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Review

Preventing Microbial Infections with Natural Phenolic Compounds

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Abstract: The struggle between humans and pathogens has taken and is continuing to take countless lives every year. As the misusage of conventional antibiotics increases, the complexity associated with the resistance mechanisms of pathogens has been evolving into gradually more clever mechanisms, diminishing the effectiveness of antibiotics. Hence, there is a growing interest in discovering novel and reliable therapeutics able to struggle with the infection, circumvent the resistance and defend the natural microbiome. In this regard, nature-derived phenolic compounds are gaining considerable attention due to their potential safety and therapeutic effect. Phenolic compounds comprise numerous and widely distributed groups with different biological activities attributed mainly to their structure. Investigations have revealed that phenolic compounds from natural sources exhibit potent antimicrobial activity against various clinically relevant pathogens associated with microbial infection and sensitize multi-drug resistance strains to bactericidal or bacteriostatic antibiotics. This review outlines the current knowledge about the antimicrobial activity of phenolic compounds from various natural sources, with a particular focus on the structure-activity relationship and mechanisms of actions of each class of natural phenolic compounds, including simple phenols, phenolic acids, coumarin, flavonoids, tannins, stilbenes, lignans, quinones, and curcuminoids.

Keywords: microbiota; multidrug resistance; alternative therapeutics; natural compounds; phenolic compounds; structure-function

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1. Introduction

The enthusiasm of antimicrobial discovery has sustained a defeat by the growing resistance of bacterial strains by virtue of the over usage and maladministration of antibiotics for decades [1,2]. Antibiotic resistance stands as an increasing public health concern that causes nearly 50,000 deaths annually across Europe and the US [3]. Additionally, according to United Nations Foundation, in the upcoming years, the scenario may pose dramatic consequences to human health worldwide. Thus, considerable efforts have been devoted to creating novel antimicrobial agents able to combat microbial infections and also overcome the antibiotic resistance reported for nearly every antibiotic used in clinical practice [4]. Besides the fabrication of new antibiotics, which is time-consuming, novel alternative therapeutic strategies are required to turn the tide in this battle as new resistance will arise, and there are no treatments on the horizon for particular infections. Therefore, antibiotic-resistance breakers are urgently needed to fill the void in the development of novel antibiotics [5]. To achieve this, priority antibiotics and bacteria must be clearly identified, along with an extensive survey to recognize and categorize potential resistance breakers for diverse bacterial species and strains. Nevertheless, it is undoubtful that the key feature to this challenge must surely be beyond the simple development of innovative drugs and also include a multidisciplinary culture of change [3].

Antibiotics and/or antimicrobial agents treat infections by affecting the growth or viability of microbial cells. Bactericidal compounds induce bacterial cell death via inhibiting cell wall synthesis, cell membrane function, or protein/enzyme synthesis, whereas bacteriostatic compounds suppress bacterial cellular activity and growth [6]. The concept of bactericidal and bacteriostatic outlines the indications, mechanisms, and contraindications of antimicrobial agents [7]. Nevertheless, over time, microbial species such as bacteria and fungi developed the ability to defeat the mechanisms of conventional antibiotics being designed to kill them. The mechanisms by which microbial pathogens acquire resistance to antibiotics can be summarized as follows: (i) changing the cellular permeability to inhibit the entrance of antibiotics into the microbial cells, (ii) changing the molecular targets of antibiotics so that they are no longer active (iii) enzymatic modification of antibiotics to make them nonfunctioning, and (iv) expression of efflux pumps to pump out antibiotics from the cell [8]. At this point, natural-based compounds have the ability to interact with the microbial cell through multiple antimicrobial mechanisms, making them a top-interest candidate in combating microbial infections and preventing the emergence of drug-resistant strains [9,10]. In the scope of this view, this review will be concentrated on the potential efficiency of natural phenolic compounds to prevent microbial infections owing to their remarkable features.

This review provides an in-depth survey of the up-to-date knowledge of a broad assortment of natural phenolic compounds as possible alternatives for antibiotics. For each class, the antimicrobial mechanism and structure-activity relationship of potential antimicrobial agent candidates from natural sources will be highlighted with a particular focus. In addition, a detailed list and description of the prominent and studied natural phenolic compounds with potential against clinically relevant pathogens will be specified, which may serve different research dedicated to discovering and resupplying these natural compounds with active antimicrobial properties. Lastly, we will also address the main hurdles, future prospects, and issues to overcome.

2. Natural Phenolic Compounds against Microbes

Phenolic compounds are molecules with at least one phenol unit that can be obtained from bacteria, fungi, and marine organisms, but mostly from plants [11,12]. Based on their chemical structure, phenolic compounds are subdivided into diverse subcategories, including simple phenols, phenolic acids, coumarins, flavonoids, tannins, stilbenes, lignans, quinones, and curcuminoids [13,14]. Natural phenolic compounds exhibit broad-range biological activities, including antibacterial, antifungal, anti-inflammatory, antiviral, hepatoprotective, antithrombotic, anticarcinogenic, antiallergic, and antioxidant actions [12,15–22]. Therefore, phenolics are considered potential therapeutic agents against diabetes, cancer, cardiovascular dysfunctions, neurodegenerative diseases, inflammatory diseases, and anti-aging [23,24]. A summarized catalogue of phenolics and polyphenolics compounds with antimicrobial properties against a wide panel of microorganisms is disclosed in Table 1.

2.1. Simple Phenols and Phenolic Acids

Simple phenols are described as compounds presenting an aromatic ring with one or more hydroxyl groups attached [25]. Representative examples of simple phenols include catechol, hydroquinone, resorcinol, and phloroglucinol, as illustrated in Figure 1 [26]. Although these compounds are hardly found alone in plants, they usually appear joint with either cinnamic acids or benzoic acid [25,27]. The main benefit of phenolic acids is their metabolizing capability by natural microbes [27]. Phenolic acids encompass a carboxylic acid linked to an aromatic compound, a phenol [28]. According to their structure, phenolic acids comprise two key classes, including benzoic acid and cinnamic acid derivatives [29]. Hydroxycinnamic acids are common phenolic acids within plant species and are generally derived from cinnamic acid [30]. These natural compounds can be found as their esters, glycosides, and/or conjugated with proteins [31,32]. The utmost common hydroxycinnamic acids derivatives are caffeic acid, ferulic acid, and coumaric acid, as shown in their chemical

structure in Figure 1 [25]. Hydroxybenzoic acid (HBA) derivatives are phenolic compounds with a basic structure of C_6-C_1. Although HBAs can be identified as free acids, they mainly occur in conjugated form, generally as esters [33]. The basic skeleton structure of benzoic acid and the chemical structure of some representative examples of benzoic acid derivatives isolated from natural sources are shown in Figure 1.

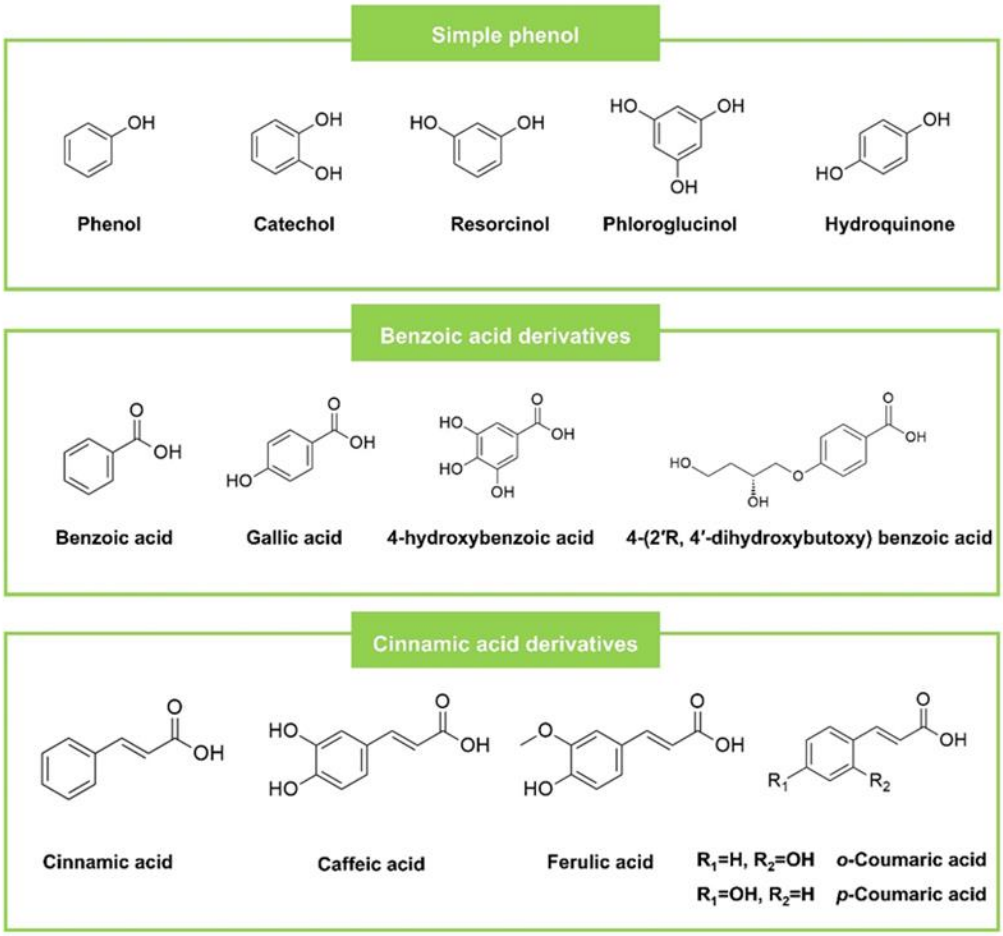

Figure 1. Representative chemical structures of simple phenol, benzoic acid derivatives and cinnamic acid derivatives.

As previously mentioned, even though phenolic acids and their derivatives are widely isolated from the plant kingdom, recent investigations indicated their presence in other sources, including marine-derived microorganisms, plant-derived endophytic fungus, marine organisms, and bacterium species [34–37]. Several studies have been conducted to emphasize the importance of phenolic compounds in the ability to develop resistance in multidrug-resistant bacteria. As a representative example, two phenolic acids (vanillic acid as a hydroxybenzoic acid derivative and 2-Hydroxycinnamic acid as a hydroxycinnamic acid derivative) and an antibiotic (Vancomycin) were exposed continuously to Methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteria. The resistance ability was assessed by ascertaining the MIC values of the tested compounds before, during, and after exposure of MRSA and MSSA bacteria to sub-inhibitory concentrations of these compounds. These data demonstrated that MRSA and MSSA did not acquire resistance to both vanillic acid and 2-hydroxycinnamic acid; by contrast, vancomycin caused the acquisition of resistance of both strains [38]. In another study, benzoic acid, purified from the endophytic fungus strain Neurospora crassa, displayed prominent antimicrobial activity against six different multidrug-resistant (MDR) clinical pathogens (see Table 1) and also confirmed its nontoxicity [39]. These findings indicate the promising aspect of phenolic acids in preventing the emergence of new resistant

bacterial strains and combating with the MDR pathogens. On the other hand, a clinical study on *Staphylococcus aureus* (*S. aureus*) strains documented that caffeic acid exhibited a promising antibacterial effect with the MICs ranging between 256 μg/mL and 1024 μg/mL against reference strains and clinical isolates of MRSA and MSSA from infected wounds. In addition, the study verified that the combination of caffeic acid with the antibiotics (erythromycin, clindamycin, and cefoxitin) tested caused synergistic activity by sensitizing the bactericidal and bacteriostatic action of antibiotics. It should be noted that the combination of caffeic acid with vancomycin did not show a prominent difference [40].

Research towards comprehending antibacterial mechanisms functioning at the molecular level with the purpose of exploiting these bioactive compounds in clinical settings has also advanced. To date, many studies have documented that phenolic acids and their derivatives show antimicrobial effects through bactericidal actions. This can be explained mainly by the fact that phenolic acids are weak organic acids whose lipophilicity differs from each other. The dissociation constant and lipophilicity affect the solubility of the compounds in microbial membranes and, thus, their antimicrobial activity [41]. Usually, the undissociated forms of the phenolic acids cross the cell membrane through passive diffusion, acidifying the cytoplasm by disrupting the cell membrane, causing the outflow of essential intracellular constituents and resulting in microbial cell death [41–43]. Moreover, Lou et al. [44] also assessed the antibacterial activity of *p*-coumaric acid, where it was discovered that *p*-coumaric acid triggered the death of bacterial cells by two main mechanisms, disruption of the microbial cell membrane and/or binding to the microbial genomic DNA. Another study considering the relationship between pH and bacterial growth of phenolic acids, including chlorogenic acid and the hydroxycinnamic acids, caffeic acid, *p*-coumaric acid, and ferulic acid, reported that all tested hydroxycinnamic acids had a bactericidal effect at pH 4.5 and bacteriostatic effect at higher pH against *Listeria Monocytogenes (L. monocytogenes)* [45]. However, further studies on their action mechanisms are needed to prove the existence of possible bacteriostatic effects.

The antimicrobial actions of phenolic acids depend on the chain length, and number and position of substituents on the core benzene ring [46]. The antibacterial behavior of caffeic acid alkyl esters tends to increase with the increase in alkyl chain length. However, in the presence of a long alkyl chain, their antimicrobial activity diminishes due to the possible steric hindrance [47,48]. As mentioned earlier, due to their partly lipophilic character, the ability of these compounds to acidify the cytoplasm by passing through the cell membrane by passive diffusion depends on the number of hydroxyls (–OH), methoxy ($–OCH_3$), carboxyl (−COOH), functional groups and saturation of alkyl side chain [27,43].

2.2. Coumarin

Coumarin (1-benzopyran-2-one) derivatives are chemical compounds of the benzopyrone class, comprised of fused benzene and α-pyrone rings, that can be discovered in bacteria, fungi, and plants [140]. Coumarin is poorly water-soluble; however, thanks to its 4-hydroxy substitution, the compound is water-soluble in slightly alkali conditions [141]. To date, over 1300 coumarin types have been described and obtained through plant extraction or microbial synthesis [142,143]. Natural coumarins can be categorized into four primary classes, including simple coumarins, pyrano coumarins, furanocoumarins, and bicoumarins (dicoumarin), as illustrated in Figure 2 [144,145]. These compounds are mostly isolated from plants, nonetheless, some of them can also be produced by microorganisms [146]. The most prominent coumarin members obtained by microbial sources are novobiocin, clorobiocin, and coumermycin from *Streptomyces* species. Novobiocin, coumermycin A1 and chlorobiocin are amino-coumarin antibiotics with an antibacterial mechanism of action based on bacteriostatic action through the bacterial DNA gyrase inhibition [147,148]. Novobiocin was confirmed as an effective antibiotic for the handling of infections triggered by multiple resistant Gram-positive bacteria, specifically *Staphylococcus epidermidis* (*S. epidermidis*) and *S. aureus* [149].

Table 1. Minimum inhibitory concentration (μg/mL) of phenolic and polyphenolic compounds against different pathogenic microorganisms.

Secondary Metabolite Class	Subclasses	Compound	Source	Microorganism			Positive Control			Ref.
				Gram-Positive Bacteria	Gram-Negative Bacteria	Fungi	Gram-Positive Bacteria	Gram- Negative Bacteria	Fungi	
Phenolic acids	Benzoic acid derivatives	Benzoic acid	*Neurospora crassa* (Microorganism)	*SA* [a] (587)	*EC* [a] (274), *PA* [a] (302)	*CA* [a] (347), *AN* [a] (570)	Streptomycin *SA* [a] (44), *EC* [a] (210), *PA* [a] (210)		Ketoconazole *CA* [a] (200), *AN* [a] (200)	[39]
		Gallic acid	*Caesalpinia mimosoides* Lamk (Plant)	*SA* (1250)			Streptomycin *SA* (0.16)			[49]
			Diospyros virginiana L. (Plant)	*LM* (40), *SA* (10), *BC* [c] (25)	*EC* (40), *ST* (10), *PA* (25)	*AN* (30), *AV* (10), *AF* (25)	Streptomycin *LM* (150), *SA* (250), *BC* [c] (50),	Streptomycin *EC* (100), *ST* (50), *PA* (50)	Ketoconazole *AN* (200), *AV* (200), *AF* (200)	[50]
			Mezoneuron benthamianum (Plant)	*SA* [c] (100)	*EC* [c] (25), *PA* [c] (100)		-	-		[51]
		4- Hydroxybenzoic acid	*Ganoderma lucidum* (Plant)	*LM* (30), *SA* (3), *BC* (3)	*EC* (30), *ST* (3), *PA* (3)	*AN* (30), *AV* (3), *AF* [c] (120)	Streptomycin *LM* (170), *SA* (40), *BC* (90)	Streptomycin *EC* (170), *ST* (170), *PA* (170)	Ketoconazole *AN* (200), *AV* (200), *AF* [c] (200)	[52]
		4-(2′R, 4′-dihydroxybutoxy) benzoic acid	*Penicillium* sp. of *Nerium indicum* (Microorganism)		*EC* (125), *PA* (125)			Streptomycin sulfate *EC* (7.81), *PA* (7.81)		[53]
		Vanillic acid	*Stenoloma chusanum* (Plant)			*CA* (50), *AN* (100), *TR* (50)			-	[54]
	Cinnamic acid derivatives	Cinnamic acid	*Ganoderma lucidum* (Plant)	*LM* (7), *SA* (1.5), *BC* (1.5)	*EC* (7), *ST* (1.5), *PA* (0.7)	*AN* (30), *AV* (7), *AF* (7)	Streptomycin *LM* (170), *SA* (40), *BC* (90)	Streptomycin *EC* (170), *ST* (170), *PA* (170)	Ketoconazole *AN* (200), *AV* (200), *AF* (200)	[52]
		Caffeic acid	*Nauclea latifolia leaf* (Plant)	*SA* (5000)	*EC* (625), *PA* (2500)		Streptomycin *SA* (125)	Streptomycin *EC* (125), *PA* (500)		[55]
		p-Coumaric acid	*Stereospermum zenkeri* (Plant)	*SA* [a] (37.50)			Ampicillin *SA* [a] (0.80)			[56]
		trans-*o*-coumaric acid	*Distichochlamys benenica* (Plant)	*SA* (249.5)	*EC* (1001.4), *PA* (1001.4)		Ciprofloxacin *SA* (0.215)	Ciprofloxacin *EC* (0.013), *PA* (0.013)		[57]

Table 1. *Cont.*

Secondary Metabolite Class	Subclasses	Compound	Source	Microorganism			Positive Control			Ref.
				Gram-Positive Bacteria	Gram-Negative Bacteria	Fungi	Gram-Positive Bacteria	Gram- Negative Bacteria	Fungi	
Coumarins	Simple coumarins	Umbelliferone	*Loeselia Mexicana* (Plant)			*CA* (50), *TR* (25)			Nystatin *CA* (8), *TR* (-) Miconazole *CA* (-), *TR* (4)	[58]
			Ferulago Species (Plant)	*SA* (250)	*EC* (500), *PA* (250)	*CA* (125)	Streptomycin *SA* (6.25)	Streptomycin *EC* (25), *PA* (25)	Ketoconazole *CA* (25) Miconazole *CA* (3)	[59]
		Osthol	*Magydaris tomentosa* (Plant)	*SA* (64), *SE* (32)	*EC* (256), *PA* (128)		Cefotaxime *SA* (2), *SE* (0.1)	Cefotaxime *EC* (0.1), *PA* (1.6)		[60]
			Prangos hulusii (Plant)	*SA* (125), *MRSA* [c] (16)			Cefotaxime *SA* (2), *MRSA* [c] (16)			[61]
			Prangos pabularia (Plant)	*MRSA* (31.25)	*PA* (31.25)		-	-		[62]
			Ferulago Species (Plant)	*SA* (500)	*EC* (500), *PA* (250)	*CA* (500)	Streptomycin *SA* (6.25)	Streptomycin *EC* (25), *PA* (25)	Ketoconazole *CA* (25) Miconazole *CA* (3)	[59]
		Novobiocin	*Nocardiopsis gilva* (Microorganism)	*SA* (64)			Kanamycin *SA* (4)			[63]
			Streptomyces strain (Microorganism)	*MRSA* (0.25)			-			[64]
		Ulopterol	*Toddalia asiatica* (L.) Lam. (Plant)	*SA* (125), *MRSA* [c] (250), *SE* (15.6)	*EC* [c] (62.5–250), *ST* (125), *SF* (62.5), *PA* (125)	*CA* (250), *AF* (15.6), *TR* (250)	Streptomycin *SA* (6.25), *MRSA* [c] (6.25), *SE* (25)	Streptomycin *EC* [c] (25), *ST* (30), *SF* (6.25), *PA* (25)	Ketoconazole *CA* (25), *AF* (<12.5), *TR* (<12.5)	[65]
			Ferulago Species (Plant)	*SA* (500)	*EC* (500), *PA* (500)	*CA* (250)	Streptomycin *SA* (6.25)	Streptomycin *EC* (25), *PA* (25)	Ketoconazole *CA* (25) Miconazole *CA* (3)	[59]

Table 1. *Cont.*

Secondary Metabolite Class	Subclasses	Compound	Source	Microorganism			Positive Control			Ref.
				Gram-Positive Bacteria	Gram-Negative Bacteria	Fungi	Gram-Positive Bacteria	Gram- Negative Bacteria	Fungi	
	Furanocoumarins	Peucedanin	*Peucedanum luxurians* (Plant)	*SA* (1500), *SE* (1750)	*EC* (2750), *PA* (1400)		Netilmicin *SA* (4), *SE* (4)	Netilmicin *EC* (10), *PA* (88)		[66]
		Oxypeucedanin hydrate	*Angelica pancicii Vandas* (Apiaceae) (Plant)	*LM* (1000), *SA* (1000)	*EC* (1000), *ST* (1000), *PA* (1000)		Streptomycin *LM* (170), *SA* (40)	Streptomycin *EC* (170), *ST* (170), *PA* (170)		[67]
			Angelica lucida (Plant)	*SA* (650), *SE* (600)	*EC* (650), *PA* (810)		Netilmicin *SA* (4), *SE* (4)	Netilmicin *EC* (10), *PA* (3)		[68]
		(R)-(+) oxypeucedanin hydrate	*Ficus exasperata* (Plant)	*MRSA* [c] (78.12), *BC* [c] (9.76)	*EC* [b,c] (39.06), *PA* [b,c] (156.25)	*CA* [c] (39.06)	Gentamicin *MRSA* [c] (4.88), *BC* [c] (4.88)	Gentamicin *EC* [b,c] (4.88), *PA* [b,c] (9.76)	Nystatin *CA* [c] (19.53)	[69]
		Imperatorin	*Heracleum mantegazzianum Sommier* and *Levier* (Apiaceae) (Plant)	*SA* (250–1000), *BC* (500), *SE* (1000)	*EC* (1000), *ST* (1000), *PA* (1000)	*CA* (250)	-	-	-	[70]
			Magydaris tomentosa (Plant)	*SA* (32), *SE* (32)	*EC* (32), *PA* (64)		Cefotaxime *SA* (2), *SE* (0.1)	Cefotaxime *EC* (0.1), *PA* (1.6)		[60]
			Angelica lucida (Plant)	*SA* (45), *SE* (35)	*EC* (25), *PA* (70)		Netilmicin *SA* (4), *SE* (4)	Netilmicin *EC* (10), *PA* (3)		[68]
			Prangos pabularia (Plant)	*MRSA* (62.5)	*PA* (65.5)		-	-		[62]
		5-methoxy-3-(3-methyl-2,3-Dihydroxybutyl) psoralen	*Dorstenia turbinata* (Plant)	*MRSA* [c] (39.06)	*EC* [b,c] (78.12), *PA* [b,c] (39.06)	*CA* [c] (19.53), *CG* [c] (39.06), *TR* [c] (9.76)	Gentamycin *MRSA* [c] (9.76)	Gentamycin *EC* [b,c] (4.88), *PA* [b,c] (9.76)	Nystatin *CA* [c] (19.53)	[71]
	Pyrano coumarins	Agasyllin	*Ferulago campestris* (Plant)	*SA* [a,c] (64)	*PA* [a,c] (125)	-	Cefotaxime *SA* [a,c] (resistant)	Cefotaxime *PA* [a,c] (32)		[72]
			Zosima absinthifolia (Plant)	*SA* (5000)	*EC* (5000)		Gentamycin *SA* (8)	Gentamycin *EC* (8)		[73]
	Bi-coumarin (Dicoumarin)	Daphnoretin	*Loeselia mexicana* (Plant)			*CA* (50), *TR* (25), *AN* (100)			Nystatin *CA* (8), *TR* (-) *AN* (-) Miconazole *CA* (-), *TR* (4) *AN* (8)	[58]

Table 1. *Cont.*

Secondary Metabolite Class	Subclasses	Compound	Source	Microorganism			Positive Control			Ref.
				Gram-Positive Bacteria	Gram-Negative Bacteria	Fungi	Gram-Positive Bacteria	Gram- Negative Bacteria	Fungi	
Flavonoids	Flavonols	Myricetin	*Diospyros virginiana* L. (Plant)	*LM* (10), *SA* (5), *BC* [c] (2.5)	*EC* (15), *ST* (15), *PA* (150)	*AN* (5), *AV* (2.5), *AF* (2.5)	Streptomycin *LM* (150), *SA* (250), *BC* [c] (50)	Streptomycin *EC* (100), *ST* (50), *PA* (50)	Ketoconazole *AN* (200), *AV* (200), *AF* (200)	[50]
		Quercetin	*Diospyros virginiana* L. (Plant)	*LM* (10), *SA* (1), *BC* [c] (2.5)	*EC* (15), *ST* (15), *PA* (200)	*AN* (5), *AV* (2.5), *AF* (2.5)	Streptomycin *LM* (150), *SA* (250), *BC* [c] (50)	Streptomycin *EC* (100), *ST* (50), *PA* (50)	Ketoconazole *AN* (200), *AV* (200), *AF* (200)	[50]
			Nauclea latifolia (Plant)	*SA* (156)	*EC* (2500), *PA* (1250)		Streptomycin *SA* (125)	Streptomycin *EC* (125), *PA* (500)		[55]
			Euphorbia schimperiana (Plant)	*LM* (450), *SA* (420), *BC* (430)	*EC* (430), *PA* (420)		-	-		[74]
			Macaranga conglomerate (Plant)	*SA* (500)	*EC* (500), *PA* (500)		Ciprofloxacin *SA* (15.6)	Ciprofloxacin *EC* (1.0), *PA* (15.6)		[75]
			Monanthotaxis littoralis (Plant)	*SA* (16)	*EC* (16), *PA* (16)	*CA* (16), *CN* (8)	Vancomycin *SA* (0.5)	Vancomycin *EC* (32), *PA* (16)	Fluconazole *CA* (1.0), *CN* (2.0)	[76]
	Flavones	6,7,4′-trimethyl flavone	*Wulfenia amherstiana* (Plant)	*SA* (127.06–128.94)	*PA* (510.98–513.02)	*CA* (127.37–128.63), *CG* (255.18–256.82), *FS* (511.02–512.98)	-	-	-	[77]
		Luteolin	*Diospyros virginiana* L. (Plant)	*LM* (1.5), *SA* (1.5), *BC* [c] (2.5)	*EC* (15), *ST* (20), *PA* (200)	*AN* (10), *AV* (5), *AF* (2.5)	Streptomycin *LM* (150), *SA* (250), *BC* [c] (50)	Streptomycin *EC* (100), *ST* (50), *PA* (50)	Ketoconazole *AN* (200), *AV* (200), *AF* (200)	[50]
	Flavanols (Flavan-3-ols)	(+)-Catechin-3′-O-rhamnopyranoside	*Neocarya macrophylla* (Sabine) *Prance* (Chrysobalanaceae) (Plant)	*SA* [c] (25)	*PA* [c] (25), *EC* [c] (25)	*CA* [c] (6.25)	-	-	-	[78]
		(−)-Catechin	*Prunus avium* L. (Plant)	*LM* (100), *SA* [a] (100), *BC* [a] (100)	*EC* (100)		-	-		[79]

Table 1. *Cont.*

Secondary Metabolite Class	Subclasses	Compound	Source	Microorganism			Positive Control			Ref.
				Gram-Positive Bacteria	Gram-Negative Bacteria	Fungi	Gram-Positive Bacteria	Gram- Negative Bacteria	Fungi	
	Isoflavones	Myrsininone A	*Ficus auriculata* (Plant)	*BC* (2.03), *SE* (0.51)	*EC* (2.03), *PA* (4.06)		Streptomycin sulfate *BC* (0.23), *SE* (0.23)	Streptomycin sulfate *EC* (0.45), *PA* (0.45)		[80]
		Daidzein	*Spatholobus parviflorus* (Plant)	*BC* (64)	*PA* (128)		Vancomycin *BC* (0.25)	Gentamycin *PA* (1.0)		[81]
		Lupalbigenin	*Maclura cochinchinensis* (Lour.) Corner (Plant)	*SA* (1), *MRSA* (1)		*CA* (4)	Vancomycin *SA* (0.5), *MRSA* (1.0)		Ampicillin *CA* (0.25)	[82]
	Flavanones	Lupinifolin	*Derris reticulata* Craib (Plant)	*SA* (12.5), *BC* (12.5), *SE* (25)			Penicillin G *SA* (0.05), *BC* (ND), *SE* (0.05)			[83]
		7-O-(2,2-dimethylallyl)-aromadendrin	*Maclura cochinchinensis* (Lour.) Corner (Plant)	*SA* (32), *MRSA* (32)		*CA* (64)	Vancomycin *SA* (0.5), *MRSA* (1.0)		Ampicillin *CA* (0.25)	[82]
Tannins	Gallotannins	Penta-O-galloylglucose	*Rhus trichocarpa* Miquel (Plant)	*SA* (64–128), *MRSA* (64–128), *BC* (32), *SE* (32)		*CA* (64)	Vancomycin *SA* (0.25–1), *MRSA* (0.25–1), *BC* (>64), *SE* (1)		Vancomycin *CA* (32)	[84]
	Ellagitannins	Punicalagin	*Punica granatum* L. (Plant)	*SA* (0.6), *SE* (0.6)	*EC* (1.2), *PA* (0.6)	*CA* (1.2)	-	-	-	[85]
		3,3′-di-O-methylellagic acid	*Euphorbia schimperiana* (Plant)	*LM* (450), *SA* (450), *BC* (450)	*EC* (450), *PA* (430)		-	-		[74]
		Isorugosins B	*Liquidambar formosana* (Plant)	*MRSA* (32.46–63.96)			Oxacillin (128.05–256.1)			[86]
		Vescalagin	Cork (Plant)	*SA* (500), *MRSA* (125)	*PA* (1000)		-		-	[87]
		Castalagin					-		-	
	Condensed tannins	A type-proanthocyanidin	*Quercus ilex* (Plant)	*LM* (100.72), *SA* (100.72), *BC* [c] (100.72)	*EC* (100.72), *ST* (100.72), *PA* (100.72)	*AN* (100.72), *AF* (100.72), *AV* (100.72)	Streptomycin *LM* (150.04), *SA* (100.03), *BC* [c] (25.01)	Streptomycin *EC* (100.03), *ST* (100.03), *PA* (100.03)	Ketoconazole *AN* (201.94), *AF* (201.94), *AV* (201.94)	[88]
	Phlorotannins	Fucofuroeckol-A	*Eisenia bicyclis* (Marine algae)			*CA* [b,c] (512)			Fluconazole *CA* [b,c] (512–8197)	[89]
		Dieckol	*Ecklonia stolonifera* (Marine algae)	*MRSA* [a,c] (64–128)	*EC* (256), *ST* (256), *SF* (256)		Ampicillin *MRSA* [a,c] (128–512)	Vancomycin *EC* (512), *ST* (512), *SF* (256)		[90]

Table 1. *Cont.*

Secondary Metabolite Class	Subclasses	Compound	Source	Microorganism			Positive Control			Ref.
				Gram-Positive Bacteria	Gram-Negative Bacteria	Fungi	Gram-Positive Bacteria	Gram- Negative Bacteria	Fungi	
Stilbenes	Stilbene Monomers	Resveratrol	*Mezoneuron benthamianum* (Plant)	*SA* [c] (25)	*EC* [c] (25), *PA* [c] (25), *PA* (200)		-	-		[51]
			Nauclea pobeguiinii (Plant)		*EC* [b,c] (32–128), *PA* [a,c] (256)			Chloramphenicol *EC* [b,c] (64), *PA* [a,c] (256)		[91]
			Gnetum gnemon L. (Plant)		*EC* (>3000)	SC (2000)		-	-	[92]
			Bacillus sp. N strain (Microorganism)	*SA* (32)	*EC* (32), *PA* (64)	CA (64)	Ciprofloxacin *SA* (5) Cefotaxime *SA* (250)	Ciprofloxacin *EC* (5), *PA* (10) Cefotaxime *EC* (100), *PA* (500)	Amphotericin B *CA* (50)	[93]
		Piceatannol	*Mezoneuron benthamianum* (Plant)	*SA* [c] (25)	*EC* [c] (25), *PA* [c] (300),		-	-		[51]
			Spirotropis longifolia (Plant)			*CA* [c] (2), *CG* [c] (4), *TR* [c] (8)			Fluconazole *CA* [c] (>64), *CG* [c] (8), *TR* [c] (2)	[94]
		Pterostilbene	Commercial Product	*LM* (64), *SA* (4), *BC* (16)	*EC* (512), *PA* (512)		Chlorhexidine *LM* (8), *SA* (32), *BC* (8)	Chlorhexidine *EC* (32), *PA* (32)		[95]
		Oxyresveratrol	*Spirotropis longifolia* (Plant)			*CA* [c] (>64), *CG* [c] (8), *TR* [c] (16)			Fluconazole *CA* [c] (>64), *CG* [c] (8), *TR* [c] (2)	[94]
			Morus alba L. (Plant)			*TR* (500)			Miconazole nitrat *TR* (1)	[96]
		Chiricanine A	*Arachis hypogaea* (Plant)	*MRSA* (12.5)			-			[97]
		3,5-Dihydroxy-4-isopropylstilbene	*Bacillus* sp. N strain (Microorganism)	*SA* (8)	*EC* (>1000), *PA* (>1000)	*CA* (24)	Ciprofloxacin *SA* (5) Cefotaxime *SA* (250)	Ciprofloxacin *EC* (5), *PA* (10) Cefotaxime *EC* (100), *PA* (500)	Amphotericin B *CA* (50)	[93]

Table 1. *Cont.*

Secondary Metabolite Class	Subclasses	Compound	Source	Microorganism			Positive Control			Ref.
				Gram-Positive Bacteria	Gram-Negative Bacteria	Fungi	Gram-Positive Bacteria	Gram- Negative Bacteria	Fungi	
			Photorhabdus luminescens (Microorganism)			*CN* (12), *AF* (12)			-	[98]
	Stilbene Dimers	Monalittorin	Monanthotaxis littoralis (Plant)	*SA* (64)	*EC* (65), *PA* (64)	*CA* (16), *CN* (16),	Vancomycin *SA* (0.5)	Vancomycin *EC* (32), *PA* (16)	Fluconazole *CA* (1.0), *CN* (2.0)	[76]
		Gnetin D	*Spirotropis longifolia* (Plant)			*CA* [c] (64), *CG* [c] (32), *TR* [c] (8)			Fluconazole *CA* [c] (>64), *CG* [c] (8), *TR* [c] (2)	[94]
		Gnetin C	*Gnetum gnemon* L. (Plant)		*EC* (1000)	*SC* (500)		-	-	[92]
		Longistylin A	*Cajanus cajan* (Plant)	*SA* (1.56), *BC* (25), *MRSA* (1.56)	*EC* (>100)		Vancomycin *SA* (1.56), *BC* (50), *MRSA* (0.78)	Vancomycin *EC* (50)		[99]
		Monalittorin	*Monanthotaxis littoralis* (Plant)	*SA* (64)	*EC* (64), *PA* (64)	*CA* (16), *CN* (16)	Vancomycin *SA* (0.5)	Vancomycin *EC* (32), *PA* (16)	Fluconazole *CA* (1.0), *CN* (2.0)	[76]
	Stilbene Oligomers	Rockiol A and Rockiol B	*Paeonia rockii* (Plant)	*SA* (25)	*EC* (200), *PA* (200)		Penicillin G *SA* (10)	Penicillin G *EC* (20), *PA* (10)		[100]
		Upunaphenol D	*Dryobalanops lanceolata* (Plant)	*SA* (45.3), *SE* (22.7)	*EC* (>906.9), *ST* (>906.9), *SF* (453.4)		Chloramphenicol *SA* (0.008), *SE* (0.008)	Chloramphenicol *EC* (323.132), *ST* (323.132), *SF* (0.010)		[101]
		Heyneanol A	*Vitis thunbergii* var. *taiwaniana* (Plant)	*SA* (2), *MRSA* (2)			Vancomycin *SA* (1), *MRSA* (1) Oxacillin *SA* (2), *MRSA* (64–128)			[102]

Table 1. *Cont.*

Secondary Metabolite Class	Subclasses	Compound	Source	Microorganism			Positive Control			Ref.
				Gram-Positive Bacteria	Gram-Negative Bacteria	Fungi	Gram-Positive Bacteria	Gram- Negative Bacteria	Fungi	
Lignans	Tetrahydrofuran Lignans	Matairesinol	*Centaurea scabiosa* (Plant)	*SA* (10), *MRSA* (1000), *SE* (10)	*EC* (10), *PA* (10)		Ciprofloxacin *SA* (2.5×10^{-4}), *MRSA* (2.5×10^{-4}), *SE* (2.5×10^{-5})	Ciprofloxacin *EC* (2.5×10^{-4}), *PA* (0.0025)		[103]
			Centaurea raphanina ssp. *Mixta* (Plant)			*AN* (100), *AV* (100)			Miconazole *AN* (1.5), *AV* (2)	[104]
		Lariciresinol	*Rubia philippinensis* (Plant)	*SA* (125)	*EC* (250)		-	-		[105]
			Sambucus williamsii (Plant)			*CA* (25)			Amphotericin B *CA* (6.25)	[106]
		Iso-hydroxymatairesinol	*Punica granatum* L. (Plant)	*SA* (1500), *SE* (190)	*EC* (560), *PA* (1500)		-	-		[107]
		Punicatannin C		*SA* (1500), *SE* (750)	*EC* (1120)		-	-		
	Furofuran Lignans	Sesamin	*Zanthoxylum paracanthum Kokwaro* (Plant)	*SA* (500)			Omacilin (0.49)			[108]
		Phillyrigeninside B	*Forsythia suspensa* (Plant)	*SA* (10)	*EC* (20)	*CA* (20)	Gentamicin *SA* (4)	Gentamicin *EC* (4)	Gentamicin *CA* (4)	[109]
		Pinoresinol	*Cinnamomum Camphora* (Plant)	*SA* (15.60)	*EC* (31.25), *PA* (7.80)		-	-		[110]
			Sambucus williamsii (Plant)			*CA* (12.5)			Amphotericin B *CA* (6.5)	[111]
	Arylnaphthalene Lignan	2,3-dimethyl-4-(4′-hydroxy-3′,5′-dimethoxyphenyl)-6-hydroxy-7-methoxy-naphthalene	*Ganoderma lipsiense* (Microorganism)	*SA* (1.25), *SE* (>10)	*EC* (10)	*CA* (>10)	Ciprofloxacin *SA* (0.156), *SE* (0.156)	Ciprofloxacin *EC* (0.156)	Ciprofloxacin *CA* (0.156)	[112]
	Arylnaphthalene-lactone Lignan	Justicidin B	*Nocardia* sp. (Microorganism)	*SA* (1), *BC* (2.5)	*EC* (0.5), *PA* (0.2)	*CA* (4.5), *CN* (0.5), *AN* (0.2)	-	-	-	[113]
	Dibenzocyclo-octadiene Lignan	Manglisin B	*Manglietiastrum sinicum* (Plant)	*SA* (0.025), *MRSA* (0.025)			Vancomycin hydrochloride *SA* (1.63×10^{-3}), *MRSA* (8.02×10^{-4})			[114]

Table 1. *Cont.*

Secondary Metabolite Class	Subclasses	Compound	Source	Microorganism			Positive Control			Ref.
				Gram-Positive Bacteria	Gram-Negative Bacteria	Fungi	Gram-Positive Bacteria	Gram- Negative Bacteria	Fungi	
Quinones	Benzoquinones	Oncocalyxone A	*Auxemma oncocalyx* (Allem) Taub (Plant)	*LM* (37.75), *SA* (18.87), *MRSA* (18.87–37.75), *SE* (9.43–37.75)	*EC* (>151), *PA* (>151)	*CA* (>151), *CN* (>151), *AF* (>151)	Vancomycin *LM* (<2.0), *SA* (1.0), *MRSA* (1.0), *SE* (2.0)	Meropenem *EC* (<0.1), *PA* (<0.39)	Itraconazole *CA* (0.25), *CN* (0.06), *AF* (0.125)	[115]
		2-methyl-6-(-3-methyl-2-butenyl)benzo-1,4-quinone	*Gunnera perpensa* (Plant)	*SA* (39), *BC* (18), *SE* (9.8)	*EC* (>6250)	*CA* (130), *CN* (70)	Ciproflaxin *SA* (0.31), *BC* (2.5), *SE* (1.25)	Ciproflaxin *EC* (0.63)	Amphotericin B *CA* (1.25), *CN* (2.5)	[116]
		3,5- dimethoxy-2-methylthio)cyclohexa-2,5 diene-1,4-dione	*Diplocentrus melici* (Animal)	*SA* (4)			Ampicillin *SA* (0.5)			[117]
		2,6-Dimethoxy-1,4-Benzoquinone	Wood tar (Plant)	*SA* (32)	*EC* (64), *ST* (32)		Chloramphenicol *SA* (32)	Chloramphenicol *EC* (32), *ST* (32)		[118]
	Naphthoquinones	Plumbagin	*Diospyros bipindensis* (Plant)	*SA* (20)			Ampicillin *SA* (0.7)			[119]
			Plumbago zeylanica L. (Plant)	*MRSA* (4–8)						[120]
			Diospyros crassiflora (Plant)			*CA* [c] (0.78), *CG* [c] (3.12), *CN* [c] (1.56), *AN* [c] (0.78)			Ketoconazole *CA* [c] (0.25), *CG* [c] (5), *CN* [c] (0.25), *AN* [c] (0.25)	[121]
			Plumbago zeylanica (Plant)	*SA* (0.5)	*EC* (8), *PA* (8)	*CA* (2)	Ciprofloxacin *SA* (1.0) Amoxicillin *SA* (0.5)	Ciprofloxacin *EC* (0.5), *PA* (0.5) Amoxicillin *EC* (4), *PA* (128)	Ketoconazole *CA* (256)	[122]
			Plumbago indica (Plant)	*SA* (3.12), *SE* (0.018)			Tetracycline HCl *SA* (0.38), *SE* (0.048)			[123]
		2-methyl-1,4-naphthoquinone (vitamin K3)	*Pulsatilla koreana* (Plant)	*SA* (2.6–4)	*PA* (4)	*CA* (32–96), *CG* (8)	Tetracycline *SA* (0.5)	Tetracycline *PA* (0.22–0.38)	Ketoconazole *CA* (10.6–16), *CG* (8–13.4)	[124]
		2-Methoxy-1,4-naphthoquinone	*Impatiens balsamina* L. (Plant)	*SA* (16), *BC* (64)		*CA* [c] (0.62–2.50), *CA* [a,c] (0.62–1.25), *AF* [c] (0.31)	Chloramphenicol *SA* (8), *BC* (8)		Amphotericin B *CA* [c] (1.1), *CA* [a,c] (90), *AF* [c] (1.1)	[125]

Table 1. *Cont.*

Secondary Metabolite Class	Subclasses	Compound	Source	Microorganism			Positive Control			Ref.
				Gram-Positive Bacteria	Gram-Negative Bacteria	Fungi	Gram-Positive Bacteria	Gram- Negative Bacteria	Fungi	
		Bluemomycin	*Streptomyces* sp. (Microorganism)	*SA* (NA), *MRSA* [c] (10.6–39.4), *SE* (35.6–64.4)	*EC* [a,c] (8.9–39.4), *ST* (8.9–16.1), *SF* (5.3–19.7), *PA* (5.3–19.7)	*CA* [c] (46.4–53.6), *TR* (NA)	Streptomycin *SA* (2.65–9.85), *MRSA* [c] (6.25–20.65), *SE* (17.8–32.2)	Streptomycin *EC* [a,c] (10.6–39.4), *ST* (17.8–32.2), *SF* (2.65–9.85), *PA* (10.6–39.4)	Ketoconazole *CA* [c] (10.6–39.4), *TR* (<26.9)	[126]
		5-hydroxy-3,6-dimethoxy-7-methyl-1,4-naphthalenedione	*Xanthium sibiricum* (Plant)	*SA* (2.78), *BC* (22.2)	*EC* (5.55)		Ciprofloxacin *SA* (1.39), *BC* (5.55)	Ciprofloxacin *EC* (0.69)		[127]
	Anthraquinones	Zenkequinone A	*Stereospermum zenkeri* (Plant)		*EC* [a] (37.50), *PA* [a] (18.75)			Ampicillin *EC* [a] (0.40), *PA* [a] (0.80)		[56]
		Emodin	*Rumex abyssinicus* (Plant)	*SA* (8), *MRSA* (32)	*SF* (8), *PA* (16)	*CA* (8), *CN* (8)	Ciprofloxacin *SA* (0.5), *MRSA* (4)	Ciprofloxacin *SF* (8), *PA* (0.5)	Fluconazole *CA* (1), *CN* (2)	[128]
			Cassia occidentalis (Plant)	*SA* (3.9)	*EC* (>50)		Neomycin *SA* (6.3)	Neomycin *EC* (1.6)		[129]
		Physcion	*Rumex abyssinicus* (Plant)	*SA* (8), *MRSA* (16)	*SF* (8), *PA* (8)	*CA* (8), *CN* (8)	Ciprofloxacin *SA* (0.5), *MRSA* (4)	Ciprofloxacin *SF* (8), *PA* (0.5)	Fluconazole *CA* (1), *CN* (2)	[128]
		Isoversicolorin C	*Aspergillus nidulans* (Microorganism)		*EC* (32)			Chloramphenicol *EC* (1)		[130]
		2,3-dihydroxy-9,10-anthraquinone	*Streptomyces galbus* (Microorganism)	*SA* (>100), *MRSA* [c] (12.5), *SE* (>100)	*EC* [c] (50), *ST* (12.5), *SF* (25), *PA* (12.5)	*CA* (50)	Streptomycin *SA* (6.25), *MRSA* [c] (6.25), *SE* (12.5)	Streptomycin *EC* [c] (25), *ST* (6.25), *SF* (6.25), *PA* (25)	Ketoconazole *CA* (25)	[131]
		5-Hydroxy ericamycin	*Actinoplanes* sp. (Microorganism)	*SA* [b,c] (<0.06) *MRSA* (0.016) *MRSA* [c] (<0.06), *SE* [b,c] (<0.06)	*EC* (4), *EC* [b,c] (16), *PA* (16)		Vancomycin *SA* [b,c] (1.0–8.0), *MRSA* (2.0), *MRSA* [c] (1.0), *SE*[b,c] (2.0)	Vancomycin *EC* (>64), *EC* [b,c] (>64), *PA* (ND)		[132]

Table 1. *Cont.*

Secondary Metabolite Class	Subclasses	Compound	Source	Microorganism			Positive Control			Ref.
				Gram-Positive Bacteria	Gram-Negative Bacteria	Fungi	Gram-Positive Bacteria	Gram- Negative Bacteria	Fungi	
Curcuminoids		Curcumin	*Zingiber spectabile* (Plant)	*SA* (500), *BC* (125)	*EC* (NA)		Tetracycline *SA* (3.91), *BC* (1.95)	Tetracycline *EC* (NA)		[133]
			Curcuma longa Linné	*MRSA* (125–250), *MRSA* [c] (125–250)			Oxacillin *MRSA* (500–1000, >1000), *MRSA* [c] (500–1000) Ciprofloxacin *MRSA* (7.8–250.0), *MRSA* [c] (1.95–15.6)			[134]
			Commercial product	*SA* (25)	*PA* (50)		-			[135]
			Commercial product from *Curcuma longa* L. (Plant)	*SA* (125–500), *MRSA* (>4500), *SE* (500–2000)	*EC* (2000), *EC* [c] (1500), *PA* (62.5–5000)	*CA* (1000–5000), *SC* (5000)	-	-	-	[136]
			Commercial product	*SA* (450)	*PA* (500)		-	-		[137]
			Commercial product from *Curcuma longa*			*CA* (1000), *CG* (125)			Ketoconazole *CA* (62.5), *CG* (1.95)	[138]
			Commercial product	*SA* (0.03), *BC* (0.05)	*EC* (0.225)		-	-		[139]
		Demethoxycurcumin	*Zingiber spectabile* (Plant)	*SA* (125), *BC* (125)	*EC* (500)		Tetracycline *SA* (3.91), *BC* (1.95)	Tetracycline *EC* (NA)		[133]

(-): not tested; [a]: multidrug-resistant strain; [b]: drug-resistant strain; [c]: clinical isolate; ND: not determine; NA: no activity; *LM*: *Listeria monocytogenes*; *SA*: *Staphylococcus aureus*; *MRSA*: Methicillin-resistant *Staphylococcus aureus*; *BC*: *Bacillus cereus*; *SE*: *Staphylococcus epidermidis*; *EC*: *Escherichia coli*; *ST*: *Salmonella typhimurium*; *SF*: *Shigella flexneri*; *PA*: *Pseudomonas aeruginosa*; *CA*: *Candida albicans*; *CG*: *Candida glabrata*; *SC*: *Saccharomyces cerevisiae*; *CN*: *Cryptococcus neoformans*; *AN*: *Aspergillus niger*; *AF*: *Aspergillus fumigatus*; *AV*: *Aspergillus versicolor*; *FS*: *Fusarium solani*, *TR*: *Trichophyton rubrum*.

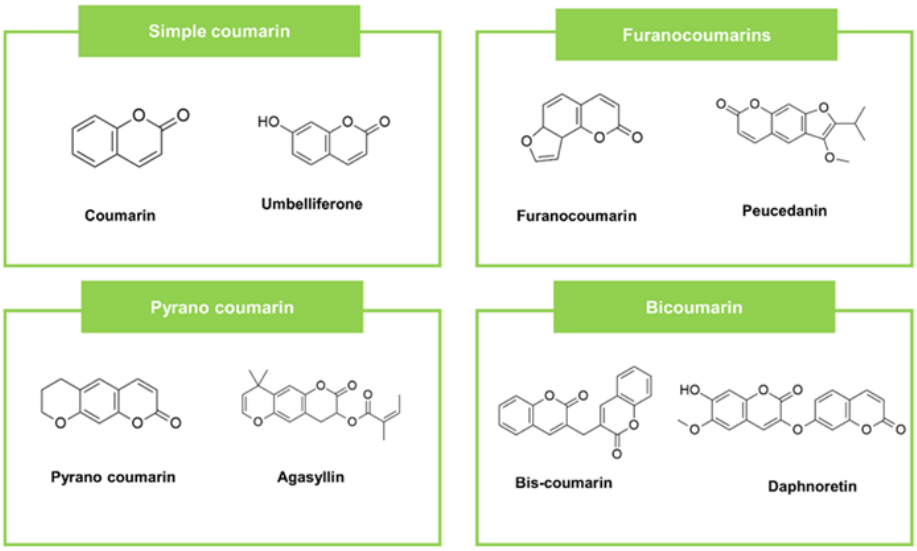

Figure 2. Representative chemical structures of different classes of coumarin and nature-derived coumarin.

The MIC values of coumarins in different subclasses, such as umbelliferone, osthol, peucedanin, imperatorin, etc., isolated from natural sources are presented in Table 1. It can be easily seen that the antimicrobial activity of these representative compounds was less than those of the antibiotics given in the related studies. Although the several studies on the antibacterial mechanism of action of coumarin and its derivatives have depicted that their antibacterial action occurs primarily through bacteriostatic effects by binding the B subunit of microbial DNA gyrase and preventing DNA supercoiling by blocking ATPase activity [150–152], further work is necessary to understand the antimicrobial mechanism of these nature-derived coumarins. Additionally, recent studies based on the toxicological properties of coumarins in humans indicates that these compounds have a tolerable dose intake (TDI) of 0.1 mg/kg of body weight [153]. However, it should be noted that the toxicity of natural and synthetic coumarins depends on the position and chemical structure of the substituents groups connected to the coumarin core [154].

Various studies on the antibacterial action and structure relationship of coumarins and their derivatives revealed the action of these compounds on the antibacterial effects of the number and binding position of substituents such as the thiazole ring, halogen, methyl, methoxy, hydroxyl, and amino, attached to the basic skeleton [155,156]. For example, the electron-donating substituents of the phenyl ring such as $–OCH_3$, $–CH_3$, and electron-withdrawing substituents such as NO_2 and halogen groups play a remarkable effect on their action [157]. Ben Jannet et al. isolated two coumarins, marmesin and scopoletin, from a plant, *Ferula lutea* (Poir.) Maire and synthesized their synthetic derivatives from these natural compounds. The isolated and synthesized compounds were evaluated for antibacterial activity against *Escherichia coli* (*E. coli*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Enterococcus faecalis* and *S. aureus*. Due to the nature of the acyl group and the aryl ring attached to the isoxazole moiety included in both marmesin and scopoletin, the synthesized derivatives exhibited potent antibacterial activity when compared to nature-derived coumarins. Marmesin was esterified with a series of acid chlorides, resulting in the formation of new ester derivatives. The phenyl group substituted with the ester moiety improved the activity compared to the methyl group against the tested Gram-positive bacteria. In addition, the presence of one or more chlorine atoms on branched-chain methyl esters provided more antibacterial activity; the chlorination of straight-chain methyl esters did not. For scopoletin and their derivatives, antibacterial data indicated that introducing the isoxazole moiety into scopoletin improved the antibacterial action. In addition, the antibacterial activity of a synthesized compound bearing *p*-Cl-phenyl attached to its isoxazole moiety

is profitable because of the introduction of a halogen, which is an electron-withdrawing substituent, into the structure. On the other hand, the study revealed that the derivatives that maintain electron-donating substituents, isopropyl, ethyl, methyl, and furan, exhibited less antibacterial activity [158]. In accordance with conducted structure-activity studies, naturally derived coumarins and their substitution with various functional groups can be considered an essential step for the development of antibacterial agents [159–161].

2.3. Flavonoids

Flavonoids are a wide class of polyphenolic compounds based on a basic structure of 2-phenyl chroman [162]. On the other side, isoflavonoids own a basic structure of 3-phenyl-chroman which is biogenetically derived from the 2-phenyl chroman skeleton of flavonoids [163]. Until now, more than 8000 flavonoid derivatives have been recognized in nature, as both free state and conjugated state, as ester or glycosidic derivatives [164–166]. Flavonoids are generally discovered in plant sources, but they may innately occur in certain microalgae and fungi [167]. As described by Jin et al., based on the oxidation degree of the main heterocycle, flavonoids are categorized into seven subclasses: flavonols, flavones, isoflavones, anthocyanidins, flavanones, flavanols, and chalcones (see Figure 3) [168]. Flavonoids and ısoflavanoids are promising antimicrobial mediators that target different microbial cells and can inhibit virulence features in drug-resistant strains [169,170]. Various studies have proposed that the compounds in this class can display antimicrobial activity through both bacteriostatic and bactericidal effects. Their bacteriostatic effects are associated with their ability to form complexes with the bacterial cell wall to inhibit the growth of bacteria. In detail, they can suppress cell growth by inhibiting microbial cell energy metabolism, nucleic acid synthesis, or cytoplasmic membrane function [171]. Their bactericidal activities are considered to be associated with irreversible damage to the cytoplasmic membrane. As a representative example, Voutquenne-Nazabadioko et al. reported the antimicrobial skills of the purified flavonoid glycosides obtained from *Graptophyllum grandulosum* plant against *Vibrio cholerae, S. aureus, Candida albicans (C. albicans),* and *Cryptococcus neoformans (C. neoformans)* [172]. Their antibacterial mechanism is based on cytoplasmic membrane damage by disturbing the membrane permeability and causing the leakage of cellular constituents. In another study scrutinizing the anti-*P. aeruginosa* activity and possible mechanism of a flavonoid isolated from *Trianthema decandra*, 2—(3′, 4′ dihydroxyphenyl) 3, 5, 7—trihydroxy-chromen-4 displayed a bactericidal effect by constraining the FabZ enzyme, according to molecular docking studies, although additional findings are wanted to fully elucidate its mechanism [173]. Additionally, some flavonoids exhibit the aptitude to boost the therapeutic effect when pooled with existing antibiotic drugs [174]. For example, Sathiya Deepika et al. investigated the anti-biofilm efficacy of rutin from *Citrus sinensis* peels and its synergistic effects in combination with conventional bactericidal antibiotic gentamicin against multidrug-resistant *P. aeruginosa*. Rutin and a combination of rutin-gentamicin prevented biofilm development by inducing reactive oxygen species (ROS) generation in *P. aeruginosa*, which led to oxidative stress, induction of cell wall disruption, and eventually to bacteria killing. A synergistic effect was further observed by combining gentamicin with rutin. Herein the bactericidal effect of the flavonoids is related to their antioxidant properties. They act as pro-oxidants against microbial pathogens and cause oxidative stress by generating ROS to induce cell death [175]. Additionally, Table 1 provides the list of MIC values of flavonoids obtained from different plant species. As can be seen in Table 1, some flavonoids exhibit higher antimicrobial activity than conventional antibiotics, indicating their potential to prevent microbial infections. On the other hand, it should be noted that flavonoids with higher MICs than antibiotics can display possible enhanced effects in combination with antibiotics due to their multiple target mechanisms.

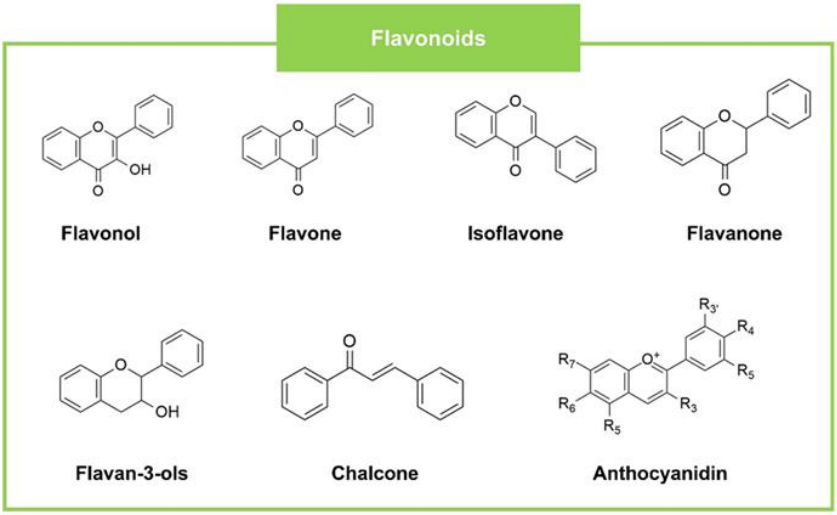

Figure 3. Representative chemical structures of different classes of flavonoids.

2.4. Tannin

Tannins are a heterogeneous class of high-molecular-weight polyphenolic substances [176]. Previously, tannins have been categorized as hydrolyzable tannins and condensed tannins. Accordingly, it was assumed that hydrolyzable tannins included two sub-groups, as gallotannins and ellagitannins. Nevertheless, the existence of some ellagitannins, which cannot be hydrolyzed on account of more additional C-C bonding of the polyphenolic moieties with the polyol unit, caused an update in their classification. Thus, the revised classification of these compounds is sub-categorized into five groups, gallotannins, ellagitannins, condensed tannins (proanthocyanidins), complex tannins and phlorotannins (see Figure 4) [177]. Gallotannins form by one or more galloyl units bounded to a polyol, triterpenoid or catechin unit, while ellagitannins are composed of hexahydroxydiphenoyl esters coupled to sugar, mostly glucose [178,179]. Condensed tannins exist in the plants as a form that is free or bound to protein and fiber [180]. Their chemical structure is formulated of flavan-3-ols that are bound through single C-C bonds, which are typically C4 → C6′ or C4 → C8′ (B-type) or doubly coupled with a further bond at C2 → O → C7′ (A-type) [181,182]. On the other hand, complex tannins are a class of tannins with high molecular weight in which a catechin unit is linked to either gallotannins or ellagitannins [176]. In the last two decades, investigations on their isolations and biological activities have been limited because of, presumably, their complex structure. Melasquanins A–D can be exemplified as complex tannins, which were isolated from *Melaleuca squarrosa*, but their biological properties need to be elucidated [183]. Additionally, the particular type of tannins, commonly isolated from marine algae, is named phlorotannins due to their occurrence by polymerizing phloroglucinol units [184]. Tannins are naturally found in higher plants and marine algea and also possess a defensive function for the plant against diverse environmental factors, pathogens, or herbivores [179]. Inspired by the biochemical shield against herbivores and pathogens offered by tannins existing in plants, the interest of the scientific community arises on their usage as an antimicrobial agent [185–188]. Previous studies have revealed the tannins to display several biological features, such as antimicrobial activity. This feature is rooted in their chemical structure, allowing them to own antimicrobial activity through bacteriostatic or bactericidal actions [189]. In detail, the chemical nature of tannins owns plenty of hydroxyl groups, providing them with a hydrophilic character. This mainly allows the tannins to form complexes with proteins or enzymes of microbial cell membrane by hydrogen bonds and hydrophobic interactions, which can affect the morphology of the cell wall and increasing membrane permeability [190]. Another purposed antimicrobial mechanism is the generation of complexes between metal ions and tannins. Tannins may chelate many metal ions, hindering the accessibility of such indispensable ions for microorganisms [189,191].

As mentioned earlier, the phlorotannins discovered in marine algae led to a need for more investigations into their biological potential. Recently, Kim et al. reported that

phlorofucofuroeckol-A, extracted from brown alga *Eisenia bicyclis*, displayed anti-MRSA activity by blocking the production or function of penicillin-binding protein 2a, which is regarded as the primary reason for methicillin resistance [192]. Hereby, this compound can be considered a promising candidate due to its potential in inhibiting the growth of antibiotic resistance related to mediating suppressive effects on methicillin resistance-associated genes. In another study, persimmon tannins from young astringent persimmon fruit showed antibacterial activity with an MIC value of 1000 µg/mL against some MRSA isolates from pork. Performed studies on the mechanism of antibacterial action indicated that persimmon tannins showed bactericidal and bacteriostatic activities by multiple mechanisms, including damage to cell wall and membrane, leading to membrane hyperpolarization, reduction of intracellular ATP concentration, losing bacterial membrane integrity, whole cell protein, and cell cycle depression [187]. Anti-MRSA molecular mechanisms of persimmon tannins were elucidated deeply using transcriptome and metabolome analyses by the same research group. Results demonstrated that persimmon tannins adversely affected the cell membrane permeability and integrity, amino acid, and energy metabolism and also caused iron deprivation [193]. A survey of recently reported antimicrobial activities of representative compounds in different classes of tannins is given in Table 1. Considering the MIC values of the tannin compounds and the relevant antibiotics, further investigations should be concentrated on in vivo assays and clinical trials to depict the effectiveness of these antimicrobial agents in clinical settings.

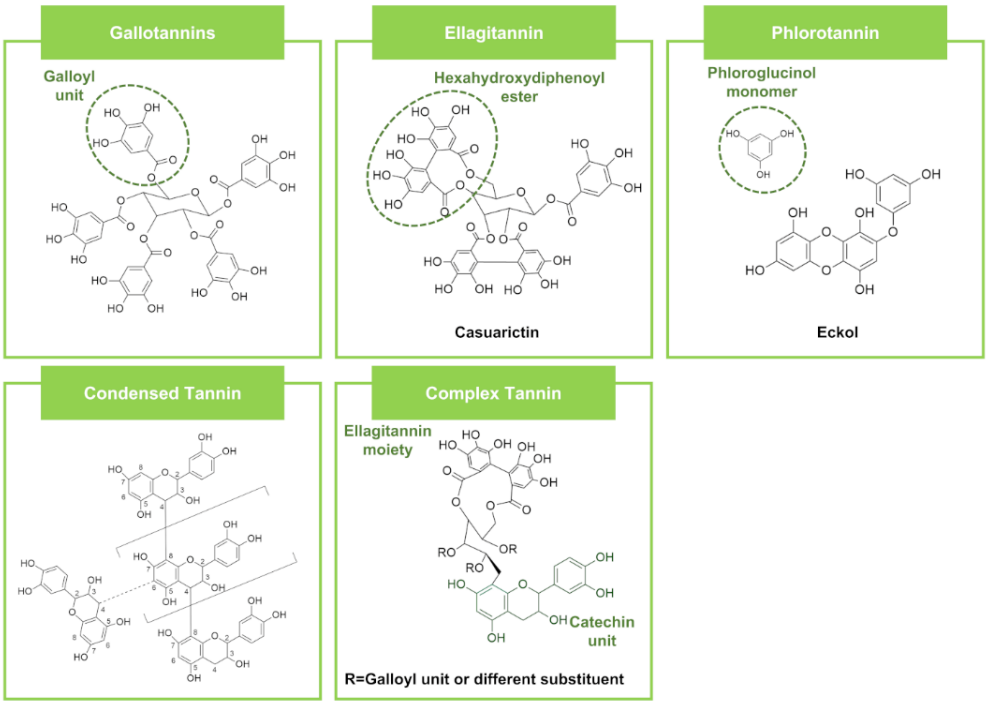

Figure 4. Representative chemical structures of different classes of tannins.

2.5. Stilbenes

Stilbenes are widely found in plants, but also, their basic forms or various substitutions can be isolated from the pathogenic strains [194]. Although stilbenes are typically encountered in the plant kingdom, several studies on their isolation from microorganisms and marine organisms have also been reported [98,195,196]. In general, these metabolites are unearthed in plants as both free and glycosylated forms [197]. Their chemical structure comprises a 1,2-diphenylethylene core with substituted hydroxyl groups on the aromatic rings [198]. The sorting of different subclasses of stilbenes is a challenge owing to their broad structural diversity; we basically classified them into four main subclasses: monomeric, dimeric, oligomeric, and miscellaneous stilbenes. Although stilbenes stand

out in multiple fields owing to their antitumoral [199], antioxidant [200], cardioprotective [201], hypolipidemic [202], and immunosuppressive [203] activities, their antimicrobial properties occupy a noteworthy position in combating various microbial infections. Resveratrol, piceatannol, isorhapontigenin, pinosylvin, and oxyresveratrol are widely recognized monomeric stilbenes (see Figure 5). Among the representative monomeric stilbenes, resveratrol and pterostilbene were commercially available on the bench due to their prominent properties such as antihypertensive, antioxidant, anti-inflammatory, and anti-cancer activities. Thus, investigations on the discovery and biological potential of naturally derived stilbenes are in progress. Various reports on their antimicrobial mechanism have documented that stilbenes induce cell membrane damage and DNA degradation mediated by oxidative stress and increase cell membrane permeability, causing the leakage of intracellular nucleic acids and proteins [204–208]. As a representative example, Longistylin A, a pinosylvin-derived monomeric stilbene isolated from the leaves of *Cajanus cajan* (L.) Millspaugh, was tested against MRSA, *S. aureus, E. coli*. and *Bacillus cereus (B. cereus)*. This compound exhibited notable antibacterial activity against tested gram-positive bacterial strains (see Table 1). Moreover, studies on the underlying mechanism of anti-MRSA action revealed that Longistylin A demonstrated bactericidal activity by disrupting bacterial membranes and increasing membrane permeability. Furthermore, Longistylin A exhibited much faster bactericidal activity (3-log reduction in MRSA survival within 8 h) compared to vancomycin used as a positive control, indicating the promising potency of Longistylin A in fighting with MRSA-associated infections [99].

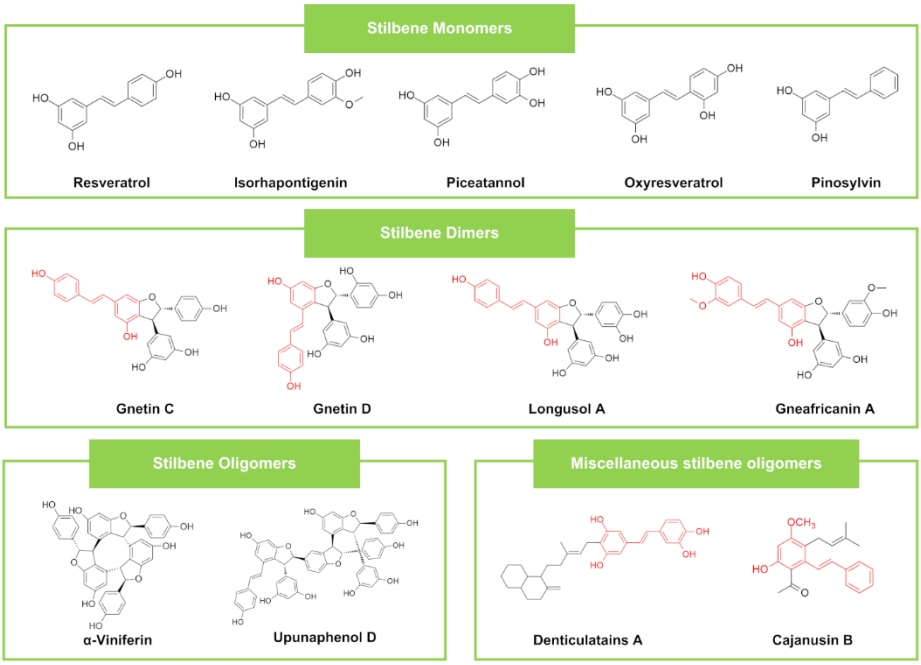

Figure 5. Representative chemical structures of different classes of stilbene and nature-derived stilbenes.

Dimeric stilbenes occur from two monomeric units; for instance, Gnetin C is formed from two resveratrol monomers, or Longusol A arose from two distinct monomeric units, a resveratrol unit and a piceatannol unit [209]. Gnetin D, a dimeric stilbene, was isolated from the roots of *Spirotropis longifolia* and showed effective antifungal activity against, especially, *C. albicans, Candida parapsilosis,* and *Candida krusei (C. krusei)* strains among the ten different tested fungal stains (see Table 1) [94]. Another study on the antibacterial activity of fifteen resveratrol-derived stilbenoids verified that the dehydro-δ-viniferin, a stilbene dimer, displayed the most potent antibacterial activity among others. The mechanism of action of this compound against *L. monocytogenes* was demonstrated to be accomplished by more than one specific mechanism, including membrane depolarization followed by damaging the cytoplasmic membrane and the destruction of membrane integrity and

severe morphological changes [95]. Oligomeric stilbenes are generated by a coupling reaction between monomeric units of stilbenes following the pattern of a homogeneous or heterogeneous oligomerization [210]. Miscellaneous oligomeric stilbenes were described as complex stilbene oligomers with diverse structural skeletons comprising distinct stilbene units excepting resveratrol and oxyresveratrol units in the comprehensive study where Shen et al. updated the classification of stilbenes [211]. In recent decades, prenylated stilbenes, which are considered a class of miscellaneous stilbenes, have been attracting widespread interest due to their unique structures and biological potential. For instance, denticulatains A and B, prenylated stilbenes with stilbene-diterpene type skeleton were isolated from a plant species *Macaranga denticulata* [210]. In another study, prenylated stilbenes, cajanusins A-D and their derivatives were isolated from *Cajanus cajan* (See the structure of cajanusin B in Figure 5) [212]. Besides the extensive research on the isolation of these compounds from various natural sources, the studies on their antimicrobial aptitude is still scarce.

Interactions of stilbenoids, particularly resveratrol, with conventional antibiotics have been investigated as combinatorial therapy, which can potentially improve the effectiveness of antimicrobials and hinder the emergence of resistant strains due to the synergistic effect. In vitro antibacterial activity of resveratrol was assessed alone and in combination with the bactericidal antibiotic, colistin, against a collection of colistin-resistant (COL-R) Gram-negative pathogens, including *E. coli, Klebsiella pneumoniae, Enterobacter cloacae, Stenotrophomonas maltophilia, Citrobacter braakii*, and polymyxin-resistant enterobacterial species [213]. The results revealed that the 512 mg/L concentration of resveratrol did not show antimicrobial activity against all Gram-negative pathogens tested. Nevertheless, in the combination, resveratrol (at 128 mg/L) potentiated the bactericidal effect of colistin (0.5 × MIC and 1 × MIC) against all strains tested except for one of the *E. coli* strains [213]. However, the synergistic mechanism of resveratrol and colistin against COL-R strains has not been elucidated. In a study investigating the antibacterial activity of the structural analogues of resveratrol, the dimeric compound of the 4,4′ dihydroxy stilbene revealed a strong antibacterial effect with 10 µg/mL of MIC value against *S. aureus* [208]. Thereupon, the same research group investigated the synergistic effect of this dimeric stilbene compound with antibiotics in their further study [214]. The combination of dimeric stilbene compound with the antibiotics targeting protein synthesis led to the decreased MIC values of antibiotics, including kanamycin, tobramycin, chloramphenicol, tetracycline, musiporin, and erythromycin, indicating the in vitro synergistic effect. The same synergistic effect was also established by combining the dimeric stilbene and kanamycin against kanamycin-resistant laboratory strains and kanamycin-resistant clinical strains. Furthermore, in vivo studies confirmed that the dimeric stilbene ameliorates *S. aureus* infection in mice, both alone and in combination with kanamycin [214]. However, the mechanism underlying this synergistic outcome has not been ascribed.

In addition, stilbenes have potential synergistic activities to combat microbial infection in combination with conventional antibiotics; it has also been reported that combining these compounds with antibiotics can lead to antagonistic interactions [215,216]. The mechanism of antagonism is proposed to involve a reduction in ROS by stilbenes due to their antioxidant properties. Increased ROS production by antibiotics causes oxidative stress, DNA damage, and, eventually, cell death in bacteria. However, in some cases, the ROS produced by bactericidal antibiotics may be suppressed through the scavenging of free radicals by stilbenes, depending on the concentration of stilbene and the target bacterial species.

To provide deep insight into the antimicrobial activity of stilbenes, several structure-activity relationship studies have been performed to date [194,208,217]. The study on resveratrol structural analogs concluded that the presence of hydroxyl groups on the aromatic rings of stilbenes plays a key role on their antimicrobial activity [208]. However, an increasing number of hydroxy groups did not provoke higher antimicrobial activity. Additionally, the presence of the methoxy group along with the hydroxy group resulted

in more potent antibacterial activity. Converting all the active hydroxy groups to acetoxy group or methoxy group caused a drastically reduced antibacterial activity. The partial transformation of hydroxy group to methoxy group resulted in enhanced antibacterial activity as a result of oxidative stress and membrane damage. Additionally, the studied stilbenes are less active against Gram-negative bacteria, as they are taken out of the cell by the efflux pump in Gram-negative bacteria. Though, surprisingly, pinosylvin and 4-Bromo resveratrol were effective even in the presence of efflux pump. This was presumably related to the fact that these compounds cause cell damage within a short time before being pumped out by the efflux pump or they are weak substrates for the efflux pump [208]. Additionally, halogenation and dimerization cause enhanced antibacterial and antifungal properties [218]. However, it should be noted that halogenation might increase cytotoxicity [219].

2.6. Lignans

Lignans are formed from the dimerization of two phenylpropanoid units through oxidative coupling reactions [220]. Their wide structural diversity has resulted in differences in their nomenclature and classification. In detail, lignans can be categorized as lignans, neolignans, or norlignans in accordance with the bonding positions of the two phenylpropanoid units and the case of lack of carbon from the parent lignan skeleton. As can be seen in Figure 6, while the basic lignan structure is composed of two phenylpropanoid (C_6C_3) units linked by a β-β′ (C8-C8′) bond, neolignan contains dimerization of C_6C_3 units linked in a form other than β-β′ (C8–C8′) bond [221]. On the other hand, the term 'norlignans' is defined as lignans that couple two phenylpropanoid units with a β-β′ bond and have one or more carbon atoms missing than those of the basic lignan skeleton. Interestingly, it should be noted that the missing carbon is assigned in the nomenclature of norlignans, as shown in Figure 1 [222–224]. According to the dissimilarities of carbon skeletons, a recent study by Tan et al. classified lignans into six subclasses: dibenzylbutane, tetrahydrofuran, arylnaphthalene, arylnaphthalenelactone, furofuran, and dibenzocyclooctadiene [222]. These compounds are frequently discovered in plants, but they may also be metabolized by gut microbiota in mammals [225]. Plant lignans exist as secoisolariciresinol, matairesinol, lariciresinol, and pinoresinol in a diversity of food sources [226,227]. Lignans from plants are metabolized into mammalian lignans, such as enterolignans, enterodiol, and enterolactone, by intestinal bacteria [228]. The mammalian and plant lignans are distinguished from each other by the presence of phenolic hydroxy groups only in the meta-position of the aromatic rings [229]. Additionally, mammalian lignans are gifted to bind to estrogen receptors owing to their chemical structural similarity to estrogen and thus can serve as antioxidant agents [230]. Many efforts are still being made on the antimicrobial potential of lignans obtained from diverse origins such as microorganisms, and plants because of their various biological potential [231,232]. As a representative example, pinoresinol, one of the structurally basic lignans, was extracted from *Cinnamomum camphora* leaves and exhibited more potent antibacterial activity against *Bacillus subtilis* (*B. subtilis*) and *P. aeruginosa* than *S. aureus*, *E. coli*, and *Salmonella enterica* [110]. In addition, studies on its mechanism of antibacterial action have reported that pinoresinol displayed bactericidal activity by increasing the permeability of bacterial plasma membrane and damaging the cell wall of *B. subtilis* and *P. aeruginosa* [110]. As an example of an arylnaphthalide lignans, justicidin B was previously extracted from various plant families, including *Justicia pectoralis*, *Linum leonii, Phyllanthus polyphyllus*, *Sesbania drummondii*, and *Justicia procumbens* [233–236]. However, Jaspars et al. isolated for the first time this compound from a microbial species, a marine-derived bacterium *Nocardia* sp. ALAA 2000 and reported its remarkable and potent antimicrobial properties (see Table 1) against fourteen microbial strains, demonstrating the promising bioactive aspect of compounds from different sources [113]. In another study, Hwang et al. [106] also isolated an enterolignan precursor, Lariciresinol, from *Sambucus williamsii* herb and confirmed it to exhibit fungicidal activities by disrupting the fungal plasma membrane of *C. albicans* (see Table 1). To date, many researchers have demonstrated

the antimicrobial activity of lignans and their derivatives from natural sources [237,238], but research to elucidate the mechanisms of action at the molecular level remains unclear.

An in-depth evaluation of their structure-antimicrobial activity relationship is essential for the assessment of these compounds and their use in the design as antimicrobial agents. Koba et al. investigated the association of antimicrobial activity and structure among compounds containing different benzylic oxidation degree and stereochemistry. These compounds exhibit antibacterial activity against the tested Gram-positive bacteria. However, the presence of a carbonyl group at C-9′ of tetrahydrofuran lignans decreased antibacterial activity in the absence of benzylic oxygen. In addition, full oxidation of the benzylic positions on 2,3-dibenzyl-4-butanolide triggers more potent antibacterial activity than that of 2,3-dibenzyl-4-butanolide, thus indicating the importance of benzylic carbonyl groups for a prominent antibacterial effect [239]. Another study investigating the structure-activity relationship of tetrahydrofuran lignan, 9-O,9′-*O*-demethyl (+)-virgatusin indicated that the antibacterial activity might vary on the presence and location of methoxy substitutions. For example, the 3′-methoxy group contributed to higher effective antibacterial activity than that of the 4′-substituent. Additionally, the existence of the 3,4-methylenedioxy group on the 7-phenyl group played an essential role in the enhanced antibacterial activity [240]. Similarly, a study on virgatusin and its derivatives supported the aforementioned results. For these tetrahydrofuran lignans, two methoxy groups at C-9/9′ and a 3,4-methylenedioxyphenyl group at C-7 improved antifungal activity. Additionally, among virgatusin and its derivatives, the substitution of the 4-methoxyphenyl group at C-7′ resulted in the highest antifungal activity [241]. Further investigations are in need of elucidating the structure-activity relationship, especially addressing other subclasses of lignans.

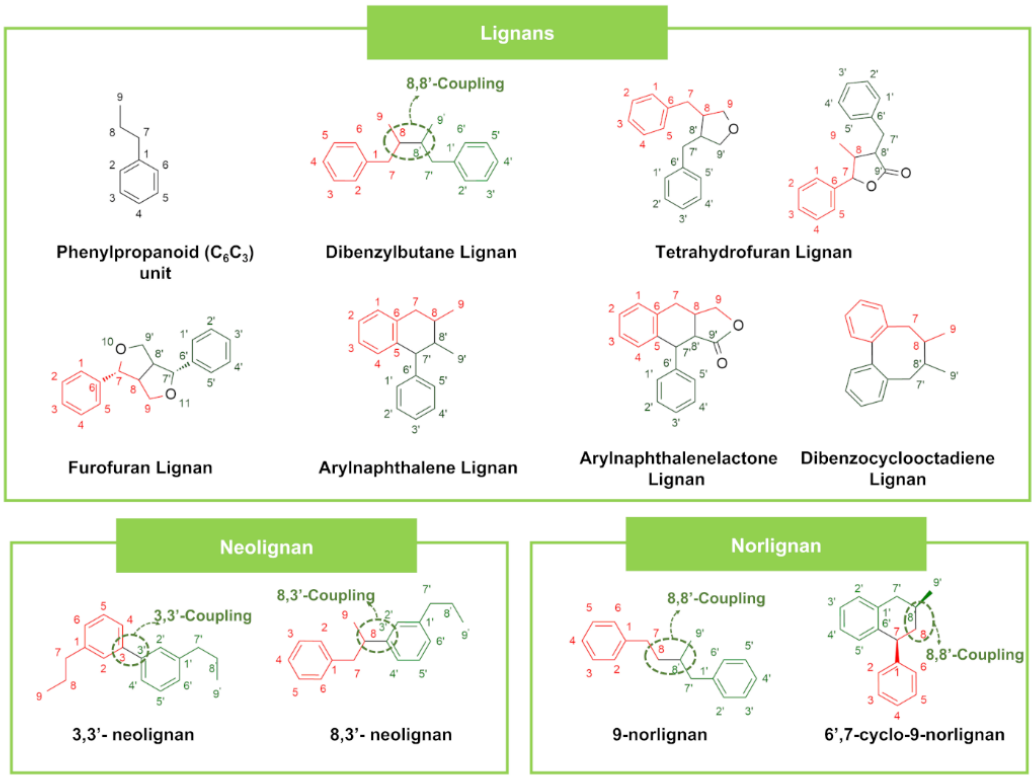

Figure 6. Representative chemical structures of different lignan types and lignan subclasses.

2.7. Quinones

Quinones are structurally defined as cyclohexadiendiones possessing carbonyl groups in the 1,2 or 1,4 positions relative to each other [242]. These compounds are found in numerous natural sources, including plants, bacteria, fungi [243], and marine organisms [244]

but can also be found in some animals such as aphids, sea urchins, lac insects, and certain scale insects [245,246]. Quinones are divided into four subclasses that include benzoquinones, naphthoquinones, anthraquinones and phenanthraquinones (see Figure 7) [14]. To date, benzoquinones and naphthoquinones derivatives have been isolated from innumerable plant sources and reported to show significant antimicrobial activities [116,124,247]. Phenanthrenequinone derivatives have also been extracted from various plants, such as *Pleione bulbocodioides* and *Cannabis sativa* [248,249]. Nevertheless, a major deficit in the literature subsists regarding the antimicrobial activities of phenanthrenequinones.

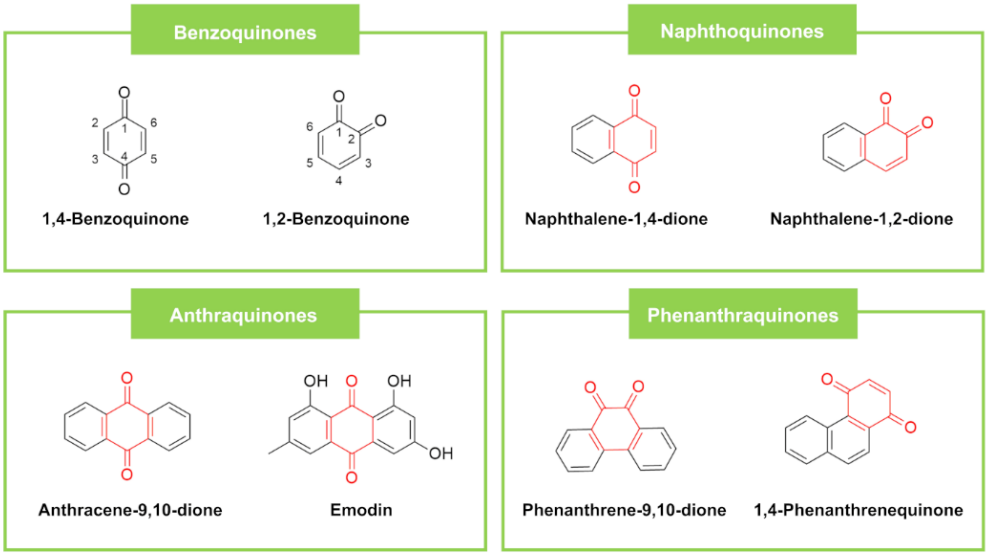

Figure 7. Representative chemical structures of different classes of quinones.

According to previously reported studies, quinones display antibacterial activity by bacteriostatic and/or bactericidal modes [250–252]. Although the mechanism by which quinone causes antimicrobial activity is complex, it has been reported that quinones generate ROS through redox cycling with their semiquinone radicals, causing intracellular oxidative stress and, thus, cell membrane damage [253,254]. A list of recently published investigations indicating good and moderate antimicrobial properties of representative compounds in different quinone classes is provided in Table 1. The discovery of these compounds provides new insight into novel antimicrobial agents for pharmaceutical development. However, more analyses are desirable on the structure-function and antimicrobial mechanisms of quinones.

2.8. Curcuminoids

Curcuminoids are linear, diarylheptanoid molecules consisting of curcumin, demethoxycurcumin, bisdemethoxycurcumin and their analogues [255,256]. Curcuminoids are commonly isolated from turmeric, a member of the ginger family (*Zingiberaceae*), and other plant species, such as *Curcuma zedoaria*, *Curcuma manga*, *Costus speciosus*, *Curcuma aromatica*, *Curcuma xanthorrhiza*, *Curcuma phaeocaulis*, *Zingiber cassumunar* and *Etlingera elatior* [257–259]. Among the curcuminoids, curcumin has been applied in several studies as an outcome of its various biological properties, such as anti-inflammatory [260,261], antimicrobial [262,263], and antitumoral [264,265] activities. Clinical studies disclosed that curcumin is non-toxic to humans at high dosages, but its low bioavailability hinders its therapeutic applications [266,267]. Several strategies have been performed to enhance the bioavailability of curcumin, including the usage of liposomal curcumin, nanocurcumin and more recently deep eutectic solvents [268–271]. As mentioned above, curcumin, which stands out with its various biological benefits, is commercially available. Therefore, Table 1 includes MIC values that evaluate the antibacterial activity of commercial curcumin along with curcumin isolated from natural sources. The antimicrobial mechanism of curcuminoids has been widely investigated [272–276]. For example, Sivasothy et al. [133]

isolated five different flavonoids and curcuminoids from the rhizomes of *Zingiber spectabile*. The antibacterial data indicated that curcuminoids present higher antibacterial activity than flavonoid-derived compounds [133]. In another promising study, Adamczak et al. [136] evaluated the usefulness of commercial curcumin from *Curcuma longa* L. against more than 100 strains from 19 different species, as represented in Table 1.

To date, curcuminoids have been the subject of numerous investigations and have been reviewed deeply. In particular, curcumin has been reported to own antibacterial activity by bacteriostatic and bactericidal modes against a wide range of bacterial strains. The bactericidal action of curcumin has been attributed to its diffusion across the bacterial membrane of *S. aureus* and *E. coli* due to its amphipathic and lipophilic character, increasing membrane permeability, leaking of intracellular constituents, and ultimately causing cell death [276].

Investigations on the bacteriostatic mechanism of curcumin at the molecular level proposed that curcumin inhibits bacterial growth by attacking different targets such as the DNA, protein, cell wall, cell membrane and quorum-sensing systems in the bacteria. As a representative example, the bacteriostatic action of curcumin against B. subtilis was reported to occur by increasing the GTPase activity of protein FtsZ, which plays an essential role in the division of bacterial cells, depending on the concentration [274]. Additionally, as curcumin is a photosensitizer, several reports surveyed its usage in antimicrobial photodynamic therapy [269,277–283]. The bactericidal action of curcumin-based photodynamic inactivation therapy against *L. monocytogenes* was proven to be membrane protein degradation and increased membrane permeability triggered by oxidative stress through intracellular ROS production [284]. In addition, another study elucidating the antibacterial mechanism of *L. monocytogenes* ascertained that the bactericidal efficacy of curcumin-based photodynamic inactivation therapy is a result of cytoplasmic DNA and protein damage [285]. According to the previous studies on curcumin, it should be noted that the mechanism of antibacterial action of curcumin may differ depending on the strain tested.

Besides their antibacterial activities, many studies have also investigated the fungistatic and fungicidal activities of curcumins against various fungal strains as potential antifungal agents. A study on the in vitro antifungal activity of curcumin has demonstrated its antifungal activity against *Candida* species, including *C. albicans*, *Candida glabrata (C. glabrata)*, and *C. krusei*, and also indicated that curcumin displayed fungistatic activity by binding to the membrane ergosterol of *C. albicans*. However, the same mechanism was not observed against *C. glabrata* and *C. krusei*, indicating that the interaction of curcumin-ergosterol is not a single mechanism of action for curcumin [138]. As a fungicidal agent, it has been proposed that curcuminoids bind to residues on the fungal cell membrane, causing cell membrane disruption, leakage of intracellular contents, and, eventually, cell death.

In addition to functioning as an antimicrobial compound by itself, curcumin has also been scrutinized for potential effects in combination with conventional antibiotics. Curcumin may have synergistic effects in combination with bacteriostatic antibiotics and fungistatic drugs to improve antimicrobial activity. For *C. albicans*, Ferreira-Pereira et al. reported that curcumin potentiates synergistically the antifungal effect of fluconazole against a clinical isolate of *C. albicans* possessing a multiple drug resistance phenotype [286]. in another study, the combination of curcumin with conventional fungicidal drugs, including fluconazole, ketoconazole, miconazole, itraconazole, voriconazole, amphotericin B, and nystatin proved a 10–35-fold reduction in the MIC_{80} values of drugs against 21 clinical *C. albicans* isolates [287]. The mechanism of synergistic activity of curcumin with amphotericin B and fluconazole was hypothesized to occur through the accumulation of ROS since the addition of an antioxidant could reverse it [287]. Moreover, various in vitro studies revealed the synergistic activity of curcumin with conventional antibiotics against several bacterial strains, such as *S. aureus*, *MRSA*, *E. coli*, *P. aeruginosa* [134,288–293].

On the other side, the combination of curcumin with the bactericidal antibiotic, ciprofloxacin, antagonized the bactericidal activity of ciprofloxacin against *Salmonella Typhi* and *Salmonella Typhimurium (S. Typhimurium)*. Furthermore, the studies on the elucidation

of the antogination mechanism indicated that curcumin reduces the antibacterial effect of the antibiotic due to its antioxidant properties. Accordingly, the oxidative stress induced by ciprofloxacin is suppressed by lowering ROS-induced filamentation in *S. Typhimurium* in the presence of curcumin [294]. These results are a significant warning against the unexpected consequences of the combination of antibiotics, which function by increasing oxidative stress, with antioxidants such as curcumin.

In accordance with the molecular structure of curcuminoids, the presence of phenolic hydroxyl groups acts as an electron donating group, interacts with the bacterial membrane, and thus increases the permeability of the bacterial membrane, enabling the targeting of antibacterial agents to bacterial cells [135]. In addition, the β-diketone moiety of curcuminoids might form a hydrogen bond containing a six-membered ring through keto−enol tautomerism as illustrated in Figure 8 [295,296]. The formed six-membered ring is a potential substrate for the aldo-keto reductase (AKR) enzymes, which are NADPH-dependent oxidoreductases. So, curcuminoids can be bound to the bacterial membrane and cause an increase in its AKR activity, the deficit of intracellular NADPH, and henceforward increase membrane permeability and bacterial cell death [297]. Although there are various studies on the contribution of the phenolic methoxy group in demethoxycurcumin and curcumin to their anti-inflammatory, anticancer and antioxidant activity [298–301], there remains a need for elucidation of the contribution of the methoxy group to antimicrobial activity.

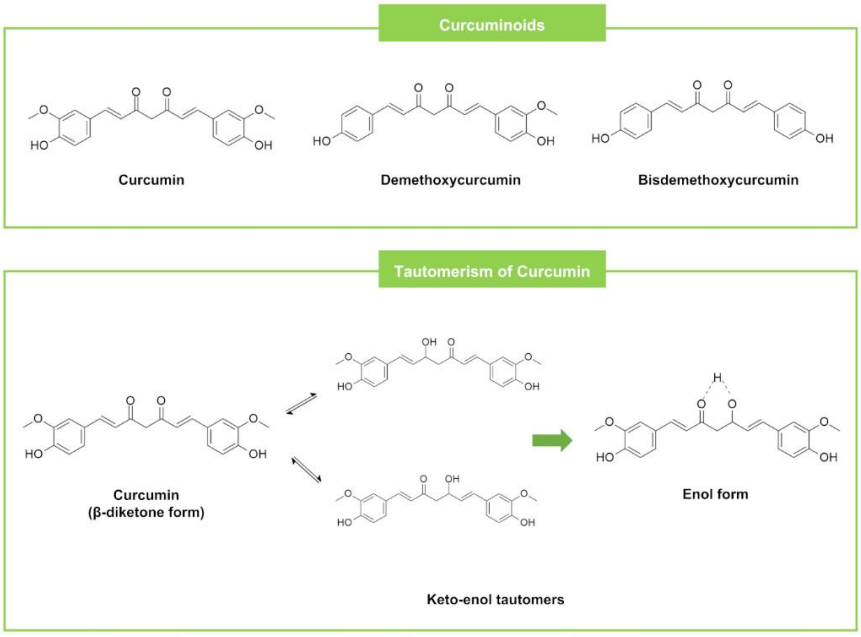

Figure 8. Representative chemical structures of curcuminoid compounds, and tautomerism of curcumin.

3. Limitations in the Therapeutic Usage of Natural Phenolic Compounds

Many natural compounds show various biological properties such as antimicrobial, antioxidant, antitumor, and anti-inflammatory activities. However, as a result of their poor water solubility and stability, these compounds can not be transported in the organism to the target site, significantly limiting their application. Alternative strategies for enhancing the efficacy of natural antimicrobials, or overcoming their limitations to use, have been explored and are still being developed. These have included encapsulation of the antimicrobial compound in varied manners, and modification of polar functional groups chemically or enzymatically to the relative compound, etc.

On the other hand, the conspicuous challenge is to overcome existing limitations on the use of natural phenolic compounds for therapeutic use, such as supply and identification of materials, scaled-up production, high throughput screening assays and possible safety issues [302–306]. In the isolation of large quantities of a particular natural compound, some circumstances may be challenging, such as low product yields or long growing

periods [307]. In addition, considering the problematic issue of the extinction of plants and other organisms due to environmental change, the large-scale supply of plants, marine organisms, or animals for industrial-scale production could have dire consequences on the ecological balance. Although progress has been made, the supply problem affecting the industrial-scale manufacture can be unraveled by developing an artificial biosynthetic pathway in cooperation with genetic engineering strategies.

Validation, characterization, and standardization of discovered natural compounds are critical for their approval into mainstream medicine. The quality of chemical components in a plant species can be impacted by different factors such as the age of the plant, geographical and seasonal variations, time, method of collection, etc. Hence, quality evaluation of the source product is time-consuming and costly, as the safety, efficacy, and quality of the isolated compound depend on the quality of the source product [308]. Efforts to provide a reliable and sustainable source product for the desired quantity and quality of the pharmacologically active substance are needed in combination with modern genetic engineering and agricultural technological methods [309].

4. Conclusions

Natural phenolic compounds with multiple-target mechanisms stand out as promising candidates for microbial infections. The mechanisms surveyed and specified in detail for each subclass include multiple mechanisms such as the hindrance of microbial cell wall biosynthesis, protein synthesis, nucleic acids synthesis, metabolic pathways, and disruption of cell membrane integrity. Hence, natural phenolic compounds do not present a specific target mechanism but multiple antibacterial mechanisms that have already been discovered and/or have yet to be discovered. The latest improvements in the therapeutic usage of nature-based compounds reveal their tremendous potential. The clinical applicability of these bioactive compounds requires a multi-disciplinary approach and synchronized actions of various fields. To date, there are still many aspects to be clarified regarding the structure-function relationships of many compounds that have been discovered or are yet to be discovered. The consequence of such novel therapeutic endeavors will open new doors in the health and pharmaceutical sector to cope with many diseases, including infections instigated by multidrug-resistant organisms.

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