TTO formulations were more effective than the drug control groups [251]. In a randomized controlled trial with 391 patients, the 5% TTO body wash was able to prevent MRSA colonization with respect to the standard non-medicated body wash. However, there were no significant differences between the two groups; TTO was evaluated as safe and well-tolerated [252]. In a randomized, double-blind clinical trial with 104 patients, the efficacy of 10% w/w TTO cream in the treatment of athlete's foot was compared with 1% tolnaftate and placebo creams. TTO cream reduced the symptomatology of the athlete's foot as effectively as tolnaftate [253].

5. Conclusions

New resistant bacterial strains have led to a paradigm shift from conventional antibiotic therapy to alternative approaches. Plants represent an attractive source of antimicrobial agents with therapeutic potential as alternatives or potentiators of antibiotics. The high chemical diversity of active constituents found in plants makes them a potential source of antibacterial agents. To this end, identifying new and valuable antibacterials from plants and testing their antibacterial properties are crucial and need to be carefully studied. Two reasons may play pivotal roles among several reasons to employ herbal-derived compounds for combating bacterial infections. First, these compounds could provide other mechanisms of antibacterial action with respect to conventional antibiotics. Second, the

use of unique traditional knowledge of herbal medicine provides the excellent potential to generate biocompatible, cost-effective, and promising solutions and will hasten the discovery of new antibacterial agents. Therefore, *in silico*, *in vitro*, and *in vivo* tests and models have been developed to evaluate phytomedicines' antibacterial activities, mechanism of action, and biological fate. Understanding their mechanisms of action helps us choose the appropriate phytomedicine for a specific situation and particular microorganism.

Despite the rapid increase in publications on antibacterial plant compounds, few plant-derived drugs are still in clinical use. This might be because phytomedicines often require complex combinational effects between their bioactive compound to synergize the activities of their components. Therefore, examining combinations of plant compounds with conventional antibiotics may be a more fruitful line of research.

Author Contributions: B.S.F.B. and M.I., contributed equally to this work. B.S.F.B. and B.K. were responsible for the article's design and content. B.K., M.I. and N.A.M.E. researched and wrote the body of the text. B.K. designed and prepared the graphical abstract. N.A.M.E. suggested the subject, and contributed to drafting and editing the paper for publication. All authors have read and agreed to the published version of the manuscript.

Funding: This research didn't receive any external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Date Availability Statement: Not applicable.

Conflicts of Interest: The authors declare that they have no competing interests.

References

1. Sarwar, A.; Butt, M.A.; Hafeez, S.; Danish, M.Z. Rapid emergence of antibacterial resistance by bacterial isolates from patients of gynecological infections in Punjab, Pakistan. *J. Infect. Public Health* **2020**, *13*, 1972–1980. [[CrossRef](#)]
2. Wang, Y.; Zhong, H.; Han, X.; Wang, N.; Cai, Y.; Wang, H.; Yu, J.; Zhang, X.; Zhang, K. Impact of antibiotic prescription on the resistance of *Klebsiella pneumoniae* at a tertiary hospital in China, 2012–2019. *Am. J. Infect. Control* **2020**, *49*, 65–69. [[CrossRef](#)]
3. Khameneh, B.; Iranshahy, M.; Soheili, V.; Bazzaz, B.S.F. Review on plant antimicrobials: A mechanistic viewpoint. *Antimicrob. Resist. Infect. Control* **2019**, *8*, 1–28. [[CrossRef](#)]
4. Khameneh, B.; Diab, R.; Ghazvini, K.; Bazzaz, B.S.F. Breakthroughs in bacterial resistance mechanisms and the potential ways to combat them. *Microb. Pathog.* **2016**, *95*, 32–42. [[CrossRef](#)]
5. World Health Organization. *World Health Organization Model List of Essential Medicines: 21st List 2019*; World Health Organization: Geneva, Switzerland, 2019.
6. Control CFD and Prevention. *Antibiotic Resistance Threats in the United States*; US Department of Health and Human Services: Atlanta, GA, USA, 2019.
7. Fleming, A. On the Antibacterial Action of Cultures of a Penicillium, with Special Reference to their Use in the Isolation of *B. influenzae*. *Br. J. Exp. Pathol.* **1929**, *10*, 226–236. [[CrossRef](#)]
8. Abraham, E.P.; Chain, E. An Enzyme from Bacteria able to Destroy Penicillin. *Nature* **1940**, *146*, 837. [[CrossRef](#)]
9. Farhadi, F.; Khameneh, B.; Iranshahi, M.; Iranshahy, M. Antibacterial activity of flavonoids and their structure–activity relationship: An update review. *Phytother Res.* **2019**, *33*, 13–40. [[CrossRef](#)]
10. Fatemi, N.; Sharifmoghadam, M.R.; Bahreini, M.; Khameneh, B.; Shadifar, H. Antibacterial and Synergistic Effects of Herbal Extracts in Combination with Amikacin and Imipenem Against Multidrug-Resistant Isolates of *Acinetobacter*. *Curr. Microbiol.* **2020**, *77*, 1959–1967. [[CrossRef](#)] [[PubMed](#)]
11. Shadifar, H.; Bahreini, M.; Khameneh, B.; Emami, S.A.; Fatemi, N.; Sharifmoghadam, M.R. Antibacterial and synergistic effects of aqueous and methanol extracts of *artemisia annua* against multidrug-resistant isolates of *acinetobacter*. *Anti-Infect. Agents* **2021**, *19*, 28–35. [[CrossRef](#)]
12. Jaktaji, R.P.; Ghalamfarsa, F. Antibacterial activity of honeys and potential synergism of honeys with antibiotics and alkaloid extract of *Sophora alopecuroides* plant against antibiotic-resistant *Escherichia coli* mutant. *Iran. J. Basic Med. Sci.* **2021**, *24*, 623–628. [[CrossRef](#)]
13. Saleem, S.; Muhammad, G.; Hussain, M.A.; Altaf, M.; Abbas Bukhari, S.N. *Withania somnifera* L.: Insights into the phytochemical profile, therapeutic potential, clinical trials, and future prospective. *Iran. J. Basic Med. Sci.* **2020**, *23*, 1501–1526. [[CrossRef](#)] [[PubMed](#)]
14. AlSheikh, H.M.A.; Sultan, I.; Kumar, V.; Rather, I.A.; Al-Sheikh, H.; Tasleem Jan, A.; Haq, Q.M.R. Plant-based phytochemicals as possible alternative to antibiotics in combating bacterial drug resistance. *Antibiotics* **2020**, *9*, 480. [[CrossRef](#)] [[PubMed](#)]

15. Bazzaz, B.S.F.; Haririzadeh, G.; Imami, S.A.; Rashed, M.H. Survey of Iranian Plants for Alkaloids, Flavonoids, Saponins, and Tannins [Khorasan Province]. *Int. J. Pharmacogn.* **1997**, *35*, 17–30. [[CrossRef](#)]
16. El Kolli, M.; Laouer, H.; El Kolli, H.; Akkal, S.; Sahli, F. Chemical analysis, antimicrobial and anti-oxidative properties of *Daucus gracilis* essential oil and its mechanism of action. *Asian Pac. J. Trop. Biomed.* **2016**, *6*, 8–15. [[CrossRef](#)]
17. Salarbashi, D.; Fazly Bazzaz, B.S.; Karimkhani, M.M.; Sabeti Noghabi, Z.; Khanzadeh, F.; Sahebkar, A. Oil stability index and biological activities of *Achillea biebersteinii* and *Achillea wilhelmsii* extracts as influenced by various ultrasound intensities. *Ind. Crops. Prod.* **2014**, *55*, 163–172. [[CrossRef](#)]
18. Fazly Bazzaz, B.S.; Seyedi, S.; Goki, N.H.; Khameneh, B. Human Antimicrobial Peptides: Spectrum, Mode of Action and Resistance Mechanisms. *Int. J. Pept. Res. Ther.* **2021**, *27*, 801–816. [[CrossRef](#)]
19. Bazzaz, B.S.F.; Khameneh, B.; Namazi, N.; Iranshahi, M.; Davoodi, D.; Golmohammadzadeh, S. Solid lipid nanoparticles carrying *Eugenia caryophyllata* essential oil: The novel nanoparticulate systems with broad-spectrum antimicrobial activity. *Let. Appl. Microbiol.* **2018**, *66*, 506–513. [[CrossRef](#)] [[PubMed](#)]
20. Gameda, N.; Tadele, A.; Lemma, H.; Girma, B.; Addis, G.; Tesfaye, B.; Abebe, A.; Gemechu, W.; Yirsaw, K.; Teka, F.; et al. Development, Characterization, and Evaluation of Novel Broad-Spectrum Antimicrobial Topical Formulations from *Cymbopogon martini* (Roxb.) W. Watson Essential Oil. *Evid-Based Complement. Altern. Med.* **2018**, *2018*, 9812093. [[CrossRef](#)]
21. Cheesman, M.J.; Ilanko, A.; Blonk, B.; Cock, I.E. Developing New Antimicrobial Therapies: Are Synergistic Combinations of Plant Extracts/Compounds with Conventional Antibiotics the Solution? *Pharm. Rev.* **2017**, *11*, 57–72.
22. Chitsazian-Yazdi, M.; Agnolet, S.; Lorenz, S.; Schneider, B.; Es'haghi, Z.; Kasaian, J.; Khameneh, B.; Iranshahi, M. Foetithiophenes C-F, thiophene derivatives from the roots of *Ferula foetida*. *Pharm. Biol.* **2015**, *53*, 710–714. [[CrossRef](#)]
23. Altemimi, A.; Lakhssassi, N.; Baharlouei, A.; Watson, D.G.; Lightfoot, D.A. Phytochemicals: Extraction, Isolation, and Identification of Bioactive Compounds from Plant Extracts. *Plants* **2017**, *6*, 42. [[CrossRef](#)] [[PubMed](#)]
24. Dittrich, P.S.; Manz, A. Lab-on-a-chip: Microfluidics in drug discovery. *Nat. Rev. Drug Discov.* **2006**, *5*, 210–218. [[CrossRef](#)] [[PubMed](#)]
25. Dhayakaran, R.; Neethirajan, S.; Weng, X. Investigation of the antimicrobial activity of soy peptides by developing a high throughput drug screening assay. *Biochem. Biophys. Rep.* **2016**, *6*, 149–157. [[CrossRef](#)] [[PubMed](#)]
26. Eduati, F.; Utharala, R.; Madhavan, D.; Neumann, U.P.; Longerich, T.; Cramer, T.; Saez-Rodriguez, J.; Merten, C.A. A microfluidics platform for combinatorial drug screening on cancer biopsies. *Nat. Commun.* **2018**, *9*, 1–13. [[CrossRef](#)]
27. Kleymann, G.; Werling, H.O. A generally applicable, high-throughput screening-compatible assay to identify, evaluate, and optimize antimicrobial agents for drug therapy. *J. Biomol. Screen.* **2004**, *9*, 578–587. [[CrossRef](#)] [[PubMed](#)]
28. Haque, S.; Nawrot, D.A.; Alakurtti, S.; Ghemtio, L.; Yli-Kauhaluoma, J.; Tammela, P. Screening and Characterisation of Antimicrobial Properties of Semisynthetic Betulin Derivatives. *PLoS ONE* **2014**, *9*, e102696. [[CrossRef](#)] [[PubMed](#)]
29. Ymele-Leki, P.; Cao, S.; Sharp, J.; Lambert, K.G.; McAdam, A.J.; Husson, R.N.; Tamayo, G.; Clardy, J.; Watnick, P.I. A high-throughput screen identifies a new natural product with broad-spectrum antibacterial activity. *PLoS ONE* **2012**, *7*, e31307. [[CrossRef](#)]
30. Sorokina, M.; Steinbeck, C. Review on natural products databases: Where to find data in 2020. *J. Chemin.* **2020**, *12*, 1–51. [[CrossRef](#)] [[PubMed](#)]
31. Phatak, S.S.; Stephan, C.C.; Cavasotto, C.N. High-throughput and in silico screenings in drug discovery. *Expert Opin. Drug Discov.* **2009**, *4*, 947–959. [[CrossRef](#)]
32. Skariyachan, S.; Muddebihalkar, A.G.; Badrinath, V.; Umashankar, B.; Eram, D.; Uttarkar, A.; Niranjana, V. Natural epiestriol-16 act as potential lead molecule against prospective molecular targets of multidrug resistant *Acinetobacter baumannii*-Insight from in silico modelling and in vitro investigations. *Infect. Genet. Evol.* **2020**, *82*, 104314. [[CrossRef](#)]
33. Álvarez-Martínez, F.; Barrajón-Catalán, E.; Herranz-López, M.; Micol, V. Antibacterial plant compounds, extracts and essential oils: An updated review on their effects and putative mechanisms of action. *Phytomedicine* **2021**, *90*, 153626. [[CrossRef](#)]
34. Gorlenko, C.L.; Kiselev, H.Y.; Budanova, E.V.; Zamyatnin, A.A., Jr.; Ikryannikova, L.N. Plant Secondary Metabolites in the Battle of Drugs and Drug-Resistant Bacteria: New Heroes or Worse Clones of Antibiotics? *Antibiotics* **2020**, *9*, 170. [[CrossRef](#)] [[PubMed](#)]
35. Porras, G.; Chassagne, F.; Lyles, J.T.; Marquez, L.; Dettweiler, M.; Salam, A.M.; Samarakoon, T.; Shabih, S.; Farrokhi, D.R.; Quave, C.L. Ethnobotany and the Role of Plant Natural Products in Antibiotic Drug Discovery. *Chem. Rev.* **2020**, *121*, 3495–3560. [[CrossRef](#)] [[PubMed](#)]
36. Othman, L.; Sleiman, A.; Abdel-Massih, R.M. Antimicrobial Activity of Polyphenols and Alkaloids in Middle Eastern Plants. *Front. Microbiol.* **2019**, *10*, 911. [[CrossRef](#)] [[PubMed](#)]
37. Mikłasińska-Majdanik, M.; Kepa, M.; Wojtyczka, R.D.; Idzik, D.; Waśik, T.J. Phenolic Compounds Diminish Antibiotic Resistance of *Staphylococcus aureus* Clinical Strains. *Int. J. Environ. Res. Public Health* **2018**, *15*, 2321. [[CrossRef](#)]
38. Bazzaz, B.S.F.; Khameneh, B.; Ostad, M.R.Z.; Hosseinzadeh, H. In vitro evaluation of antibacterial activity of verbascoside, lemon verbena extract and caffeine in combination with gentamicin against drug-resistant *Staphylococcus aureus* and *Escherichia coli* clinical isolates. *Avicenna J. Phytomedicine* **2018**, *8*, 246–253.
39. Ohene-Agyei, T.; Mowla, R.; Rahman, T.; Venter, H. Phytochemicals increase the antibacterial activity of antibiotics by acting on a drug efflux pump. *Microbiologyopen* **2014**, *3*, 885–896. [[CrossRef](#)]

40. Enioutina, E.Y.; Teng, L.; Fateeva, T.V.; Brown, J.C.; Job, K.M.; Bortnikova, V.V.; Krepkova, L.; Gubarev, M.I.; Sherwin, C. Phytotherapy as an alternative to conventional antimicrobials: Combating microbial resistance. *Expert Rev. Clin. Pharmacol.* **2017**, *10*, 1203–1214. [[CrossRef](#)]
41. Zhao, W.-H.; Hu, Z.-Q.; Hara, Y.; Shimamura, T. Inhibition of Penicillinase by Epigallocatechin Gallate Resulting in Restoration of Antibacterial Activity of Penicillin against Penicillinase-Producing *Staphylococcus aureus*. *Antimicrob. Agents Chemother.* **2002**, *46*, 2266–2268. [[CrossRef](#)]
42. Zhao, W.H.; Asano, N.; Hu, Z.Q.; Shimamura, T. Restoration of antibacterial activity of beta-lactams by epigallocatechin gallate against beta-lactamase-producing species depending on location of beta-lactamase. *J. Pharm. Pharmacol.* **2003**, *55*, 735–740. [[CrossRef](#)]
43. Nikaido, H.; Vaara, M. Molecular basis of bacterial outer membrane permeability. *Microbiol. Rev.* **1985**, *49*, 1–32. [[CrossRef](#)]
44. Eumkeb, G.; Sakdarat, S.; Siritwong, S. Reversing β -lactam antibiotic resistance of *Staphylococcus aureus* with galangin from *Alpinia officinarum* Hance and synergism with ceftazidime. *Phytomedicine* **2010**, *18*, 40–45. [[CrossRef](#)]
45. Siritwong, S.; Teethaisong, Y.; Thumanu, K.; Dunkhunthod, B.; Eumkeb, G. The synergy and mode of action of quercetin plus amoxicillin against amoxicillin-resistant *Staphylococcus epidermidis*. *BMC Pharmacol. Toxicol.* **2016**, *17*, 1–14. [[CrossRef](#)] [[PubMed](#)]
46. De Vliegher, S.; Fox, L.; Piepers, S.; McDougall, S.; Barkema, H. Invited review: Mastitis in dairy heifers: Nature of the disease, potential impact, prevention, and control. *J. Dairy Sci.* **2012**, *95*, 1025–1040. [[CrossRef](#)] [[PubMed](#)]
47. Maia, N.L.; De Barros, M.; De Oliveira, L.L.; Cardoso, S.; Dos Santos, M.; Pieri, F.; Ramalho, T.C.; Da Cunha, E.F.F.; Moreira, M.A.S. Synergism of Plant Compound With Traditional Antimicrobials Against *Streptococcus* spp. Isolated From Bovine Mastitis. *Front. Microbiol.* **2018**, *9*, 1203. [[CrossRef](#)]
48. Dias, K.S.; Januário, J.P.; Dego, J.L.D.; Dias, A.L.T.; dos Santos, M.H.; Camps, I.; Coelho, L.F.; Viegas, C., Jr. Semisynthesis and antimicrobial activity of novel guttiferone-A derivatives. *Bioorganic Med. Chem.* **2012**, *20*, 2713–2720. [[CrossRef](#)] [[PubMed](#)]
49. Ramkumar, S.R.S.; Sivakumar, N.; Vijayaraghavan, P. Enzymatic Inhibition of Phytochemical from *Garcinia imberti* on Homology Modelled Beta-lactamase Protein in *Staphylococcus sciuri*. *J. Young Pharm.* **2020**, *12*, 37–41. [[CrossRef](#)]
50. Klančnik, A.; Sikic Pogacar, M.; Trost, K.; Tusek Znidaric, M.; Mozetic Vodopivec, B.; Smole Mozina, S. Anti-Campylobacter activity of resveratrol and an extract from waste Pinot noir grape skins and seeds, and resistance of *Camp. jejuni* planktonic and biofilm cells, mediated via the CmeABC efflux pump. *J. Appl. Microbiol.* **2017**, *122*, 65–77. [[CrossRef](#)]
51. Liu, L.; Yu, J.; Shen, X.; Cao, X.; Zhan, Q.; Guo, Y.; Yu, F. Resveratrol enhances the antimicrobial effect of polymyxin B on *Klebsiella pneumoniae* and *Escherichia coli* isolates with polymyxin B resistance. *BMC Microbiol.* **2020**, *20*, 1–8. [[CrossRef](#)]
52. Mun, S.-H.; Joung, D.-K.; Kim, S.-B.; Park, S.-J.; Seo, Y.-S.; Gong, R.; Choi, J.-G.; Shin, N.-W.; Rho, J.-R.; Kang, O.-H.; et al. The Mechanism of Antimicrobial Activity of Sophoraflavanone B Against Methicillin-Resistant *Staphylococcus aureus*. *Foodborne Pathog. Dis.* **2014**, *11*, 234–239. [[CrossRef](#)]
53. Cha, J.D.; Moon, S.-E.; Kim, J.-Y.; Jung, E.-K.; Lee, Y.-S. Antibacterial activity of sophoraflavanone G isolated from the roots of *Sophora flavescens* against methicillin-resistant *Staphylococcus aureus*. *Phytother. Res.* **2009**, *23*, 1326–1331. [[CrossRef](#)]
54. Yun, B.-Y.; Zhou, L.; Xie, K.-P.; Wang, Y.-J.; Xie, M.-J. Antibacterial activity and mechanism of baicalein. *Yao Xue Xue Bao Acta Pharm. Sin.* **2012**, *47*, 1587–1592.
55. Siritwong, S.; Thumanu, K.; Hengpratom, T.; Eumkeb, G. Synergy and Mode of Action of Ceftazidime plus Quercetin or Luteolin on *Streptococcus pyogenes*. *Evid.-Based Complement. Altern. Med.* **2015**, *2015*, 759459. [[CrossRef](#)] [[PubMed](#)]
56. Yan, Y.; Li, X.; Zhang, C.; Lv, L.; Gao, B.; Li, M. Research Progress on Antibacterial Activities and Mechanisms of Natural Alkaloids: A Review. *Antibiotics* **2021**, *10*, 318. [[CrossRef](#)]
57. Mithöfer, A.; Boland, W. Plant Defense Against Herbivores: Chemical Aspects. *Annu. Rev. Plant Biol.* **2012**, *63*, 431–450. [[CrossRef](#)] [[PubMed](#)]
58. Bao, Y.; Zhang, J.-S.; Fu, Q.; Zhang, H.-T. Antibacterial Activity and Mechanism of Berberine from the Fruit of *Berberis poirerii*. *Shipin Kexue/Food Sci.* **2020**, *41*, 29–34.
59. Kristiansen, M.M.; Leandro, C.; Ordway, D.; Martins, M.; Viveiros, M.; Pacheco, T.; Molnar, J.E.; Kristiansen, J.; Amaral, L. Thioridazine reduces resistance of methicillin-resistant *Staphylococcus aureus* by inhibiting a reserpine-sensitive efflux pump. *In Vivo* **2006**, *20*, 361–366. [[PubMed](#)]
60. Beuria, T.K.; Santra, A.M.K.; Panda, D. Sanguinarine Blocks Cytokinesis in Bacteria by Inhibiting FtsZ Assembly and Bundling. *Biochemistry* **2005**, *44*, 16584–16593. [[CrossRef](#)] [[PubMed](#)]
61. Evstigneev, M.; Rybakova, K.; Davies, D. Complexation of norfloxacin with DNA in the presence of caffeine. *Biophys. Chem.* **2006**, *121*, 84–95. [[CrossRef](#)]
62. Iranshahi, M.; Hassanzadeh, K.M.; Bazzaz, S.F.B.; Sabeti, Z. High Content of Polysulphides in the Volatile Oil of *Ferula latisecta* Rech. F. et Aell. Fruits and Antimicrobial Activity of the Oil. *J. Essent. Oil Res.* **2008**, *20*, 183–185. [[CrossRef](#)]
63. Sarfraz, M.; Nasim, M.J.; Jacob, C.; Gruhlke, M.C.H. Efficacy of Allicin against Plant Pathogenic Fungi and Unveiling the Underlying Mode of Action Employing Yeast Based Chemogenetic Profiling Approach. *Appl. Sci.* **2020**, *10*, 2563. [[CrossRef](#)]
64. Lin, C.-M.; Preston, J.F.; Wei, C.-I. Antibacterial Mechanism of Allyl Isothiocyanate. *J. Food Prot.* **2000**, *63*, 727–734. [[CrossRef](#)] [[PubMed](#)]
65. Nowicki, D.; Maciąg-Dorszyńska, M.; Bogucka, K.; Szalewska-Pałasz, A.; Herman-Antosiewicz, A. Various modes of action of dietary phytochemicals, sulforaphane and phenethyl isothiocyanate, on pathogenic bacteria. *Sci. Rep.* **2019**, *9*, 1–12. [[CrossRef](#)]

66. Garg, S.S.; Gupta, J.; Sharma, S.; Sahu, D. An insight into the therapeutic applications of coumarin compounds and their mechanisms of action. *Eur. J. Pharm. Sci.* **2020**, *152*, 105424. [[CrossRef](#)] [[PubMed](#)]
67. Tan, N.; Yazıcı-Tütüniş, S.; Bilgin, M.; Tan, E.; Miski, M. Antibacterial Activities of Pyrenylated Coumarins from the Roots of *Prangos hulusii*. *Molecules* **2017**, *22*, 1098. [[CrossRef](#)] [[PubMed](#)]
68. Basile, A.; Sorbo, S.; Spadaro, V.; Bruno, M.; Maggio, A.; Faraone, N.; Rosselli, S. Antimicrobial and Antioxidant Activities of Coumarins from the Roots of *Ferulago campestris* (Apiaceae). *Molecules* **2009**, *14*, 939–952. [[CrossRef](#)]
69. Paduch, R.; Kandefer-Szerszeń, M.; Trytek, M.; Fiedurek, J. Terpenes: Substances useful in human healthcare. *Arch. Immunol. Ther. Exp.* **2007**, *55*, 315–327. [[CrossRef](#)]
70. Nostro, A.; Papalia, T. Antimicrobial Activity of Carvacrol: Current Progress and Future Prospectives. *Recent Patents Anti-Infect. Drug Discov.* **2012**, *7*, 28–35. [[CrossRef](#)] [[PubMed](#)]
71. Sharifi-Rad, M.; Varoni, E.M.; Iriti, M.; Martorell, M.; Setzer, W.N.; Contreras, M.D.M.; Salehi, B.; Soltani-Nejad, A.; Rajabi, S.; Tajbakhsh, M.; et al. Carvacrol and human health: A comprehensive review. *Phytother. Res.* **2018**, *32*, 1675–1687. [[CrossRef](#)]
72. Marchese, A.; Orhan, I.E.; Daglia, M.; Barbieri, R.; Di Lorenzo, A.; Nabavi, S.F.; Gortzi, O.; Izadi, M. Antibacterial and antifungal activities of thymol: A brief review of the literature. *Food Chem.* **2016**, *210*, 402–414. [[CrossRef](#)]
73. Khameneh, B.; Iranshahy, M.; Ghandadi, M.; Atashbeyk, D.G.; Bazzaz, B.S.F.; Iranshahi, M. Investigation of the antibacterial activity and efflux pump inhibitory effect of co-loaded piperine and gentamicin nanoliposomes in methicillin-resistant *Staphylococcus aureus*. *Drug Dev. Ind. Pharm.* **2014**, *41*, 989–994. [[CrossRef](#)] [[PubMed](#)]
74. Salleh, W.M.N.H.W.; Hashim, N.A.; Fabarani, N.P.; Ahmad, F. Antibacterial activity of constituents from piper retrofractum vahl. and piper arborescens roxb. *Agric. Conspec. Sci.* **2020**, *85*, 269–280.
75. Domadia, P.N.; Bhunia, A.; Sivaraman, J.; Swarup, S.; Dasgupta, D. Berberine Targets Assembly of Escherichia coli Cell Division Protein FtsZ. *Biochemistry* **2008**, *47*, 3225–3234. [[CrossRef](#)] [[PubMed](#)]
76. Yi, Z.-B.; Yu, Y.; Liang, Y.-Z.; Zeng, B. Evaluation of the antimicrobial mode of berberine by LC/ESI-MS combined with principal component analysis. *J. Pharm. Biomed. Anal.* **2007**, *44*, 301–304. [[CrossRef](#)]
77. Poopedi, E.; Marimani, M.; AlOmar, S.Y.; Aldahmash, B.; Ahmad, A. Modulation of antioxidant defence system in response to berberine in *Candida albicans*. *Yeast* **2020**, *38*, 157–169. [[CrossRef](#)] [[PubMed](#)]
78. Heeb, S.; Fletcher, M.P.; Chhabra, S.R.; Diggle, S.P.; Williams, P.; Cámara, M. Quinolones: From antibiotics to autoinducers. *FEMS Microbiol. Rev.* **2011**, *35*, 247–274. [[CrossRef](#)]
79. Guo, N.; Yu, L.; Meng, R.; Fan, J.-W.; Wang, D.-C.; Sun, G.; Deng, X.-M. Global gene expression profile of *Saccharomyces cerevisiae* induced by dictamnine. *Yeast* **2008**, *25*, 631–641. [[CrossRef](#)]
80. Sridevi, D.; Shankar, C.; Prakash, P.; Park, J.H.; Thamaraiselvi, K. Inhibitory effects of reserpine against efflux pump activity of antibiotic resistance bacteria. *Chem. Biol. Lett.* **2017**, *4*, 69–72.
81. Awasthi, D.; Kumar, K.; Ojima, I. Therapeutic potential of FtsZ inhibition: A patent perspective. *Expert Opin. Ther. Pat.* **2011**, *21*, 657–679. [[CrossRef](#)]
82. Fu, Y.; Liu, W.; Liu, M.; Zhang, J.; Yang, M.; Wang, T.; Qian, W. In vitro anti-biofilm efficacy of sanguinarine against carbapenem-resistant *Serratia marcescens*. *Biofouling* **2021**, *37*, 341–351. [[CrossRef](#)]
83. Dwivedi, G.R.; Maurya, A.; Yadav, D.K.; Singh, V.; Khan, F.; Gupta, M.K.; Singh, M.; Darokar, M.P.; Srivastava, S.K. Synergy of clavine alkaloid ‘chanoclavine’ with tetracycline against multi-drug-resistant *E. coli*. *J. Biomol. Struct. Dyn.* **2019**, *37*, 1307–1325. [[CrossRef](#)]
84. Siriyong, T.; Srimanote, P.; Chusri, S.; Yingyongnarongkul, B.-E.; Suaisom, C.; Tipmanee, V.; Voravuthikunchai, S.P. Conessine as a novel inhibitor of multidrug efflux pump systems in *Pseudomonas aeruginosa*. *BMC Complement. Altern. Med.* **2017**, *17*, 1–7. [[CrossRef](#)] [[PubMed](#)]
85. Siddiqui, B.S.; Ali, S.T.; Rizwani, G.H.; Begum, S.; Tauseef, S.; Ahmad, A. Antimicrobial activity of the methanolic bark extract of *Holarrhena pubescens* (Buch. Ham), its fractions and the pure compound conessine. *Nat. Prod. Res.* **2012**, *26*, 987–992. [[CrossRef](#)]
86. He, N.; Wang, P.; Wang, P.; Ma, C.; Kang, W. Antibacterial mechanism of chelerythrine isolated from root of *Toddalia asiatica* (Linn) Lam. *BMC Complement. Altern. Med.* **2018**, *18*, 1–9. [[CrossRef](#)]
87. Wang, M.; Ma, B.; Ni, Y.; Xue, X.; Li, M.; Meng, J.; Luo, X.; Fang, C.; Hou, Z. Restoration of the Antibiotic Susceptibility of Methicillin-Resistant *Staphylococcus aureus* and Extended-Spectrum β -Lactamases *Escherichia coli* Through Combination with Chelerythrine. *Microb. Drug Resist.* **2021**, *27*, 337–341. [[CrossRef](#)] [[PubMed](#)]
88. Chen, D.H. In vitro antibacterial activity of alkaloids from *Sophora flavescens*. *Chin. Anim. Health* **2010**, *12*, 28–30.
89. Liu, J.; Ding, Z.; Yang, Y.; Wang, F.; Deng, L. Antimicrobial activity of *Sophora alopecuroides* alkaloids. *J. Beijing Univ. Chem. Technol.* **2011**, *38*, 84–88.
90. He, F.; Yang, Y.; Yang, G.; Yu, L. Studies on antibacterial activity and antibacterial mechanism of a novel polysaccharide from *Streptomyces virginia* H03. *Food Control* **2010**, *21*, 1257–1262. [[CrossRef](#)]
91. Chakraborty, P.; Dastidar, D.G.; Paul, P.; Dutta, S.; Basu, D.; Sharma, S.R.; Basu, S.; Sarker, R.K.; Sen, A.; Sarkar, A.; et al. Inhibition of biofilm formation of *Pseudomonas aeruginosa* by caffeine: A potential approach for sustainable management of biofilm. *Arch. Microbiol.* **2019**, *202*, 623–635. [[CrossRef](#)]
92. Anjani, G.; Widyastuti, N.; Masruroh, Z.; Ayu Dwi Yuliana, R.; Gustin Almira, V.; Arif Tsani, A.F.; Nissa, C.; Prawira-Atmaja, M. Bioactive components and antibacterial activity in robusta coffee leaves (*Coffea canephora*). *Int. J. Pharm. Res.* **2020**, *12*, 1374–1382.

93. Feldberg, R.S.; Chang, S.C.; Kotik, A.N.; Nadler, M.; Neuwirth, Z.; Sundstrom, D.C.; Thompson, N.H. In vitro mechanism of inhibition of bacterial cell growth by allicin. *Antimicrob. Agents Chemother.* **1988**, *32*, 1763–1768. [[CrossRef](#)] [[PubMed](#)]
94. Zainal, M.; Zain, N.; Amin, I.M.; Ahmad, V.N. The antimicrobial and antibiofilm properties of allicin against *Candida albicans* and *Staphylococcus aureus*—A therapeutic potential for denture stomatitis. *Saudi Dent. J.* **2020**, *33*, 105–111. [[CrossRef](#)]
95. Torres, J.; Romero, H. In vitro antifungal activity of ajoene on five clinical isolates of *Histoplasma capsulatum* var. *capsulatum*. *Rev. Iberoam. Micol.* **2012**, *29*, 24–28. [[CrossRef](#)] [[PubMed](#)]
96. Dufour, V.; Stahl, M.; Baysse, C. The antibacterial properties of isothiocyanates. *Microbiology* **2015**, *161*, 229–243. [[CrossRef](#)] [[PubMed](#)]
97. Velliyagounder, K.; Ganeshnarayan, K.; Velusamy, S.K.; Fine, D.H. In Vitro Efficacy of Diallyl Sulfides against the Periodontopathogen *Aggregatibacter actinomycetemcomitans*. *Antimicrob. Agents Chemother.* **2012**, *56*, 2397–2407. [[CrossRef](#)] [[PubMed](#)]
98. Li, W.-R.; Ma, Y.-K.; Xie, X.-B.; Shi, Q.-S.; Wen, X.; Sun, T.-L.; Peng, H. Diallyl Disulfide From Garlic Oil Inhibits *Pseudomonas aeruginosa* Quorum Sensing Systems and Corresponding Virulence Factors. *Front. Microbiol.* **2019**, *9*, 3222. [[CrossRef](#)] [[PubMed](#)]
99. Tang, Y.; Li, F.; Gu, D.; Wang, W.; Huang, J.; Jiao, X. Antimicrobial Effect and the Mechanism of Diallyl Trisulfide against *Campylobacter jejuni*. *Antibiotics* **2021**, *10*, 246. [[CrossRef](#)] [[PubMed](#)]
100. Wu, S.-C.; Chu, X.-L.; Su, J.-Q.; Cui, Z.-Q.; Zhang, L.-Y.; Yu, Z.-J.; Wu, Z.-M.; Cai, M.-L.; Li, H.-X.; Zhang, Z.-J. Baicalin protects mice against *Salmonella typhimurium* infection via the modulation of both bacterial virulence and host response. *Phytomedicine* **2018**, *48*, 21–31. [[CrossRef](#)]
101. Cannalire, R.; Machado, D.; Felicetti, T.; Costa, S.S.; Massari, S.; Manfroni, G.; Barreca, M.L.; Tabarrini, O.; Couto, I.; Viveiros, M.; et al. Natural isoflavone biochanin A as a template for the design of new and potent 3-phenylquinolone efflux inhibitors against *Mycobacterium avium*. *Eur. J. Med. Chem.* **2017**, *140*, 321–330. [[CrossRef](#)] [[PubMed](#)]
102. Stermitz, F.R.; Cashman, K.K.; Halligan, K.M.; Morel, C.; Tegos, G.P.; Lewis, K. Polyacylated neohesperidosides From *Geranium caespitosum*: Bacterial multidrug resistance pump inhibitors. *Bioorganic Med. Chem. Lett.* **2003**, *13*, 1915–1918. [[CrossRef](#)]
103. Stermitz, F.R.; Beeson, T.D.; Mueller, P.J.; Hsiang, J.-F.; Lewis, K. *Staphylococcus aureus* MDR efflux pump inhibitors from a *Berberis* and a *Mahonia* (*sensu strictu*) species. *Biochem. Syst. Ecol.* **2001**, *29*, 793–798. [[CrossRef](#)]
104. Holler, J.G.; Christensen, S.B.; Slotved, H.-C.; Rasmussen, H.B.; Gúzman, A.; Olsen, C.E.; Petersen, B.; Mølgaard, P. Novel inhibitory activity of the *Staphylococcus aureus* NorA efflux pump by a kaempferol rhamnoside isolated from *Persea lingue* Nees. *J. Antimicrob. Chemother.* **2012**, *67*, 1138–1144. [[CrossRef](#)] [[PubMed](#)]
105. Yin, J.; Peng, X.; Lin, J.; Zhang, Y.; Zhang, J.; Gao, H.; Tian, X.; Zhang, R.; Zhao, G. Quercetin ameliorates *Aspergillus fumigatus* keratitis by inhibiting fungal growth, toll-like receptors and inflammatory cytokines. *Int. Immunopharmacol.* **2021**, *93*, 107435. [[CrossRef](#)]
106. Li, K.; Guan, G.; Zhu, J.; Wu, H.; Sun, Q. Antibacterial activity and mechanism of a laccase-catalyzed chitosan–gallic acid derivative against *Escherichia coli* and *Staphylococcus aureus*. *Food Control* **2018**, *96*, 234–243. [[CrossRef](#)]
107. Bazzaz, B.S.F.; Sarabandi, S.; Khameneh, B.; Hosseinzadeh, H. Effect of catechins, green tea extract and methylxanthines in combination with gentamicin against *Staphylococcus aureus* and *Pseudomonas aeruginosa*—Combination therapy against resistant bacteria. *J. Pharmacopunct.* **2016**, *19*, 312–318. [[CrossRef](#)] [[PubMed](#)]
108. Knidel, C.; Pereira, M.F.; Barcelos, D.H.F.; Gomes, D.C.D.O.; Guimarães, M.C.C.; Schuenck, R.P. Epigallocatechin gallate has antibacterial and antibiofilm activity in methicillin resistant and susceptible *Staphylococcus aureus* of different lineages in non-cytotoxic concentrations. *Nat. Prod. Res.* **2019**, 1–5. [[CrossRef](#)]
109. Wu, Y.; Bai, J.; Zhong, K.; Huang, Y.; Qi, H.; Jiang, Y.; Gao, H. Antibacterial Activity and Membrane-Disruptive Mechanism of 3-p-trans-Coumaroyl-2-hydroxyquinic Acid, a Novel Phenolic Compound from Pine Needles of *Cedrus deodara*, against *Staphylococcus aureus*. *Molecules* **2016**, *21*, 1084. [[CrossRef](#)] [[PubMed](#)]
110. Soobrattee, M.; Neergheen, V.; Luximon-Ramma, A.; Aruoma, O.; Bahorun, T. Phenolics as potential antioxidant therapeutic agents: Mechanism and actions. *Mutat. Res. Mol. Mech. Mutagen.* **2005**, *579*, 200–213. [[CrossRef](#)]
111. Li, B.H.; Zhang, R.; Du, Y.T.; Sun, Y.H.; Tian, W.X. Inactivation mechanism of the beta-ketoacyl-[acyl carrier protein] reductase of bacterial type-II fatty acid synthase by epigallocatechin gallate. *Biochem. Cell Biol.* **2006**, *84*, 755–762. [[CrossRef](#)]
112. Yun, Y.F.; Aisyah, L.S.; Purbaya, S.; Agustini, D.M.; Wardhani, I.P.; Alawiyah, N.; Supratman, U.; Shiono, Y. Identification of flavonoid compounds from ethyl acetate extract of *Kalanchoe millotii* (Crassulaceae) and endodontics antibacterial activity. *Res. J. Chem. Environ.* **2020**, *24*, 53–55.
113. Moura, F.C.S.; Cechinel-Filho, V.; Greco, F.A.; Venzon, L.; Meurer, M.C.; França, T.C.d.S.; Longo, B.; Somensi, L.B.; Mariano, L.N.B.; Cruz, A.B.; et al. Taxifolin and gastro-adhesive microparticles containing taxifolin promotes gastric healing in vivo, inhibits *Helicobacter pylori* in vitro and proton pump reversibly in silico. *Chem. Interact.* **2021**, *339*, 109445. [[CrossRef](#)]
114. Tyagi, P.; Singh, M.; Kumari, H.; Kumari, A.; Mukhopadhyay, K. Bactericidal Activity of Curcumin I Is Associated with Damaging of Bacterial Membrane. *PLoS ONE* **2015**, *10*, e0121313. [[CrossRef](#)] [[PubMed](#)]
115. Kareem, S.; Mahmood, S.S.; Hindi, N. Effects of Curcumin and Silymarin on the *Shigella dysenteriae* and *Campylobacter jejuni* In vitro. *J. Gastrointest. Cancer* **2019**, *51*, 824–828. [[CrossRef](#)] [[PubMed](#)]
116. Wu, D.; Kong, Y.; Han, C.; Chen, J.; Hu, L.; Jiang, H.; Shen, X. d-Alanine:d-alanine ligase as a new target for the flavonoids quercetin and apigenin. *Int. J. Antimicrob. Agents* **2008**, *32*, 421–426. [[CrossRef](#)]

117. Szatmári, Á.; Móricz, Á.M.; Schwarczinger, I.; Nagy, J.K.; Alberti, Á.; Pogány, M.; Bozsó, Z. A pattern-triggered immunity-related phenolic, acetosyringone, boosts rapid inhibition of a diverse set of plant pathogenic bacteria. *BMC Plant Biol.* **2021**, *21*, 1–20. [[CrossRef](#)]
118. Saravanakumar, T.; Park, H.-S.; Mo, A.-Y.; Choi, M.-S.; Kim, D.-H.; Park, S.-M. Detoxification of furanic and phenolic lignocellulose derived inhibitors of yeast using laccase immobilized on bacterial cellulosic nanofibers. *J. Mol. Catal. B Enzym.* **2016**, *134*, 196–205. [[CrossRef](#)]
119. Neetu, N.; Katiki, M.; Dev, A.; Gaur, S.; Tomar, S.; Kumar, P. Structural and Biochemical Analyses Reveal that Chlorogenic Acid Inhibits the Shikimate Pathway. *J. Bacteriol.* **2020**, *202*, e00248-20. [[CrossRef](#)]
120. Ouyang, J.; Sun, F.; Feng, W.; Xie, Y.; Ren, L.; Chen, Y. Antimicrobial Activity of Galangin and Its Effects on Murein Hydrolases of Vancomycin-Intermediate Staphylococcus aureus (VISA) Strain Mu50. *Chemotherapy* **2017**, *63*, 20–28. [[CrossRef](#)]
121. Morel, C.; Stermitz, F.R.; Tegos, A.G.; Lewis, K. Isoflavones As Potentiators of Antibacterial Activity. *J. Agric. Food Chem.* **2003**, *51*, 5677–5679. [[CrossRef](#)]
122. Wu, T.; He, M.; Zang, X.; Zhou, Y.; Qiu, T.; Pan, S.; Xu, X. A structure-activity relationship study of flavonoids as inhibitors of E. coli by membrane interaction effect. *Biochim. Biophys. Acta* **2013**, *1828*, 2751–2756. [[CrossRef](#)]
123. Wu, T.; Zang, X.; He, M.; Pan, S.; Xu, X. Structure-Activity Relationship of Flavonoids on Their Anti-Escherichia coli Activity and Inhibition of DNA Gyrase. *J. Agric. Food Chem.* **2013**, *61*, 8185–8190. [[CrossRef](#)] [[PubMed](#)]
124. Lee, B.W.; Park, I.-H.; Yim, D.; Choi, S.S. Comprehensive Evaluation of the Anti- Helicobacter pylori Activity of Scutellariae Radix. *Nat. Prod. Sci.* **2017**, *23*, 46. [[CrossRef](#)]
125. Lechner, D.; Gibbons, S.; Bucar, F. Plant phenolic compounds as ethidium bromide efflux inhibitors in Mycobacterium smegmatis. *J. Antimicrob. Chemother.* **2008**, *62*, 345–348. [[CrossRef](#)] [[PubMed](#)]
126. Qian, W.; Liu, M.; Fu, Y.; Zhang, J.; Liu, W.; Li, J.; Li, X.; Li, Y.; Wang, T. Antimicrobial mechanism of luteolin against Staphylococcus aureus and Listeria monocytogenes and its antibiofilm properties. *Microb. Pathog.* **2020**, *142*, 104056. [[CrossRef](#)] [[PubMed](#)]
127. Diniz-Silva, H.T.; Magnani, M.; de Siqueira, S.; de Souza, E.L.; de Siqueira-Júnior, J.P. Fruit flavonoids as modulators of norfloxacin resistance in Staphylococcus aureus that overexpresses norA. *LWT* **2017**, *85*, 324–326. [[CrossRef](#)]
128. Kubo, I.; Muroi, H.; Himejima, M. Antibacterial Activity of Totarol and Its Potentiation. *J. Nat. Prod.* **1992**, *55*, 1436–1440. [[CrossRef](#)] [[PubMed](#)]
129. Chung, K.T.; Jr, S.E.S.; Lin, W.F.; Wei, C.I. Growth inhibition of selected food-borne bacteria by tannic acid, propyl gallate and related compounds. *Lett. Appl. Microbiol.* **1993**, *17*, 29–32. [[CrossRef](#)]
130. Diniz-Silva, H.T.; Cirino, I.C.D.S.; Falcão-Silva, V.D.S.; Magnani, M.; De Souza, E.L.; Siqueira-Júnior, J.P. Tannic Acid as a Potential Modulator of Norfloxacin Resistance in Staphylococcus Aureus Overexpressing norA. *Chemotherapy* **2016**, *61*, 319–322. [[CrossRef](#)] [[PubMed](#)]
131. Hisano, M.; Yamaguchi, K.; Inoue, Y.; Ikeda, Y.; Iijima, M.; Adachi, M.; Shimamura, T. Inhibitory effect of catechin against the superantigen staphylococcal enterotoxin B (SEB). *Arch. Dermatol. Res.* **2003**, *295*, 183–189. [[CrossRef](#)] [[PubMed](#)]
132. Sinsinwar, S.; Vadivel, V. Catechin isolated from cashew nut shell exhibits antibacterial activity against clinical isolates of MRSA through ROS-mediated oxidative stress. *Appl. Microbiol. Biotechnol.* **2020**, *104*, 1–19. [[CrossRef](#)] [[PubMed](#)]
133. Razavi, S.M.; Imanzadeh, G.; Jahed, F.S.; Zarrini, G. Pyranocoumarins from Zosima absinthifolia (Vent) link roots. *Russ. J. Bioorganic Chem.* **2013**, *39*, 215–217. [[CrossRef](#)]
134. Venugopala, K.N.; Rashmi, V.; Odhav, B. Review on natural coumarin lead compounds for their pharmacological activity. *BioMed. Res. Int.* **2013**, *2013*, 963248. [[CrossRef](#)]
135. Tsai, F.T.; Singh, O.M.; Skarzynski, T.; Wonacott, A.J.; Weston, S.; Tucker, A.A.; Pauptit, R.; Breeze, A.L.; Poyser, J.P.; O'Brien, R.; et al. The high-resolution crystal structure of a 24-kDa gyrase B fragment from E. coli complexed with one of the most potent coumarin inhibitors, clorobiocin. *Proteins Struct. Funct. Bioinform.* **1997**, *28*, 41–52. [[CrossRef](#)]
136. Yadav, N.; Agarwal, D.; Kumar, S.; Dixit, A.; Gupta, R.D.; Awasthi, S.K. In vitro antiplasmodial efficacy of synthetic coumarin-triazole analogs. *Eur. J. Med. Chem.* **2018**, *145*, 735–745. [[CrossRef](#)]
137. Lv, X.-H.; Liu, H.; Ren, Z.-L.; Wang, W.; Tang, F.; Cao, H.-Q. Design, synthesis and biological evaluation of novel flavone Mannich base derivatives as potential antibacterial agents. *Mol. Divers.* **2018**, *23*, 299–306. [[CrossRef](#)] [[PubMed](#)]
138. Bazzaz, B.S.F.; Memariani, Z.; Khashiarmansh, Z.; Iranshahi, M.; Naderinasab, M. Effect Of Galbanic Acid, A Sesquiterpene Coumarin From Ferula Szowitsiana, As An Inhibitor Of Efflux Mechanism In Resistant Clinical Isolates of Staphylococcus Aureus. *Braz. J. Microbiol.* **2010**, *41*, 574–580. [[CrossRef](#)] [[PubMed](#)]
139. Bazzaz, B.S.F.; Iranshahi, M.; Naderinasab, M.; Hajian, S.; Sabeti, Z.; Masumi, E. Evaluation of the effects of galbanic acid from Ferula szowitsiana and conferol from F. badrakema, as modulators of multi-drug resistance in clinical isolates of Escherichia coli and Staphylococcus aureus. *Res. Pharm. Sci.* **2010**, *5*, 21–28.
140. Yang, L.; Ding, W.; Xu, Y.; Wu, D.; Liang, Y.; Chen, J.; Guo, B. New Insights into the Antibacterial Activity of Hydroxycoumarins against Ralstonia solanacearum. *Molecules* **2016**, *21*, 468. [[CrossRef](#)]
141. Liu, W.; Mei, J.; Xie, J. Elucidating Antibacterial Activity and Mechanism of Daphnetin against Pseudomonas fluorescens and Shewanella putrefaciens. *J. Food Qual.* **2020**, *2020*, 6622355. [[CrossRef](#)]
142. Yang, L.; Wu, L.; Yao, X.; Zhao, S.; Wang, J.; Li, S.; Ding, W. Hydroxycoumarins: New, effective plant-derived compounds reduce Ralstonia pseudosolanacearum populations and control tobacco bacterial wilt. *Microbiol. Res.* **2018**, *215*, 15–21. [[CrossRef](#)]

143. Konuk, H.B.; Ergüden, B. Phenolic –OH group is crucial for the antifungal activity of terpenoids via disruption of cell membrane integrity. *Folia Microbiol.* **2020**, *65*, 775–783. [[CrossRef](#)] [[PubMed](#)]
144. Horie, H.; Chiba, A.; Wada, S. Inhibitory effect of soy saponins on the activity of β -lactamases, including New Delhi metallo- β -lactamase 1. *J. Food Sci. Technol.* **2018**, *55*, 1948–1952. [[CrossRef](#)] [[PubMed](#)]
145. Wijesundara, N.M.; Lee, S.F.; Cheng, Z.; Davidson, R.; Rupasinghe, H.P.V. Carvacrol exhibits rapid bactericidal activity against *Streptococcus pyogenes* through cell membrane damage. *Sci. Rep.* **2021**, *11*, 1–14. [[CrossRef](#)] [[PubMed](#)]
146. Wang, X.; Tian, L.; Fu, J.; Liao, S.; Yang, S.; Jia, X.; Gong, G. Evaluation of the membrane damage mechanism of thymol against *Bacillus cereus* and its application in the preservation of skim milk. *Food Control* **2021**, *131*, 108435. [[CrossRef](#)]
147. Jeyakumar, G.E.; Lawrence, R. Mechanisms of bactericidal action of Eugenol against *Escherichia coli*. *J. Herb. Med.* **2020**, *26*, 100406. [[CrossRef](#)]
148. Togashi, N.; Inoue, Y.; Hamashima, H.; Takano, A. Effects of Two Terpene Alcohols on the Antibacterial Activity and the Mode of Action of Farnesol against *Staphylococcus aureus*. *Molecules* **2008**, *13*, 3069–3076. [[CrossRef](#)]
149. Memariani, Z.; Sharifzadeh, M.; Bozorgi, M.; Hajimahmoodi, M.; Farzaei, M.H.; Gholami, M.; Siavoshi, F.; Saniee, P. Protective effect of essential oil of *Pistacia atlantica* Desf. on peptic ulcer: Role of α -pinene. *J. Tradit. Chin. Med.* **2017**, *37*, 57–63. [[CrossRef](#)]
150. Costa, M.D.S.; Rocha, J.E.; Campina, F.F.; Silva, A.R.; Da Cruz, R.P.; Pereira, R.L.; Quintans-Júnior, L.J.; De Menezes, I.R.; Araújo, A.A.D.S.; De Freitas, T.S.; et al. Comparative analysis of the antibacterial and drug-modulatory effect of d-limonene alone and complexed with β -cyclodextrin. *Eur. J. Pharm. Sci.* **2018**, *128*, 158–161. [[CrossRef](#)]
151. Shayegan, S.; Khodavandi, A. Inhibitory effect of menthol on expression of aspartyl proteinase 1 in fluconazole-resistant *Candida albicans*. *J. Herb. Med. Pharmacol.* **2019**, *8*, 35–40. [[CrossRef](#)]
152. Wang, F.; Liu, Z.; Zhang, D.; Niu, X. In vitro activity of farnesol against vaginal *Lactobacillus* spp. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2017**, *212*, 25–29. [[CrossRef](#)]
153. de Moura, D.F.; Rocha, T.A.; Barros, D.d.M.; Silva, M.M.d.; Santana, M.D.S.; Neta, B.M.; Cavalcanti, I.M.F.; Martins, R.D.; Silva, M.V. Evaluation of the antioxidant, antibacterial, and antibiofilm activity of the sesquiterpene nerolidol. *Arch. Microbiol.* **2021**, *203*, 4303–4311. [[CrossRef](#)] [[PubMed](#)]
154. De Carvalho, C.C.; Da Fonseca, M.M.R. Carvone: Why and how should one bother to produce this terpene. *Food Chem.* **2006**, *95*, 413–422. [[CrossRef](#)]
155. Liu, J. Oleanolic acid and ursolic acid: Research perspectives. *J. Ethnopharmacol.* **2005**, *100*, 92–94. [[CrossRef](#)] [[PubMed](#)]
156. Qian, W.; Li, X.; Shen, L.; Wang, T.; Liu, M.; Zhang, J.; Yang, M.; Li, X.; Cai, C. RETRACTED: Antibacterial and antibiofilm activity of ursolic acid against carbapenem-resistant *Enterobacter cloacae*. *J. Biosci. Bioeng.* **2019**, *129*, 528–534. [[CrossRef](#)]
157. Catteau, L.; Reichmann, N.T.; Olson, J.; Pinho, M.G.; Nizet, V.; Van Bambeke, F.; Quetin-Leclercq, J. Synergy between Ursolic and Oleanolic Acids from *Vitellaria paradoxa* Leaf Extract and β -Lactams against Methicillin-Resistant *Staphylococcus aureus*: In Vitro and In Vivo Activity and Underlying Mechanisms. *Molecules* **2017**, *22*, 2245. [[CrossRef](#)] [[PubMed](#)]
158. Zhang, Y.B.; Liu, X.Y.; Jiang, P.P.; Li, W.D.; Wang, Y.F. Mechanism and antibacterial activity of cinnamaldehyde against *Escherichia coli* and *Staphylococcus aureus*. *Mod. Food Sci. Technol.* **2015**, *31*, 31–35. [[CrossRef](#)]
159. Pereira, W.; Pereira, C.; Assunção, R.; da Silva, I.; Rego, F.; Alves, L.; Santos, J.; Nogueira, F.; Zagnignan, A.; Thomsen, T.; et al. New Insights into the Antimicrobial Action of Cinnamaldehyde towards *Escherichia coli* and Its Effects on Intestinal Colonization of Mice. *Biomolecules* **2021**, *11*, 302. [[CrossRef](#)]
160. Wang, J.; Zhang, C.-J.; Ni Chia, W.; Loh, C.C.Y.; Li, Z.; Lee, Y.M.; He, Y.; Yuan, L.-X.; Lim, T.K.; Liu, M.; et al. Haem-activated promiscuous targeting of artemisinin in *Plasmodium falciparum*. *Nat. Commun.* **2015**, *6*, 10111. [[CrossRef](#)] [[PubMed](#)]
161. Nguyen, H.V.; Meile, J.C.; Lebrun, M.; Caruso, D.; Chu-Ky, S.; Sarter, S. Litsea cubeba leaf essential oil from Vietnam: Chemical diversity and its impacts on antibacterial activity. *Lett. Appl. Microbiol.* **2018**, *66*, 207–214. [[CrossRef](#)]
162. Liu, X.; Cai, J.; Chen, H.; Zhong, Q.; Hou, Y.; Chen, W.; Chen, W. Antibacterial activity and mechanism of linalool against *Pseudomonas aeruginosa*. *Microb. Pathog.* **2020**, *141*, 103980. [[CrossRef](#)]
163. Silva, V.A.; Sousa, J.P.; Guerra, F.Q.S.; Pessôa, H.L.F.; Freitas, A.F.R.; Coutinho, H.D.M.; Alves, L.B.N.; Lima, E.O. Antibacterial activity of the monoterpene linalool: Alone and in association with antibiotics against bacteria of clinical importance. *Int. J. Pharm. Phytochem. Res.* **2015**, *7*, 1022–1026.
164. Cui, H.; Zhang, X.; Zhou, H.; Zhao, C.; Xiao, Z.; Lin, L.; Li, C. Antibacterial Properties of Nutmeg Oil in Pork and Its Possible Mechanism. *J. Food Saf.* **2015**, *35*, 370–377. [[CrossRef](#)]
165. Matias, E.F.; Alves, E.F.; Silva, M.K.; Carvalho, V.R.; Figueredo, F.G.; Ferreira, J.V.; Coutinho, H.D.; Silva, J.M.; Ribeiro-Filho, J.; Costa, J.G. Seasonal variation, chemical composition and biological activity of the essential oil of *Cordia verbenacea* DC (Boraginaceae) and the sabinene. *Ind. Crop. Prod.* **2016**, *87*, 45–53. [[CrossRef](#)]
166. Carson, C.F.; Mee, B.J.; Riley, T.V. Mechanism of Action of *Melaleuca alternifolia* (Tea Tree) Oil on *Staphylococcus aureus* Determined by Time-Kill, Lysis, Leakage, and Salt Tolerance Assays and Electron Microscopy. *Antimicrob. Agents Chemother.* **2002**, *46*, 1914–1920. [[CrossRef](#)]
167. Li, L.; Shi, C.; Yin, Z.; Jia, R.; Peng, L.; Kang, S.; Li, Z. Antibacterial activity of α -terpineol may induce morphostructural alterations in *Escherichia coli*. *Braz. J. Microbiol.* **2014**, *45*, 1409–1413. [[CrossRef](#)]
168. Lopez-Romero, J.C.; González-Ríos, H.; Borges, A.; Simões, M. Antibacterial Effects and Mode of Action of Selected Essential Oils Components against *Escherichia coli* and *Staphylococcus aureus*. *Evid. Based Complement. Altern. Med.* **2015**, *2015*, 795435. [[CrossRef](#)]

169. Pereira, F.d.O.; Mendes, J.M.; Lima, I.O.; de Lira Mota, K.S.; de Oliveira, W.A.; de Oliveira Lima, E. Antifungal activity of geraniol and citronellol, two monoterpenes alcohols, against *Trichophyton rubrum* involves inhibition of ergosterol biosynthesis. *Pharm. Biol.* **2015**, *53*, 228–234. [[CrossRef](#)]
170. Sieniawska, E.; Swatko-Ossor, M.; Sawicki, R.; Ginalska, G. Morphological Changes in the Overall Mycobacterium tuberculosis H37Ra Cell Shape and Cytoplasm Homogeneity due to *Mutellina purpurea* L. Essential Oil and Its Main Constituents. *Med. Princ. Pract.* **2015**, *24*, 527–532. [[CrossRef](#)]
171. Firat, Z.; Demirci, F.; Demirci, B.; Baser, K.H.C. Microbial transformation of α -Bisabolol towards bioactive metabolites. *J. Biotechnol.* **2017**, *256*, S52–S53. [[CrossRef](#)]
172. e Nogueira, J.O.; Campolina, G.A.; Batista, L.R.; Alves, E.; Caetano, A.R.S.; Brandão, R.M.; Nelson, D.L.; Cardoso, M.D.G. Mechanism of action of various terpenes and phenylpropanoids against *Escherichia coli* and *Staphylococcus aureus*. *FEMS Microbiol. Lett.* **2021**, *368*, fnab052. [[CrossRef](#)]
173. Bazzaz, B.S.F.; Fork, S.D.; Ahmadi, R.; Khameneh, B. Deep insights into urinary tract infections and effective natural remedies. *Afr. J. Urol.* **2021**, *27*, 1–13. [[CrossRef](#)]
174. Afshar, K.; Fleischmann, N.; Schmiemann, G.; Bleidorn, J.; Hummers-Pradier, E.; Friede, T.; Wegscheider, K.; Moore, M.; Gágyor, I. Reducing antibiotic use for uncomplicated urinary tract infection in general practice by treatment with uva-ursi (REGATTA)—A double-blind, randomized, controlled comparative effectiveness trial. *BMC Complement. Altern. Med.* **2018**, *18*, 203. [[CrossRef](#)]
175. Larsson, B.; Jonasson, A.; Fianu, S. Prophylactic effect of UVA-E in women with recurrent cystitis: A preliminary report. *Curr. Ther. Res.* **1993**, *53*, 441–443. [[CrossRef](#)]
176. Howell, A.B.; Foxman, B. Cranberry juice and adhesion of antibiotic-resistant uropathogens. *JAMA* **2002**, *287*, 3082–3083. [[CrossRef](#)] [[PubMed](#)]
177. Burger, O.; Ofek, I.; Tabak, M.; Weiss, E.I.; Sharon, N.; Neeman, I. A high molecular mass constituent of cranberry juice inhibits *Helicobacter pylori* adhesion to human gastric mucus. *FEMS Immunol. Med. Microbiol.* **2000**, *29*, 295–301. [[CrossRef](#)] [[PubMed](#)]
178. Di Martino, P.; Agniel, R.; David, K.; Templer, C.; Gaillard, J.L.; Denys, P.; Botto, H. Reduction of *Escherichia coli* adherence to uroepithelial bladder cells after consumption of cranberry juice: A double-blind randomized placebo-controlled cross-over trial. *World J. Urol.* **2006**, *24*, 21–27. [[CrossRef](#)]
179. Tao, Y.; Pinzón-Arango, P.A.; Howell, A.B.; Comesano, T.A. Oral Consumption of Cranberry Juice Cocktail Inhibits Molecular-Scale Adhesion of Clinical Uropathogenic *Escherichia coli*. *J. Med. Food* **2011**, *14*, 739–745. [[CrossRef](#)] [[PubMed](#)]
180. Dason, S.; Dason, J.T.; Kapoor, A. Guidelines for the diagnosis and management of recurrent urinary tract infection in women. *Can. Urol. Assoc. J.* **2013**, *5*, 316–322. [[CrossRef](#)]
181. Davidson, E.; Zimmermann, B.F.; Jungfer, E.; Chrubasik-Hausmann, S. Prevention of Urinary Tract Infections with *Vaccinium* Products. *Phytother. Res.* **2013**, *28*, 465–470. [[CrossRef](#)] [[PubMed](#)]
182. Bag, A.; Bhattacharyya, S.; Chattopadhyay, R. Medicinal plants and urinary tract infections: An update. *Pharmacogn. Rev.* **2008**, *2*, 277.
183. Head, K.A. Natural approaches to prevention and treatment of infections of the lower urinary tract. *Altern. Med. Rev.* **2008**, *13*, 227–244.
184. Vichkanova, S.A.; Tolkachev, O.N.; Martynova, R.G.; Arzamastsev, E.V. Sanguiritrin, a new antimicrobial drug. *Pharm. Chem. J.* **1982**, *16*, 925–929. [[CrossRef](#)]
185. Dvorak, Z.; Simanek, V. Metabolism of Sanguinarine: The Facts and The Myths. *Curr. Drug Metab.* **2007**, *8*, 173–176. [[CrossRef](#)]
186. Spiridonov, N.A.; Foigel, A.G.; Fomkina, M.G.; Arkhipov, V.V.; Shipulina, L.D. Mechanism of action of some antimicrobial preparations of plant origin. *Pharm. Chem. J.* **1996**, *30*, 400–403. [[CrossRef](#)]
187. Semkina, O.A.; Sokol'Skaya, T.A.; Krasnyuk, I.I.; Okhotnikova, V.F.; Krutikova, N.M.; Vichkanova, S.A. Eucalimin: Antimicrobial and antiinflammatory medicinal plant preparation. *Pharm. Chem. J.* **2006**, *40*, 459–462. [[CrossRef](#)]
188. Osawa, K.; Yasuda, H.; Morita, H.; Takeya, A.K.; Itokawa, H. Macrocarpals H, I, and J from the Leaves of *Eucalyptus globulus*. *J. Nat. Prod.* **1996**, *59*, 823–827. [[CrossRef](#)]
189. Zhukovich, E.N.; Bobrenko, L.M.; Semenova, M.Y.; Bokareva, S.Y. Chemical Studies of *Eucalyptus* Tincture. *Pharm. Chem. J.* **2014**, *48*, 323–327. [[CrossRef](#)]
190. Xing, S.; Wang, M.; Peng, Y.; Li, X. Effects of intestinal microecology on metabolism and pharmacokinetics of oral wogonoside and Baicalin. *Nat. Prod. Comm.* **2017**, *12*, 509–514. [[CrossRef](#)]
191. Zhao, Q.; Chen, X.; Martin, C. *Scutellaria baicalensis*, the golden herb from the garden of Chinese medicinal plants. *Sci. Bull.* **2016**, *61*, 1391–1398. [[CrossRef](#)] [[PubMed](#)]
192. Fox, J.T.; Sakamuru, S.; Huang, R.; Teneva, N.; Simmons, S.; Xia, M.; Tice, R.R.; Austin, C.P.; Myung, K. High-throughput genotoxicity assay identifies antioxidants as inducers of DNA damage response and cell death. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 5423–5428. [[CrossRef](#)]
193. Zhao, T.; Tang, H.; Xie, L.; Zheng, Y.; Ma, Z.; Sun, Q.; Li, X. *Scutellaria baicalensis* Georgi. (Lamiaceae): A review of its traditional uses, botany, phytochemistry, pharmacology and toxicology. *J. Pharm. Pharmacol.* **2019**, *71*, 1353–1369. [[CrossRef](#)] [[PubMed](#)]
194. Jang, E.-J.; Cha, S.-M.; Choi, S.-M.; Cha, J.-D. Combination effects of baicalein with antibiotics against oral pathogens. *Arch. Oral Biol.* **2014**, *59*, 1233–1241. [[CrossRef](#)]

195. Cai, W.; Fu, Y.; Zhang, W.; Chen, X.; Zhao, J.; Song, W.; Li, Y.; Huang, Y.; Wu, Z.; Sun, R.; et al. Synergistic effects of baicalein with cefotaxime against *Klebsiella pneumoniae* through inhibiting CTX-M-1 gene expression. *BMC Microbiol.* **2016**, *16*, 181. [[CrossRef](#)] [[PubMed](#)]
196. Siritwong, S.; Pimchan, T.; Naknarong, W.; Eumkeb, G. Mode of Action and Synergy of Ceftazidime and Baicalein against *Streptococcus pyogenes*. *Trop. J. Pharm. Res.* **2015**, *14*, 641. [[CrossRef](#)]
197. Chan, B.C.; Ip, M.; Lau, C.; Lui, S.; Jolival, C.; Ganem-Elbaz, C.; Litaudon, M.; Reiner, N.E.; Gong, H.; See, R.H.; et al. Synergistic effects of baicalein with ciprofloxacin against NorA over-expressed methicillin-resistant *Staphylococcus aureus* (MRSA) and inhibition of MRSA pyruvate kinase. *J. Ethnopharmacol.* **2011**, *137*, 767–773. [[CrossRef](#)] [[PubMed](#)]
198. Arweiler, N.B.; Pergola, G.; Kuenz, J.; Hellwig, E.; Sculean, A.; Ausschill, T.M. Clinical and antibacterial effect of an anti-inflammatory toothpaste formulation with *Scutellaria baicalensis* extract on experimental gingivitis. *Clin. Oral Investig.* **2010**, *15*, 909–913. [[CrossRef](#)] [[PubMed](#)]
199. Vijayakumar, A.; Sarveswari, H.; Vasudevan, S.; Shanmugam, K.; Solomon, A.; Neelakantan, P. Baicalein Inhibits *Streptococcus mutans* Biofilms and Dental Caries-Related Virulence Phenotypes. *Antibiotics* **2021**, *10*, 215. [[CrossRef](#)]
200. Liu, T.; Luo, J.; Bi, G.; Du, Z.; Kong, J.; Chen, Y. Antibacterial synergy between linezolid and baicalein against methicillin-resistant *Staphylococcus aureus* biofilm in vivo. *Microb. Pathog.* **2020**, *147*, 104411. [[CrossRef](#)]
201. Hemalatha, S.; Kumar, M.; Prasad, S. A current update on the phytopharmacological aspects of *Houttuynia cordata* Thunb. *Pharmacogn. Rev.* **2014**, *8*, 22–35. [[CrossRef](#)]
202. Hou, B.-Y.; Zhang, L.; Du, G.H. *Houttuynin*. In *Natural Small Molecule Drugs from Plants*; Springer: Singapore, 2018; pp. 415–420.
203. Lu, X.; Yang, X.; Li, X.; Lu, Y.; Ren, Z.; Zhao, L.; Hu, X.; Jiang, J.; You, X. In Vitro Activity of Sodium New Houttuynofonate Alone and in Combination with Oxacillin or Netilmicin against Methicillin-Resistant *Staphylococcus aureus*. *PLoS ONE* **2013**, *8*, e68053. [[CrossRef](#)] [[PubMed](#)]
204. Liu, X.; Zhong, L.; Xie, J.; Sui, Y.; Li, G.; Ma, Z.; Yang, L. Sodium houttuynofonate: A review of its antimicrobial, anti-inflammatory and cardiovascular protective effects. *Eur. J. Pharmacol.* **2021**, *902*, 174110. [[CrossRef](#)]
205. Sekita, Y.; Murakami, K.; Yumoto, H.; Mizuguchi, H.; Amoh, T.; Ogino, S.; Matsuo, T.; Miyake, Y.; Fukui, H.; Kashiwada, Y. Anti-bacterial and anti-inflammatory effects of ethanol extract from *Houttuynia cordata* poultice. *Biosci. Biotechnol. Biochem.* **2016**, *80*, 1205–1213. [[CrossRef](#)]
206. Kim, G.S.; Kim, D.H.; Lim, J.J.; Lee, J.J.; Han, D.Y.; Lee, W.M.; Jung, W.C.; Min, W.G.; Gil Won, C.; Rhee, M.H.; et al. Biological and Antibacterial Activities of the Natural Herb *Houttuynia cordata* Water Extract against the Intracellular Bacterial Pathogen *Salmonella* within the RAW 264.7 Macrophage. *Biol. Pharm. Bull.* **2008**, *31*, 2012–2017. [[CrossRef](#)] [[PubMed](#)]
207. Lu, H.; Wu, X.; Liang, Y.; Zhang, J. Variation in Chemical Composition and Antibacterial Activities of Essential Oils from Two Species of *Houttuynia* THUNB. *Chem. Pharm. Bull.* **2006**, *54*, 936–940. [[CrossRef](#)] [[PubMed](#)]
208. Huo, J.; Deng, S.; Li, J. Preparation of Flavonoids of *Houttuynia cordata* Thunb. and the Antibacterial Mechanism on *Bacillus subtilis*. *J. Chin. Inst. Food Sci. Technol.* **2017**, *17*, 82–89. [[CrossRef](#)]
209. Cui, X.H.; Wang, L.; Li, Y.P.; Deng, S.L.; Li, T.Q.; Shang, H.C. Efficacy of *Houttuynia cordata* Injection for respiratory system diseases: A meta-analysis. *Chin. J. Evid. Based Med.* **2011**, *11*, 786–798.
210. Petronio Petronio, G.; Cutuli, M.A.; Magnifico, I.; Venditti, N.; Pietrangelo, L.; Vergalito, F.; Pane, A.; Scapagnini, G.; Di Marco, R. In Vitro and In Vivo Biological Activity of Berberine Chloride against Uropathogenic *E. coli* Strains Using *Galleria mellonella* as a Host Model. *Molecules* **2020**, *25*, 5010. [[CrossRef](#)] [[PubMed](#)]
211. Xu, C.; Wang, F.; Huang, F.; Yang, M.; He, D.; Deng, L. Targeting effect of berberine on type I fimbriae of *Salmonella Typhimurium* and its effective inhibition of biofilm. *Appl. Microbiol. Biotechnol.* **2021**, *105*, 1563–1573. [[CrossRef](#)]
212. Shi, C.; Li, M.; Muhammad, I.; Ma, X.; Chang, Y.; Li, R.; Li, C.; He, J.; Liu, F. Combination of berberine and ciprofloxacin reduces multi-resistant *Salmonella* strain biofilm formation by depressing mRNA expressions of luxS, rpoE, and ompR. *J. Veter. Sci.* **2018**, *19*, 808–816. [[CrossRef](#)] [[PubMed](#)]
213. Lin, Y.; Si, S.Y.; Jiang, J.D. Antibacterial activity of berberine. *Yaoxue Xuebao* **2018**, *53*, 163–168. [[CrossRef](#)]
214. Salari, R.; Rajabi, O.; Khashyarmansh, Z.; Najafi, M.F.; Bazzaz, B.S.F. Characterization of Encapsulated Berberine in Yeast Cells of *Saccharomyces cerevisiae*. *Iran. J. Pharm. Res. IJPR* **2015**, *14*, 1247–1256.
215. Salari, R.; Bazzaz, B.S.F.; Rajabi, O.; Khashyarmansh, Z. New aspects of *Saccharomyces cerevisiae* as a novel carrier for berberine. *DARU J. Pharm. Sci.* **2013**, *21*, 73. [[CrossRef](#)]
216. Kokoska, L.; Kloucek, P.; Leuner, O.; Novy, P. Plant-Derived Products as Antibacterial and Antifungal Agents in Human Health Care. *Curr. Med. Chem.* **2019**, *26*, 5501–5541. [[CrossRef](#)]
217. Chauhan, R.K.S.; Jain, A.M.; Bhandari, B. Berberine in the treatment of childhood diarrhoea. *Indian J. Pediatr.* **1970**, *37*, 577–579. [[CrossRef](#)]
218. Chauhan, R.K.S.; Jain, A.M.; Dube, M.K.; Bhandari, B. A combination of sulfadimidine, neomycin and berberine in the treatment of infectious diarrhoea. *Indian J. Pediatr.* **1969**, *36*, 242–244. [[CrossRef](#)]
219. Sharma, R.; Joshi, C.K.; Goyal, R.K. Berberine tannate in acute diarrhoea. *Indian Pediatr.* **1970**, *7*, 496–501.
220. Lahiri, S.C.; Dutta, N.K. Berberine and chloramphenicol in the treatment of cholera and severe diarrhoea. *J. Indian Med. Assoc.* **1967**, *48*, 1–11.
221. Khin Maung, U.; Myo, K.; Nyunt Nyunt, W.; Aye, K.; Tin, U. Clinical trial of berberine in acute watery diarrhoea. *Br. Med. J.* **1985**, *291*, 1601–1605. [[CrossRef](#)] [[PubMed](#)]

222. Koutsoudaki, C.; Krsek, M.; Rodger, A. Chemical Composition and Antibacterial Activity of the Essential Oil and the Gum of *Pistacia lentiscus* var. *chia*. *J. Agric. Food Chem.* **2005**, *53*, 7681–7685. [[CrossRef](#)] [[PubMed](#)]
223. Miyamoto, T.; Okimoto, T.; Kuwano, M. Chemical Composition of the Essential Oil of Mastic Gum and their Antibacterial Activity Against Drug-Resistant *Helicobacter pylori*. *Nat. Prod. Bioprospecting* **2014**, *4*, 227–231. [[CrossRef](#)] [[PubMed](#)]
224. Kottakis, F.; Lamari, F.; Matragkou, C.; Zachariadis, G.; Karamanos, N.; Choli-Papadopoulou, T. Arabino-Galactan Proteins from *Pistacia lentiscus* var. *chia*: Isolation, characterization and biological function. *Amino Acids* **2007**, *34*, 413–420. [[CrossRef](#)]
225. Al-Habbal, M.J.; Al-Habbal, Z.; Huwez, F.U. A double-blind controlled clinical trial of mastic and placebo in the treatment of duodenal ulcer. *Clin. Exp. Pharmacol. Physiol.* **1984**, *11*, 541–544. [[CrossRef](#)] [[PubMed](#)]
226. Dabos, K.; Sfika, E.; Vlatta, L.; Giannikopoulos, G. The effect of mastic gum on *Helicobacter pylori*: A randomized pilot study. *Phytomedicine* **2010**, *17*, 296–299. [[CrossRef](#)] [[PubMed](#)]
227. Kottakis, F.; Kouzi-Koliakou, K.; Pendas, S.; Kountouras, J.; Choli-Papadopoulou, T. Effects of mastic gum *Pistacia lentiscus* var. *Chia* on innate cellular immune effectors. *Eur. J. Gastroenterol. Hepatol.* **2009**, *21*, 143–149. [[CrossRef](#)] [[PubMed](#)]
228. Fukai, T.; Marumo, A.; Kaitou, K.; Kanda, T.; Terada, S.; Nomura, T. Anti-*Helicobacter pylori* flavonoids from licorice extract. *Life Sci.* **2002**, *71*, 1449–1463. [[CrossRef](#)]
229. Asha, M.K.; Debraj, D.; Prashanth, D.; Edwin, J.R.; Srikanth, H.; Muruganatham, N.; Dethe, S.; Anirban, B.; Jaya, B.; Deepak, M.; et al. In vitro anti-*Helicobacter pylori* activity of a flavonoid rich extract of *Glycyrrhiza glabra* and its probable mechanisms of action. *J. Ethnopharmacol.* **2013**, *145*, 581–586. [[CrossRef](#)]
230. Wittschier, N.; Fallner, G.; Hensel, A. Aqueous extracts and polysaccharides from Licorice roots (*Glycyrrhiza glabra* L.) inhibit adhesion of *Helicobacter pylori* to human gastric mucosa. *J. Ethnopharmacol.* **2009**, *125*, 218–223. [[CrossRef](#)]
231. Puram, S.; Suh, H.C.; Kim, S.U.; Bethapudi, B.; Joseph, J.A.; Agarwal, A.; Kudiganti, V. Effect of GutGard in the Management of *Helicobacter pylori*: A Randomized Double Blind Placebo Controlled Study. *Evid.-Based Complement. Altern. Med.* **2013**, *2013*, 263805. [[CrossRef](#)]
232. Bardhan, K.D.; Cumberland, D.C.; Dixon, R.A.; Holdsworth, C.D. Clinical trial of deglycyrrhizinised licorice in gastric ulcer. *Gut* **1978**, *19*, 779–782. [[CrossRef](#)]
233. Hollanders, D.; Green, G.; Woolf, I.L.; Boyes, B.E.; Wilson, R.Y.; Cowley, D.J.; Dymock, I.W. Prophylaxis with deglycyrrhizinised licorice in patients with healed gastric ulcer. *BMJ* **1978**, *1*, 148. [[CrossRef](#)]
234. Kato, T.; Iijima, H.; Ishihara, K.; Kaneko, T.; Hirai, K.; Naito, Y.; Okuda, K. Antibacterial effects of Listerine on oral bacteria. *Bull. Tokyo Dent. Coll.* **1990**, *31*, 301–307.
235. Sharma, N.C.; Charles, C.H.; Qaqish, J.G.; Galustians, H.J.; Zhao, Q.; Kumar, L.D. Comparative effectiveness of an essential oil mouthrinse and dental floss in controlling interproximal gingivitis and plaque. *Am. J. Dent.* **2002**, *15*, 351–355.
236. Charles, C.H.; Mostler, K.M.; Bartels, L.L.; Mankodi, S.M. Comparative antiplaque and antigingivitis effectiveness of a chlorhexidine and an essential oil mouthrinse: 6-month clinical trial. *J. Clin. Periodontol.* **2004**, *31*, 878–884. [[CrossRef](#)]
237. Sharma, N.C.; Araujo, M.W.B.; Wu, M.M.; Qaqish, J.; Charles, C.H. Superiority of an essential oil mouthrinse when compared with a 0.05% cetylpyridinium chloride containing mouthrinse: A six-month study. *Int. Dent. J.* **2010**, *60*, 175–180.
238. Singh, A.; Daing, A.; Dixit, J. The effect of herbal, essential oil and chlorhexidine mouthrinse on de novo plaque formation. *Int. J. Dent. Hyg.* **2012**, *11*, 48–52. [[CrossRef](#)] [[PubMed](#)]
239. Stoeken, J.E.; Paraskevas, S.; Van Der Weijden, G.A. The Long-Term Effect of a Mouthrinse Containing Essential Oils on Dental Plaque and Gingivitis: A Systematic Review. *J. Periodontol.* **2007**, *78*, 1218–1228. [[CrossRef](#)]
240. Kraivaphan, P.; Amornchat, C.; Maneepitsa, Y. Bactericidal Effects of Three Mint Essential Oils on *Porphyromonas gingivalis* in Planktonic and Biofilm Cells. *Res. J. Med. Plant* **2013**, *7*, 100–106. [[CrossRef](#)]
241. Renggli, H.H. The effect of Parodontax mouthwash and its constituents on the microorganisms of subgingival plaque. *J. Clin. Dent.* **1988**, *1*, A30–A33. [[PubMed](#)]
242. Arweiler, N.B.; Auschill, T.M.; Reich, E.; Netuschil, L. Substantivity of toothpaste slurries and their effect on reestablishment of the dental biofilm. *J. Clin. Periodontol.* **2002**, *29*, 615–621. [[CrossRef](#)] [[PubMed](#)]
243. Ozaki, F.; Pannuti, C.M.; Imbronito, A.V.; Pessotti, W.; Saraiva, L.; De Freitas, N.M.; Ferrari, G.; Cabral, V.N. Efficacy of a herbal toothpaste on patients with established gingivitis: A randomized controlled trial. *Braz. Oral Res.* **2006**, *20*, 172–177. [[CrossRef](#)]
244. Verkaik, M.J.; Busscher, H.J.; Jager, D.; Slomp, A.M.; Abbas, F.; van der Mei, H.C. Efficacy of natural antimicrobials in toothpaste formulations against oral biofilms in vitro. *J. Dent.* **2010**, *39*, 218–224. [[CrossRef](#)]
245. Paparoupa, M.; Gillissen, A. Is Myrtol® standardized a new alternative toward antibiotics? *Pharm. Rev.* **2016**, *10*, 143–146. [[CrossRef](#)]
246. Sengespeik, H.C.; Zimmermann, T.; Peiske, C.; De Mey, C. Myrtol standardized in the treatment of acute and chronic respiratory infections in children/A multicenter post-marketing surveillance study. *Arzneim.-Forsch. Drug Res.* **1998**, *48*, 990–994.
247. Meister, R.; Wittig, T.; Beuscher, N.; De Mey, C. Efficacy and tolerability of myrtol standardized in long-term treatment of chronic bronchitis: A double-blind, placebo-controlled study. *Arzneim. Drug Res.* **1999**, *49*, 351–358. [[CrossRef](#)]
248. Matthys, H.; De Mey, C.; Carls, C.; Rys, A.; Geib, A.; Wittig, T. Efficacy and tolerability of myrtol standardized in acute bronchitis: A multi-centre, randomised, double-blind, placebo-controlled parallel group clinical trial vs. cefuroxime and ambroxol. *Arzneim. Drug Res.* **2000**, *50*, 700–711. [[CrossRef](#)]
249. Bassett, I.B.; Barnetson, R.S.C.; Pannowitz, D.L. A comparative study of tea-tree oil versus benzoyl peroxide in the treatment of acne. *Med. J. Aust.* **1990**, *153*, 455–458. [[CrossRef](#)]

250. Jooya, A.; Siadat, A.H.; Iraj, F.; Enshaieh, S. The efficacy of 5% topical tea tree oil gel in mild to moderate acne vulgaris: A randomized, double-blind placebo-controlled study. *Indian J. Dermatol. Venereol. Leprol.* **2007**, *73*, 22–25. [[CrossRef](#)]
251. Dryden, M.; Dailly, S.; Crouch, M. A randomized, controlled trial of tea tree topical preparations versus a standard topical regimen for the clearance of MRSA colonization. *J. Hosp. Infect.* **2004**, *56*, 283–286. [[CrossRef](#)]
252. Blackwood, B.; Thompson, G.; McMullan, R.; Stevenson, M.; Riley, T.V.; Alderdice, F.A.; Trinder, T.J.; Lavery, G.G.; McAiley, D.F. Tea tree oil (5%) body wash versus standard care (johnson's baby softwash) to prevent colonization with methicillin-resistant staphylococcus aureus in critically ill adults: A randomized controlled trial. *J. Antimicrob. Chemother.* **2013**, *68*, 1193–1199. [[CrossRef](#)]
253. Tong, M.M.; Altman, P.M.; Barnetson, R.S. Tea tree oil in the treatment of tinea pedis. *Australas. J. Dermatol.* **1992**, *33*, 145–149. [[CrossRef](#)]