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Review

Insights on phytochemicals as antimicrobial potentiators: a review

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Abstract

Ethnopharmacological research has been focused on finding novel anti-infective drugs in the last few decades. Many studies have been conducted on the antimicrobial activity of natural plant extracts used in traditional medicine, essential oils, or isolated compounds consisting of quinones, alkaloids, flavonoids, terpenes, coumarins, etc. These studies have focused on the therapeutic properties of plants or their active ingredients in terms of fighting a particular pathological microorganism.

The pharmaceutical industry is moving toward the expansion of structural chemotypes, since natural products are the main source of antibacterial leads. This emphasizes the immediate use of virtual libraries of more adaptable compounds, which have a propensity to be less structurally diverse.

Moreover, the majority of these drugs are derived from older drug classes that are currently in use and are susceptible to bacterial resistance mechanisms. Thus, the need to develop new medication classes is important. In order to incorporate novel natural products and guarantee that promising high-potential antimicrobial agents from structure-based drug design may be properly settled on target sites within the bacterial cell, it should be highlighted that diversification of screening libraries is necessary.

The objective of this work is to integrate knowledge from the vast, often scattered, literature on antimicrobial agents in order to select those with direct inhibitory activity and those that enhance antibiotic activity. Natural products should be thoroughly provided as soon as their chemotherapeutic or chemopreventive potential can be assessed in a manner relevant to our pharmacological research. This report will facilitate a preliminary inventory of the frequent use of medicinal plants containing active substances of curative interest, in order to screen the main natural products of interest. The objective of this work is to compile an exhaustive list of bioactive substances in order to correlate, on the one hand, their activity with their structure and, on the other hand, their modes of action with their antimicrobial potential.

Keywords:
Antimicrobials, Phytochemicals, Virtual libraries, Chemotherapeutic, Chemoprophylactic.

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1. Introduction

The concept of medicinal plants, from which the main molecules responsible for their antimicrobial activity would be designed today, was widely held long before the scientific recognition of microbes [1]. Natural products serve as the main precursors of many new drugs, insofar as 75% of infectious disease drugs are obtained from natural products [2]. After the development of sulfonamides and penicillin during the first half of the 20th century, which led to improved treatment of bacterial infections, the discovery of additional drug classes and their derivatives during the so-called "golden era of antibacterial drug discovery" has resulted in the widespread beneficial use of antibacterial drugs [3] [4]. The functional strategies of these natural product-based libraries are described in some recent works [5].

The therapeutic use of these molecules is currently based on rational scientific criteria, as much research deals with their antimicrobial properties and their mechanisms of action, which are responsible for causing significant damage to the microbial cell wall and membrane [6]. Nevertheless, the setting of their chemical structures, their proportions, the kind of their functional groups (phenols, alcohols, aldehydes, ketones, etc.), and therefore their synergistic effect can influence their antibacterial efficiency [7].

Poor selection of alternative antimicrobials, frequent switching between different antimicrobial treatments, and the widespread use of antibiotics-whether prescribed therapeutically or preventively-without following appropriate medical guidelines have all significantly contributed to the serious problem of bacterial resistance [8]. Besides mutations, the primary factors responsible for resistance transmission within distinct bacterial populations are mobile genetic components such as insertion sequences, plasmids, transposing, and integrative conjunctive elements [9].

Since flavonoids, alkaloids, and tannins are the main plant-derived substances with significant potential to be used as antimicrobial agents or as regulators of antibiotic resistance against bacterial infections, a lot of research has recently focused on studying plant extracts, essential oils, and pure secondary metabolites as potential antimicrobial agents [10] [11] [12]. Moreover, conventional approaches rely on herbal treatments with these natural products, which frequently prevent microbial resistance [13] [14].

It is worth noting that flavonoids can selectively target bacterial cells and additionally inhibit virulence factors and other microbial threats, including the formation of biofilms [15]. In the same way, essential oils extracted from parsley, basil, and thyme can disturb the physiological state of bacteria; thus, cell permeability improvement, cell constituent leakage, bacterial wall and membrane alterations, ATP loss, pH disruption, intracytoplasmic and DNA damage, protein synthesis, and quorum sensing inhibition are the main signs of this antimicrobial effect [16] [17].

This review draws up a comprehensive list of some antimicrobial molecules selected from natural product libraries, focusing on their chemical interactions and their mechanistic insights in mitigating the lethal consequences of multidrug-resistant microorganisms.

2. Main subclasses of plant-based antimicrobials

Plants represent a great reservoir of bioactive substances, thanks to their unlimited capacity to synthesize secondary metabolites. In many cases, these substances form part of the plants' defense mechanisms against predation by microorganisms, insects, and herbivores. Some molecules, such as terpenoids, give plants their odor; others, such as quinones and tannins, are responsible for plant pigmentation. Several compounds, such as capsaicin, are responsible for plant flavor [18].

Since the relatively recent advent of high-throughput organic synthesis in the drug discovery process, several design approaches have been applied to the construction of screening libraries. Libraries of natural-product derivatives and natural-product-like compounds prepared by total synthesis are several such approaches [19]. Our work will outline this library on the basis of the classification of natural products into various categories with their antimicrobial activities, as described and summarized in **Table 1**. These bioactive compounds are subdivided into many classes: phenolic compounds, quinones, flavonoids, tannins, coumarins, terpenoids, and alkaloids.

Table 1. List of some natural products used as antimicrobial agents.

Phytochemicals	Compound	Bioactivity	Microflora	References
Flavonoids	Ampelopsin	Antibacterial	*Staphylococcus aureus* (ATCC 6538), *Escherichia coli* (ATCC 8739),	[20]
	Myricetin	Antibacterial	*Staphylococcus aureus* (ATCC 6538), *E. coli* (ATCC 8739),	[20]
	Dihydrokaempferol	Antibacterial	*Staphylococcus aureus* (ATCC 29213), *Staphylococcus aureus* (clinical isolate 155),	[21]
	(+)-(2*R*)-Naringenin	Antibacterial	*Staphylococcus aureus* (ATCC 29213), *Staphylococcus aureus* (clinical isolate 155),	[21]
	3,7,3’ -Trihydroxy-4’-methoxy-8-prenylisoflavone	Antibacterial	*Staphylococcus aureus* (MRSA), *Enterococcus faecium,*	[22]
	8-(3-Hydroxy-3-methylbutyl)- 5,7,3’, 4’ -tetrahydroxyisoflavone	Antibacterial	*Staphylococcus aureus* (MRSA),	[22]
	8-(3-Hydroxy-3-methylbutyl)-5,7,4’ -trihydroxy-3’ -methoxyisoflavone	Antibacterial	*Staphylococcus aureus* (MRSA), *Enterococcus faecium,*	[22]
	8-(3-Hydroxy-3-methylbutyl)-5,7,3’ -trihydroxy-4’ -methoxyisoflavone	Antibacterial	*Staphylococcus aureus* (MRSA),	[22]
	3-*O*-*α*-*L*-Rhamnopyranosylquercetin	Antibacterial	*Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 6538),	[23]
	3-*O*-*α*-L-Rhamnopyranosylkaempferol	Antibacterial	*Staphylococcus aureus* (ATCC 6538),	[23]
	(*E*)-3’ -*O*-*β*-*D*-Glucopyranosyl-4,5,6,4’ -tetrahydroxy-7,2’ –dimethoxyaurone	Antibacterial	*Staphylococcus epidermidis*, *Pseudomonas aeruginosa* (ATCC 27853), *Pseudomonas aeruginosa* (290D),	[24]
	Tiliroside	Antibacterial	*S. aureus* (ATCC 25923), *S. aureus* (AS-1199B),	[24] [25]

Continued

	2'-Hydroxy-4,4',6'-trimethoxychalcone	Antibacterial	*S. aureus* (ATCC 25923),	[26]
	2'-Hydroxy-3,4,4',6'-tetramethoxychalcone	Antibacterial	*S. aureus* (ATCC 25923),	[26]
	3,2'-Dihydroxy-4,4',6'-trimethoxychalcone	Antibacterial	*S. aureus* (ATCC 25923),	[26]
	Genkwanin	Antibacterial	*S. aureus* (AS-1199B),	[27]
	7,4'-Dimethylapigenin	Antibacterial	*S. aureus* (AS-1199B),	[27]
	Trimethylapigenin	Antibacterial	*S. aureus* (AS-1199B),	[27]
	Cirsimaritin	Antibacterial	*S. aureus* (AS-1199B),	[27]
	Tetramethylscutellarein	Antibacterial	*S. aureus* (AS-1199B),	[27]
Coumarins	Tanizin	Antibacterial	*Bacillus cereus* (ATCC 33019), *Enterococcus* spp (ATCC 6589), *Enterobacter aerogenes* (ATCC 13048), *P. aeruginosa* (ATCC 9027), *E. coli* (ATCC 25922), *Burkholderia cepacia* (ATCC 17759), *Shigella sonnei* (ATCC 25931), *Salmonella typhimurium* (ATCC 14028), *Morganella morganii* (ATCC 25829),	[28]
	Gravellifenore	Antibacterial	*B. subtilis* (ATCC 6633), *B. cereus* (ATCC 33019), *Enterococcus* spp (ATCC 6589), *E. aeruginosa* (ATCC 9027), *E. coli* (ATCC 25922), *B. cepacia* (ATCC 17759), *S. sonnei* (ATCC 25931), *S. typhimurium* (ATCC 14028), *M. morganii* (ATCC 25829),	[28]
	3,4-Dihydroxy-2-methoxyxanthone	Antibacterial	*S. aureus* (SA-1199B), *S. aureus* (XU212), *S. aureus* (ATCC 25923), *S. aureus* (RN4220), *S. aureus* (EMRSA-15), *S. aureus* (EMRSA-16),	[29]
	5-Hydroxy-1,3-dimethoxyxanthone	Antibacterial	*S. aureus* (SA-1199B), *S. aureus* (ATCC 25923), *S. aureus* (EMRSA-16),	[29]
	4-Hydroxy-2,3-dimethoxyxanthone	Antibacterial	*S. aureus* (SA-1199B), *S. aureus* (XU212), *S. aureus* (EMRSA-16),	[29]

Continued

Xanthones	1,3,7'-Trihydroxy-2-(3-methylbut-2-enyl)-xanthone	Antibacterial	*S. aureus* (ATCC 25922), *E. coli* (ATCC 25922), *B. subtilis* (ATCC 6623), *P. aeruginosa* (ATCC 15442),	[30]
	8-Carboxymethyl-1,3,5,6-tetrahydroxy xanthone	Antibacterial	*S. aureus* (ATCC 25923), *B. subtilis* (ATCC 19659), *P. aeruginosa* (ATCC 27853),	[31]
	1,5-Dihydroxyxanthone	Antibacterial	*B. cereus* (ATCC 14579), *S. aureus* (ATCC 6538P), *S. saprophyticus* (ATCC 35552), *S. agalactiae* (ATCC 13813),	[32]
Hydrolyzable Tannins	Tannic acid	Antibacterial	*S. aureus,* *B. subtilis,* *Enterococcus faecalis,* *P. aeruginosa,* *Pectobacterium chrysanhemi,* *Bacteroides fragilis,* *Clostridium perfringens,* *E. coli,* *Enterobacter cloacae,* *Clostridium clostridioforme,*	[33] [34], [35] [36]
	Strictinin	Antibacterial	*Propioni bacterium acnes,* *S. epidermidis,*	[37]
	Tellimagrandin I	Antibacterial	*H.pylori,* *S. aureus* (MRSA),	[38] [39]
	Tellimagrandin II	Antibacterial	*S. aureus* (MRSA), *S. aureus* (MSSA), *H. pylori,*	[38] [40]
	Corilagin	Antibacterial	*E. coli,* *S. aureus,* *B. subtilis,* *K. pneumoniae,* *P. aeruginosa,* *Proteus mirabilis*	[41] [42]
		Antifungal	*Candida albicans,*	[41]
	Geraniin	Antibacterial	*E. coli,* *S. aureus,* *H. pylori,* *P. aeruginosa,* *P. cichorii,* *P. fluorescens*	[38][43]

Continued

	Rugosin D	Antibacterial	*E. coli*, *S. aureus*, *B. cereus*, *Salmonella* sp., *H. pylori*,	[38][44]
	Casurinin	Antibacterial	*H.pylori*,	[38]
	Pedunculagin	Antibacterial	*S. aureus*, *Salmonella arizonae*, *Salmonella anatum*, *Salmonella serotype O*, Nonpathogenic *E. coli*, Enterohemorrhagic *E. coli*, Enteroinvasive *E. coli*, Enterotoxigenic *E. coli*, *Vibrio cholerae*, *Vibrio parahaemolyticus*, *Vibrio vulnificus*,	[45]
	1,2,6-Tri-*O*-galloyl-*β*-*D*-glucopyranose	Antibacterial	Multidrug-resistant *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *S. aureus*,	[46]
	1,3,6-Tri-*O*-galloyl-*β*-*D*-glucopyranose	Antibacterial	*S. aureus* (MRSA),	[47]
	1,2,3,6-Tetra-*O*-galloyl-*β*-*D*-glucopyranose	Antibacterial	*H. pylori*, *B. subtilis*,	[48]
Flavanols	Catechin	Antibacterial	*B. subtilis*, *E. coli*, *P. vulgaris*, *P. fluorescens*, *Salmonella* spp., *S. aureus*,	[49]
		Antiprotozoal	*Trypanosoma cruzi*,	[50]

Continued

Condensed Tannins	Proanthocyanidins	Antibacterial	*Aeromonas* spp., *Bacillus* spp., *Clostridium botulinum,* *Clostridium perfringens,* *Enterobacter* spp., *Klebsiella* spp., *Proteus* spp., *Pseudomonas* spp., *Shigella* spp., *S. aureus,* *Streptococcus* spp., *Vibrio* spp.,	[51]
		Antiprotozoal	*Giardia lamblia,* *Entamoeba histolytica,* *Trypanosoma brucei,*	[52][53]
Terpenoids	Lupeol	Antibacterial	*E. coli,* *Mycobacterium smegmatis,*	[54]
Alkaloids	Berberine	Antibacterial	*Staphylococcus aureus* (MRSA), *Clostridium perfringens,* *Salmonella typhimurium,* *Vibrio parahaemolyticus,*	[55][56]
		Antifungal	*Trichophyton mentagrophytes*	[55]

2.1. Phenolic compounds

Some bioactive molecules, with simple chemical structures, contain a single substituted phenolic cycle; specifically, cinnamic acid and caffeic acid are the prevalent substrates of phenylpropane derivatives that represent the highest oxidation state. Notably, tarragon and thyme are famous plants containing caffeic acid, which has proven to be effective against viruses [57], bacteria [58], and fungi [58].

Catechol and pyrogallol, which have two and three hydroxyl groups, respectively, were found to be toxic to microorganisms. In fact, the position and number of hydroxyl groups on the phenol molecule are probably linked to the degree of toxicity to microorganisms, as strong hydroxylation makes a molecule more toxic [59]. Therefore, researchers have found that highly oxidized phenols are the best inhibitors [60]. The mechanisms responsible for phenolic toxicity to microorganisms, in particular enzymatic inhibition under the action of oxidized compounds, may be linked to reactions with sulfhydryl groups or to their non-specific interactions with proteins [61]. Non-oxygenated phenolic compounds with a three-carbon side chain at a lower oxidation degree, corresponding to essential oils, are often also evaluated as antimicrobial agents. Eugenol, a major constituent of clove oil, has a bacteriostatic effect against fungi [58] and bacteria [62].

2.2. Quinones

Quinones are ubiquitous substances in nature, serving as highly reactive colorants responsible for the reddening reaction of cut or damaged fruit and vegetables.
They play an intermediate role in the synthetic pathway of melanin in human skin [65], and their presence in the henna gives it tinctorial properties [63].
In many biological systems, the redox potential of a certain quinone-hydroquinone combination is very important, as shown by the role of ubiquinone (coenzyme Q10) in the mammalian electron transport system, as well as the fact that vitamin K, a naphthoquinone complex, has anti-hemorrhagic activity, which may be linked to its convenient oxidation in body tissues [64]. Hydroxylated amino acids can be converted to quinones in the presence of appropriate enzymes, such as polyphenol oxidase [68], and the reaction converting tyrosine to quinone is illustrated in **Figure 1**.

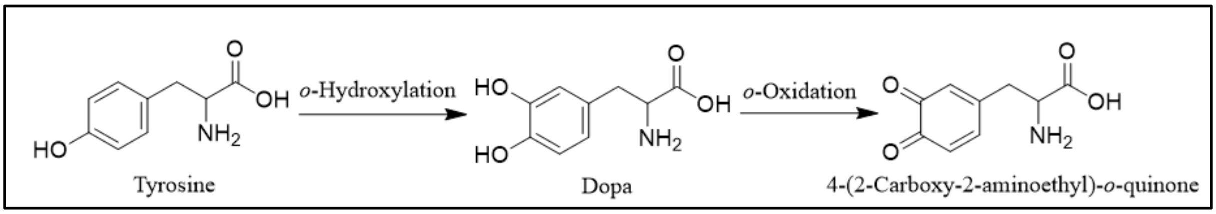


Figure 1. Conversion of tyrosine to the corresponding quinone.

In addition to their availability as a stable source of free radicals, quinones are known for their irreversible complexation with nucleophilic amino acids in proteins [65], often leading to the inactivation of these proteins and the loss of their function. As a result, a wide range of microbial targets, including membrane-bound enzymes, cell wall polypeptides, and surface-exposed adhesins, could be the focus of quinone's antibacterial actions.
Kazmi et *al.* [70] reported that anthraquinone, a molecule extracted from the *Cassia italica* species, which is a Pakistani tree, has a bacteriostatic effect on *Bacillus anthracis*, *Corynebacterium pseudodiphthericum* and *Pseudomonas aeruginosa*, but a bactericidal effect on *Pseudomonas pseudomallei*, as well as hypericin, an anthraquinone obtained from peppermint (*Hypericum perforatum*), has recently attracted the attention of the popular press as an antidepressant. In addition, Duke confirmed its general antimicrobial properties [58].

2.3. Flavonoids and their derivatives

Flavonoids are synthesized by plants in response to a microbial infection, so it is not surprising that they have proven effective in vitro against a wide range of microorganisms.
Their activity is probably due to their ability to complex with extracellular soluble proteins and, thus, with bacterial cell walls. Lipophilic flavonoids can also disrupt microbial membranes [66]. Catechin is the smallest form of unit C3 in flavonoid compounds. The chemical structure of some flavonoids that possess antimicrobial features is illustrated in **Figure 2**.
These flavonoids have been the subject of many papers due to their presence in the green tea of the oolong plant. It has been observed that tea exerts antimicrobial activity [67] and contains a mixture of catechin compounds that have inhibited *in vitro* bacteria such as: *Vibrio cholerae* O1 [68], *Streptococcus mutans* [69], *Shigella* [70] and other microorganisms involved in caries [71]. The catechin inactivated the cholera toxin in *Vibrio* [68] and inhibited the bacterial glycosyltransferases isolated from *S.mutans* [72], due to their complication activity, which was confirmed via *in vivo* tests on conventional rats. When rats were fed a diet containing 0.1% tea catechin, dental caries (caused by *S. mutans*) were reduced by 40% [73].
The researchers suggest that the small differences of the compound structures are beneficial for their activity by emphasizing their low toxicity.

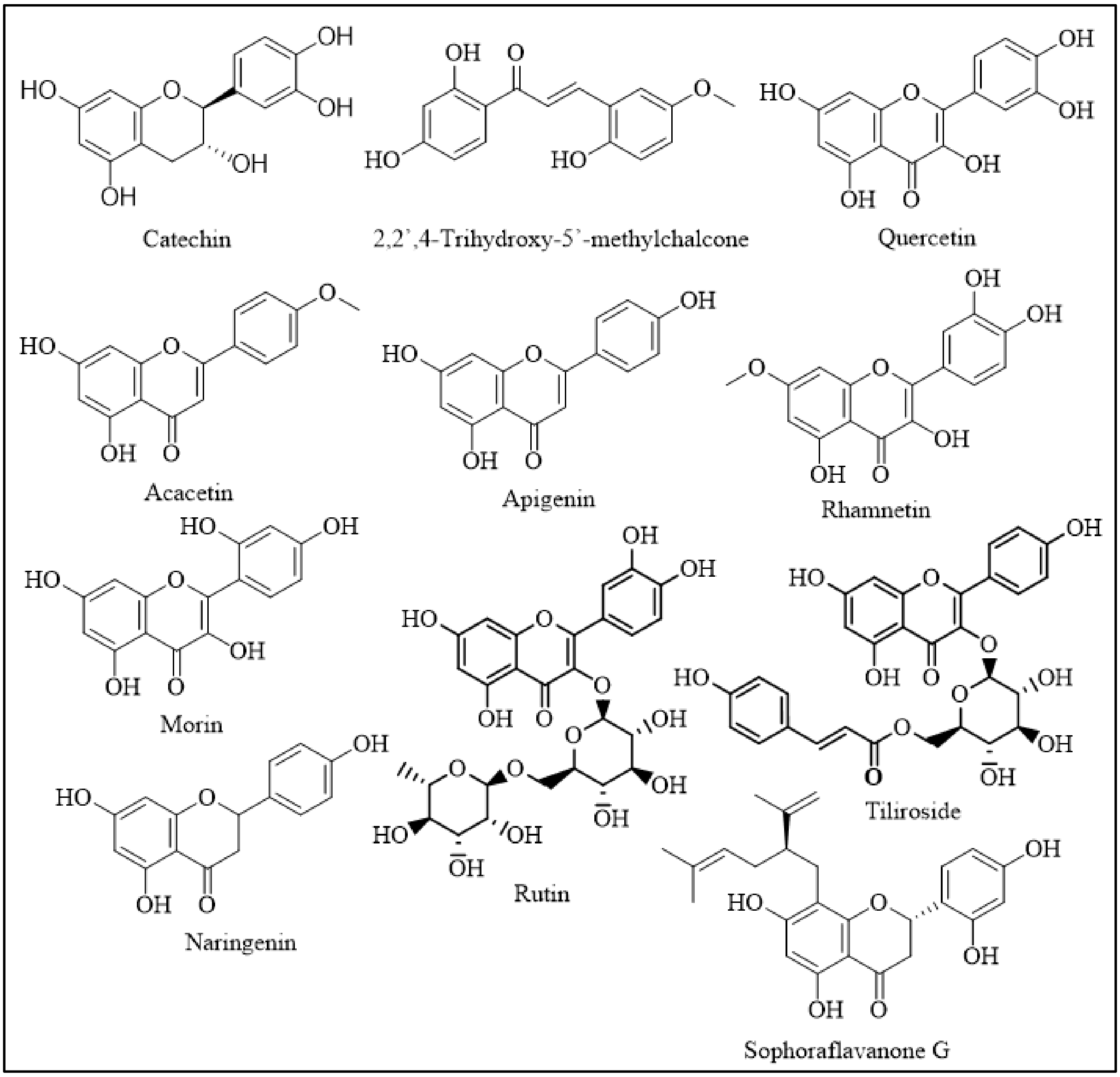
Alpinumisoflavone is an isoflavone found in a West African legume that prevents schistosomal infection when applied topically [74]. Fluoretin, which is found in some apple serotypes, may have antimicrobial activity against a variety of microorganisms [75]. Galangin (3,5,7-trihydroxyflavone), extracted from the perennial herb *Helichrysum auronitens,* was revealed to be active against a wide range of Gram-positive bacteria as well as fungi [76] and viruses such as : HSV-1 and coxsackie B virus type-1 [77].

Petalostemumol, isolated from the purple prairie clover, *Petalostemum purpureum*, is moderately active against gram-negative bacteria: *Escherichia coli* ATCC 10536, *Cryptococcus neoformans* ATCC 32264, and gram-positive bacteria: *Mycobacterium intracellulare* ATCC 23068; as well as *Candida albicans*, but this natural product is endowed with excellent activity against *Bacillus subtilis* and *Staphylococcus aureus* [185].

The delimitation of the possible mechanisms of action of flavones and flavonoids is hampered by contradictory results. Flavonoids without hydroxy groups in their B-cycles are more active against microorganisms than those with hydroxy groups [78]. This observation endorses the idea that their microbial target is the membrane (**Figure 3**). Lipophilic compounds would be more disruptive to this structure. However, several researchers have also observed the opposite effect; when hydroxylation increases, antimicrobial activity is significant [79]. This latter finding reflects the same result with simple phenolic compounds. **Table 2** presents the mode of action of some flavonoids proven to be antibacterial agents.

Table 2. List of some flavonoids used as antimicrobial agents with their modes of action.

Mode of action	Flavonoid classes	References
Membrane disruption	Catechin	[80]
	2,4,6’-Trihydroxy-5’-methylchalcone	[81]
	Quercetin	[82][83]
	Flavones (acacetin, apigenin), **Flavonols** (morin, rhamnetin)	[84]
	Flavanones (naringenin, sophoraflavanone G)	[85]
	Flavonols glycoside (rutin, tiliroside)	[83]
Biofilm formation	Epigallocatechin gallate (EGCG), 3-*O*-octanoyl-epicatechin	[86][87]
	Galangin	[88]
	Isovitexin, Epicatechin, 5,7,4'-trihydroxyflavan-3-ol	[89]
	Apigenin, kaempferol, quercetin, naringenin	[90][87][91]
	Epicatechin gallate (ECG)	[87]
	Proanthocyanidin A	[92]
	6-Aminoflavone, 6-hydroxyflavone, apigenin, chrysin, **isoflavones** (daidzein, genistein), **dihydrochalcones** (phloretin)	[93][91]
	Pinostrobin	[94]
Inhibition of cell envelope synthesis	Quercetin, apigenin, sakuranetin	[95][96][97]
	Eriodictyol, naringenin, taxifolin	[98]
	5,6,7,4’,5’-Pentahydroxyflavone, 5-hydroxy-4’,7-dimethoxyflavone.	[99]
	EGCG	[100][97][101]
	Kaempferol, fisetin, morin, myricetin, baicalein, luteolin	[97][101]
	Chalcones (2,2’,4’-Trihydroxychalcone, butein, isoliquiritigenin), fisetin.	[102]
	Galangin, kaempferide, kaempferide-3-*O*-glucoside	[103]
Inhibition of nucleic acid synthesis	Quercetin, apigenin, 3,6,7,3’,4’-pentahydroxyflavone	[104]
	Chrysin, kaempferol	[105]
	Genistein	[106]
	Luteolin, morin, myricetin	[107][108][109]
	Baicalein	[109]
	EGCG	[110][108]
	Robinetin	[108]
Inhibition of bacterial toxins	Myricetin, quercetin	[111]
	Catechin, proanthocyanidin A	[112][113]
	Genistein, kaempferol, kaempferol-3-*O*-rutinoside, isoquercetin.	[114]
	Pinocembrin	[115]
	EGCG, gallocatechin gallate (GCG)	[116]
Inhibition of electron transport chain and ATP synthesis	Isobavachalcone, 6-prenylapigenin	[117]
	Baicalein, morin, EC, silibinin, silymarin, quercetin, isoquercetin,quercetin-3-*O*-rhamnoside	[118]
	EGCG	[119]
	4’, 5’, 5-Trihydroxy-6,7-dimethoxyflavone	[99]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Acacetin
Apigenin
Rhamnetin
Morin
Rutin
Tiliroside
Naringenin
Sophoraflavanone G

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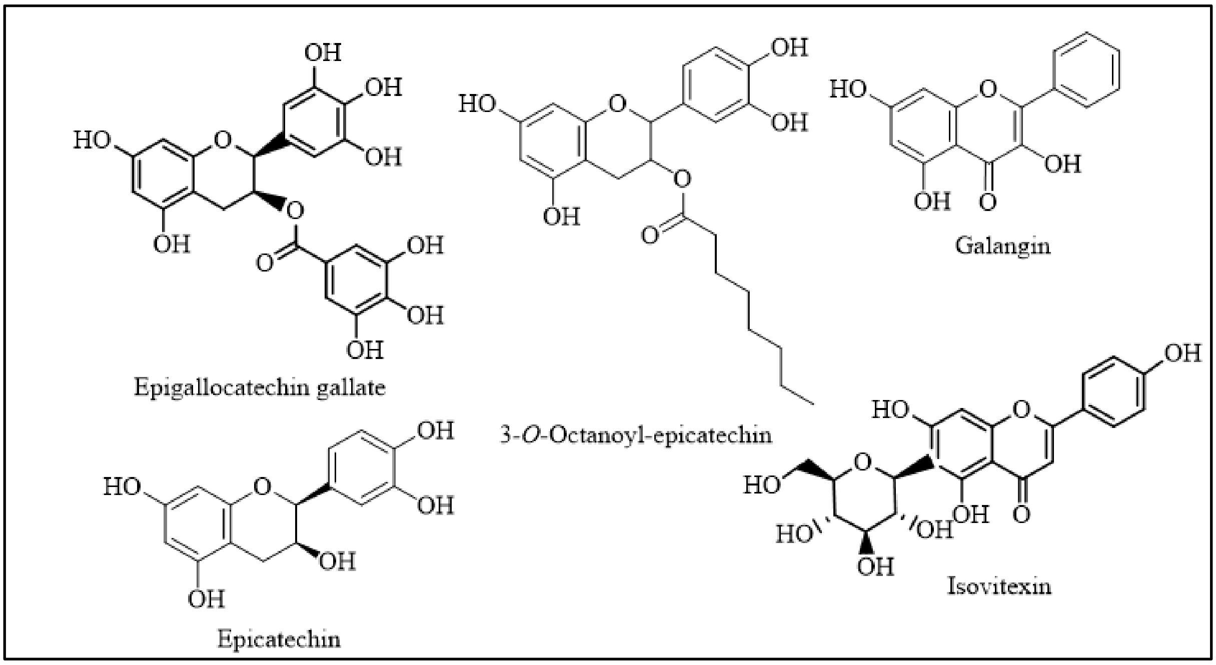
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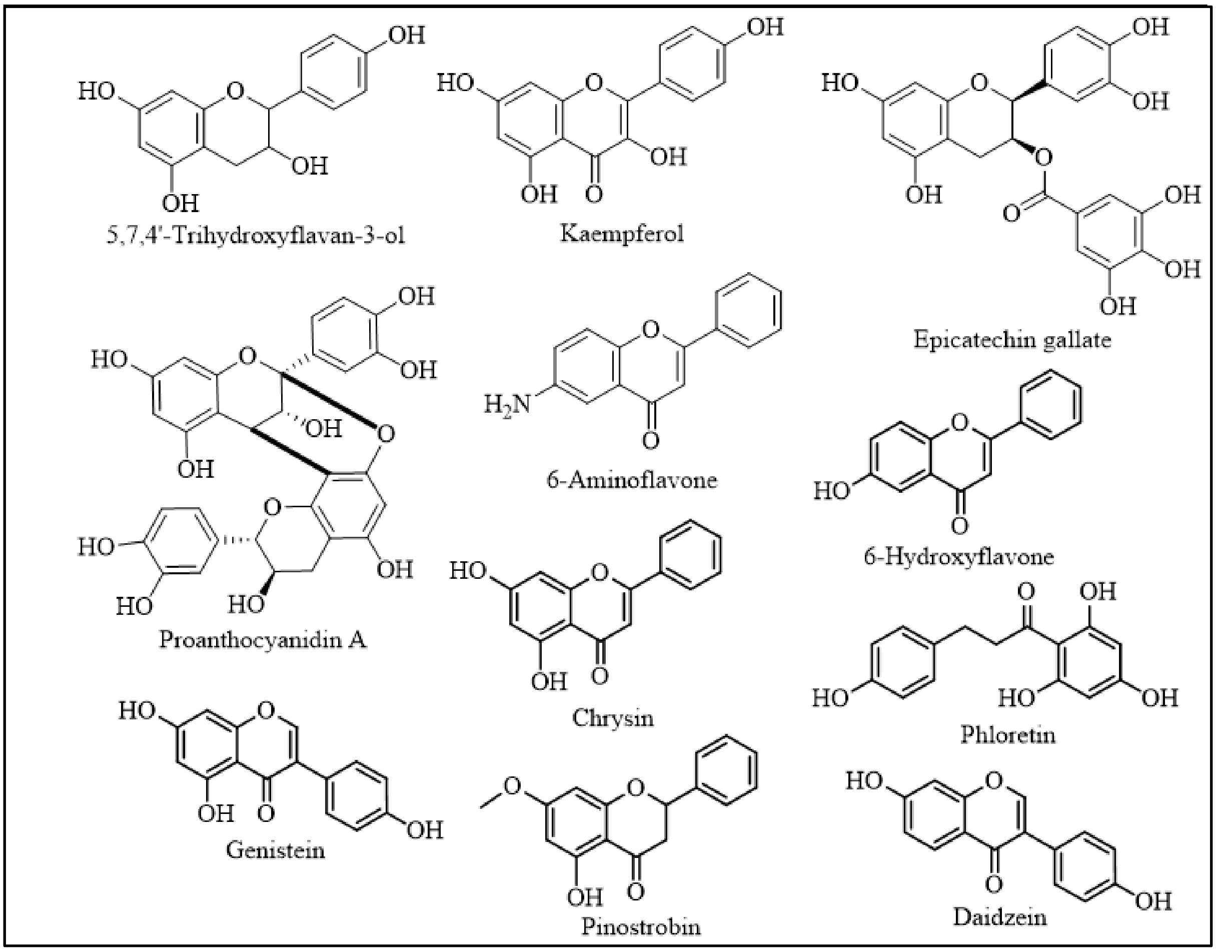
Galangin
Epicatechin
Isovitexin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Epicatechin gallate
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Genistein
Pinostrobin
Daidzein

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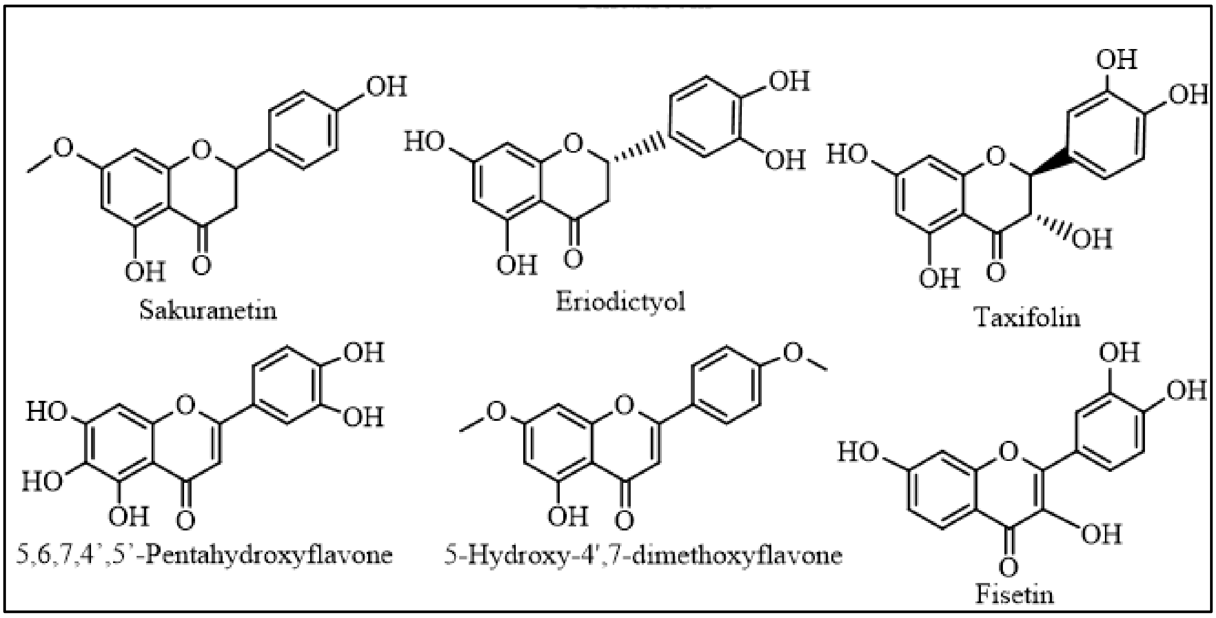
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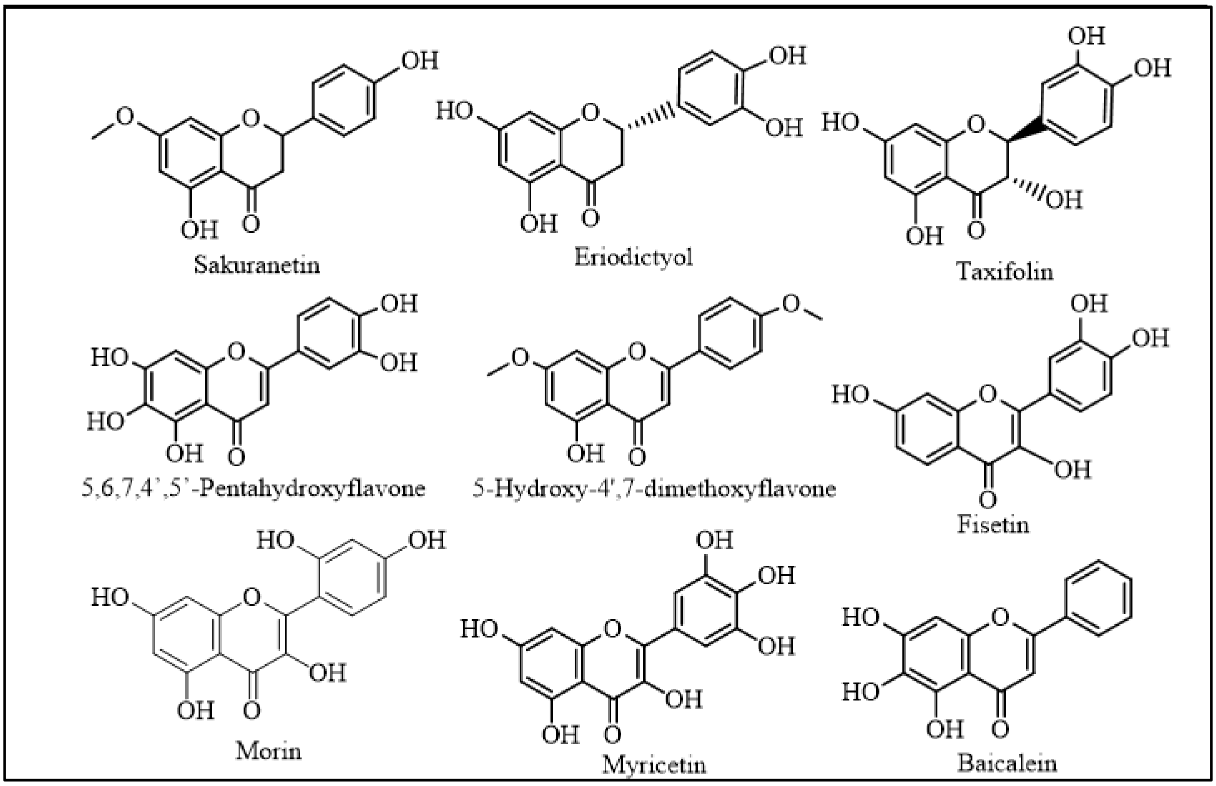
Fisetin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Taxifolin
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Morin
Myricetin
Baicalein

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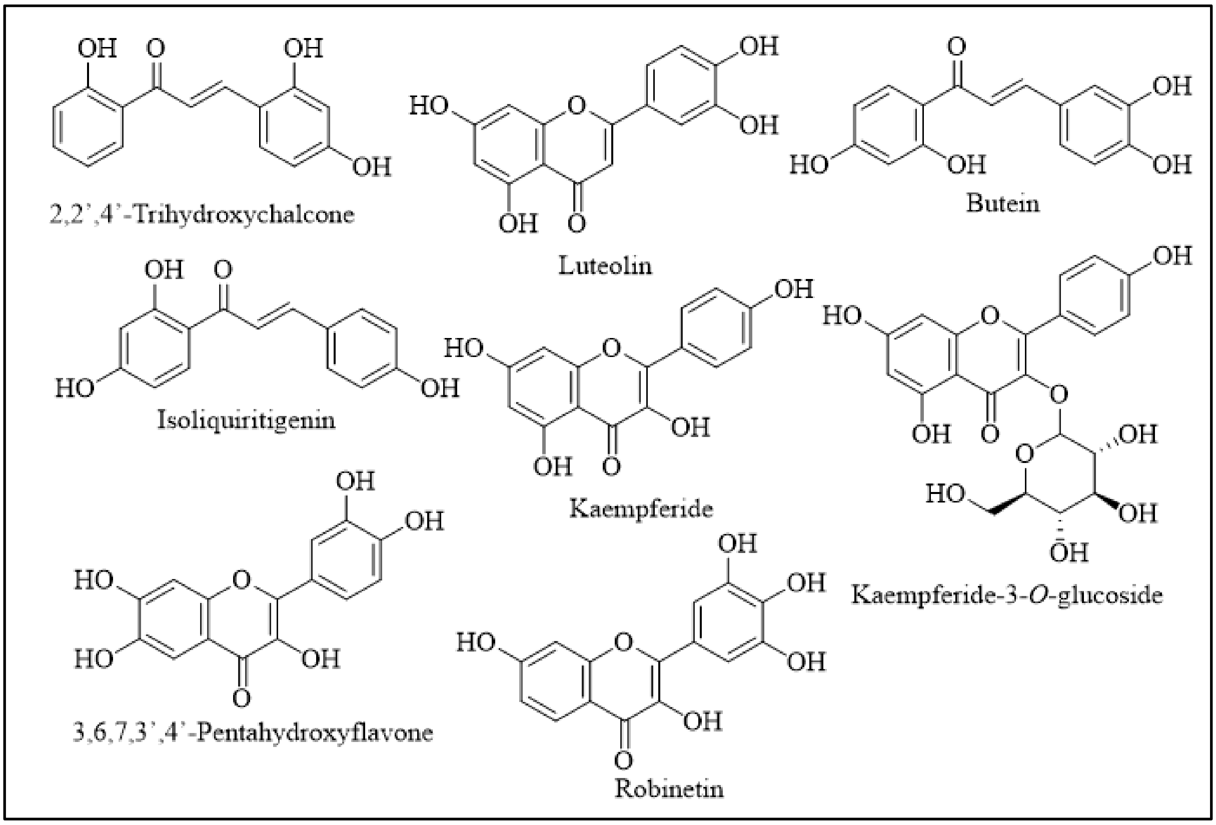
2,2',4'-Trihydroxychalcone
Luteolin
Butein
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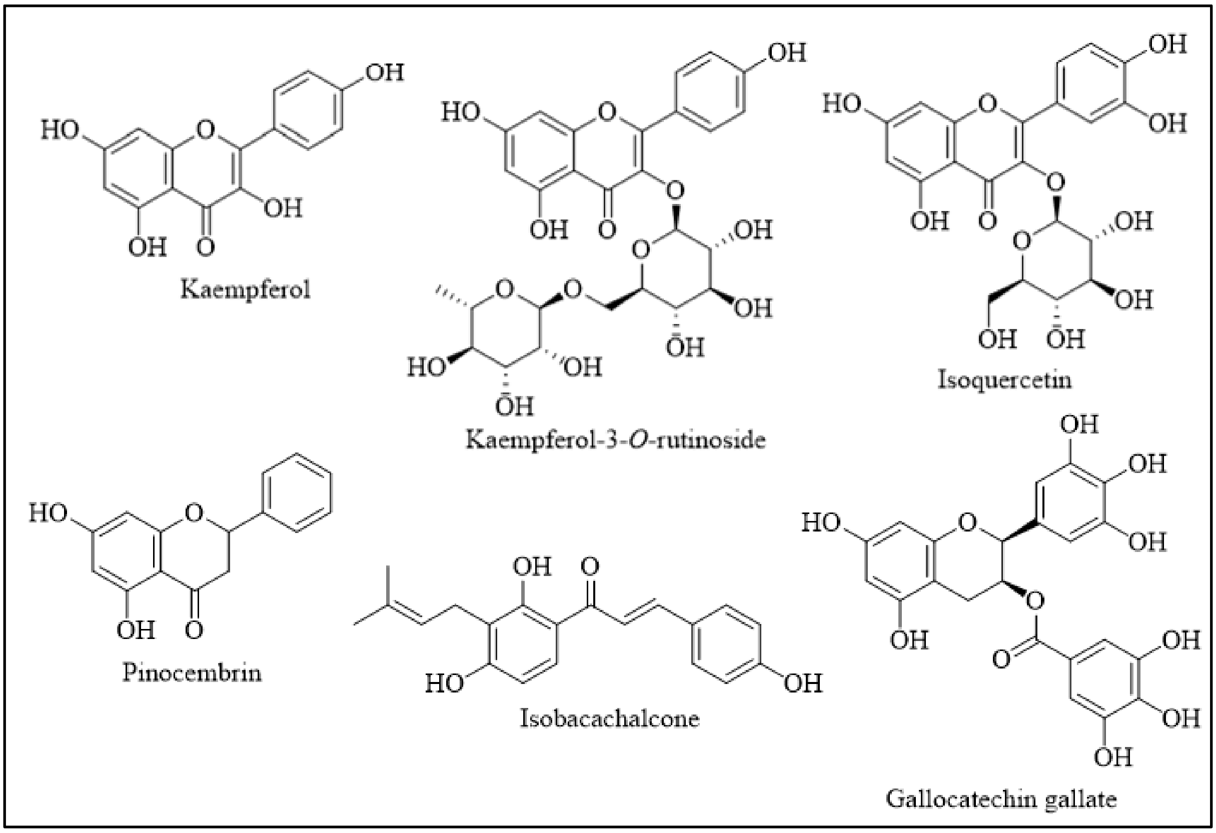
Kaempferide-3-*O*-glucoside
3,6,7,3',4'-Pentahydroxyflavone
Robinetin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Kaempferol-3-*O*-rutinoside
Isoquercetin
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Isobacachalcone
Gallocatechin gallate

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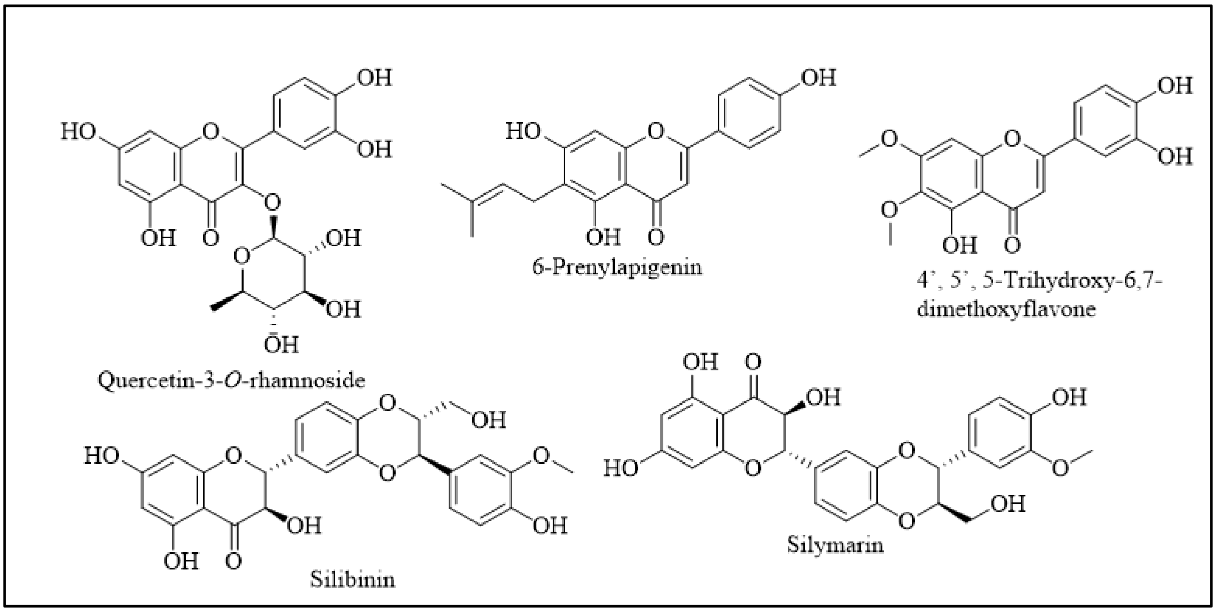


Figure 2. Chemical structures of some flavonoids possessing antimicrobial activities.

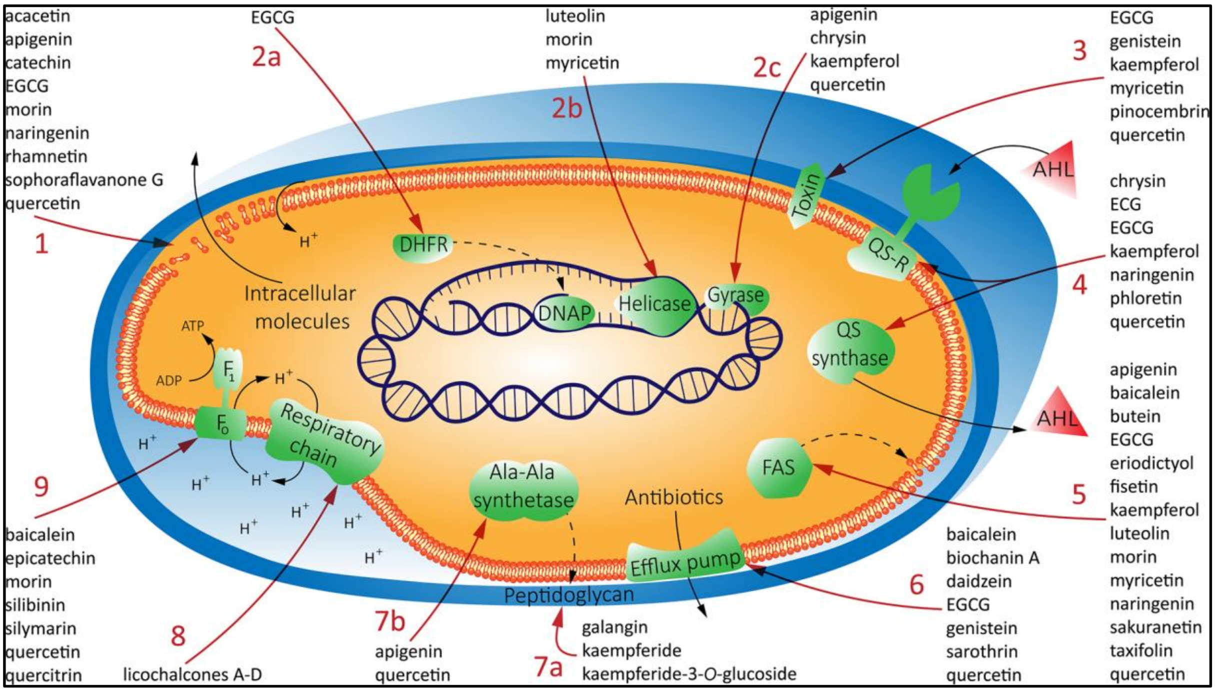


Figure 3. Schematic representation of the action mechanism of flavonoids used as antibacterial agents. Flavonoids generally, act either as killer or inhibitor of bacterial cells, such as causing : (1) membrane disruption, (2) inhibition of nucleic acid synthesis (2a- inhibition of dihydrofolate reductase (DHFR), 2b- helicase inhibition, 2c- gyrase/topoisomerase inhibition), (3) inhibition of the bacterial virulence, e.g. toxins, (4) quorum sensing, which impairs their ability to form biofilms, (5) inhibition of cell envelope synthesis, which involves inhibition of fatty acid synthase (FAS), (6) inhibition of the efflux pumps as well, which can lead to reversing antimicrobial resistance; (7) inhibition of peptidoglycan synthesis (7a- inhibition of Ala–Ala dipeptide synthesis, 7b- inhibition of peptidoglycan cross-linking), (8) inhibition of NADH-cytochrome c reductase activity in the bacterial respiratory chain and (9) inhibition of ATP synthase [15].

2.4. Tannins

Tannins are found in almost all parts of the plant: bark, wood, leaves, fruits, and roots [60]. Two types are distinguished: hydrolysable tannins and condensed tannins.

Hydrolysable tannins are based on gallic acid, usually in the form of multiple esters with *D*-glucose, while condensed tannins (often called proanthocyanidins) are derived from flavonoid monomers.

On the one hand, tannins can be formed from the condensation of flavone derivatives that are transported to plant tissues. On the other hand, they can be formed from the polymerization of quinone patterns [60]. It should be noted that the consumption of drinks containing tannins, especially green tea, can cure or prevent a variety of pathologies [120].

Many human physiological activities, such as phagocyte cell stimulation, host-mediated tumor activity, and a wide range of anti-infection actions, have been attributed to tannins [121]. One of their molecular actions is to complex with proteins through non-specific forces between different chemical bonds such as hydrogen bonds, covalent bonds, and hydrophobic effects [65]. Their antimicrobial mode of action may be related to their ability to disable microbial adhesins, enzymes, and transport proteins involved in the cellular envelope. They are also intricate with polysaccharides (**Figure 4**) [122]. In addition, there is evidence of direct inactivation of microorganisms: low concentrations of tannins alter the morphology of the germ tubes of *Crinipellis perniciosa* [123]. Thus, tannins inhibit insect growth [124] and disrupt the digestive system in ruminants [125].

According to Scalbert et *al*. [60], tannins can be toxic to filamentous fungi, yeasts and bacteria. They found that condensed tannins attach to the cell walls of ruminal bacteria, preventing their growth and protease activity [126]. Although still speculative, tannins are responsible for the antibiotic activity of methanol extracts from the bark of *Terminalia alata*, a plant endemic to Nepal [127]. This activity is enhanced under the influence of UV light (320 to 400 nm). Tannins have been demonstrated in other research to inhibit reverse viral transcriptases [128]. O'May and Tufenkji [129] showed that proanthocyanidins (PACs), which are mainly condensed tannins, interfere with bacterial adhesion and decrease the swarming motility of *Pseudomonas aeruginosa*, both in terms of distance traveled and swarming pattern complexity, by modifying the biofilms produced by *P. aeruginosa* when applied continuously to the culture, which is consistent with published results for other Gram-negative bacteria such as *Escherichia coli* [130] and *Porphyromonas gingivalis* [131]. In addition, other studies have revealed that type-A (PACs) reduce *E. coli* adhesion to surfaces via P-fimbriae [132]. The PACs have been shown to have an effect on a wide variety of bacterial systems, their main mechanism being iron chelation, an effect already known in *E. coli* [133].

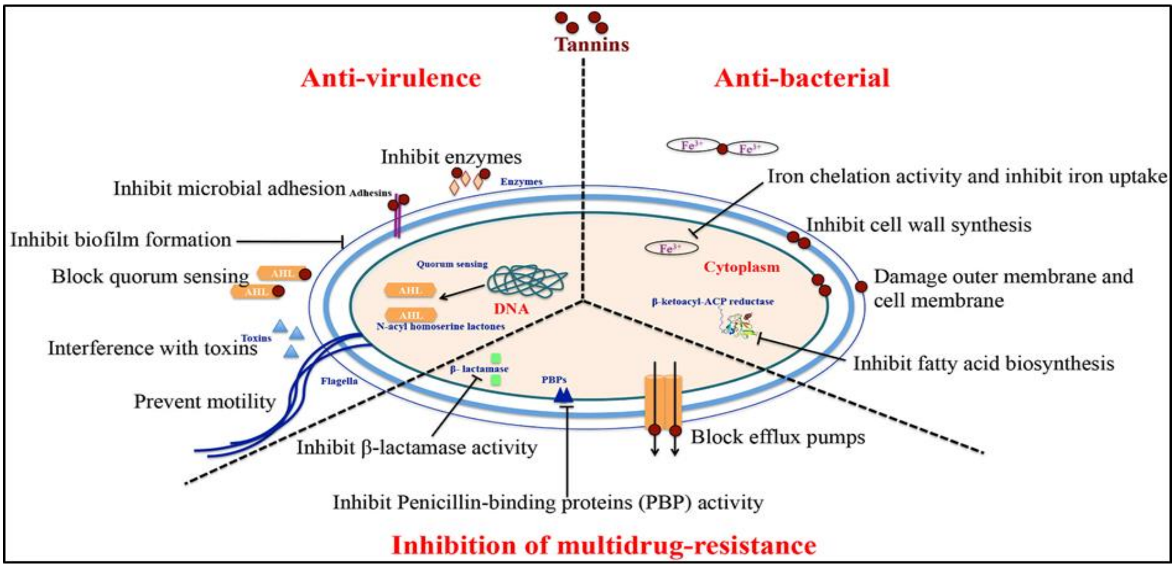


Figure 4. Schematic illustration of the mechanism of action of tannins as antibacterial agents [134].

2.5. Coumarins

Coumarins, whose name is derived from the *Coumarouna odorata* plant (*Dipteryx odorata*) from which the simplest coumarin molecule was isolated by Vogel in 1820 [135], represent a vast family of secondary metabolites identified in numerous plant species as well as fungi and microorganisms [136]. These benzopyrone compounds can be subdivided into the benzo-α-pyrones to which the coumarins belong and the benzo-γ-pyrones, of which the flavonoids are principal members [137]. These compounds are classified into four main subtypes: simple coumarins (e.g. coumarin,7- hydroxycoumarin and 6,7-dihydroxycoumarin), furanocoumarins consist of a five-membered furan ring attached to the coumarin nucleus, divided into linear or angular types with substitution at one or both of the remaining benzene positions [138], pyranocoumarins are analogous to the furanocoumarins, but contain a six-membered ring; and pyrone-substituted coumarins including 4-hydroxycoumarin [139]. Among the most common coumarins found in nature, umbelliferone, esculetin and scopoletin are considered the best-known.
During the synthesis of these compounds, *o*-hydroxylation should take place on *p*-coumaric, caffeic and ferulic acids. Simple coumarins are interesting candidates for further skeletal derivatization, as their pharmacological characteristics and therapeutic applications depend on the substitution pattern; they are therefore proposed for use in clinical medicine and should be evaluated for the treatment of various clinical infections. While some toxic coumarin derivatives are excreted and eliminated safely in human urine [140]. Thornes et *al*. (1954) found that coumarins are very active against *Candida albicans* during their *in vitro* tests when looking for a treatment for vaginal candidiasis that can affect pregnant patients. In consecutive *in vivo* trials on rabbits, the feeding water supply of coumarins was inadvertently administered to all the animals and turned out to contain a powerful contraceptive when breeding programs began to fail [106].
Generally, coumarin stimulates macrophages [140], which could have an indirect negative effect on infections. It has been demonstrated that the coumarins connected to hydroxycinnamic acids are more active against Gram-positive bacteria [141]. Several studies have demonstrated that certain coumarin derivatives (**Table 3**) have powerful antimicrobial activity, as in the case of (+)-calanolide A, a tetracyclic dipyranocoumarin, and its derivatives, which have been shown to be active against *Mycobacterium tuberculosis* (H37Rv), a strain resistant to standard anti-tuberculosis drugs [142]. Xu *et al*. reported that (+)-calanolide A can inhibit 96% of this strain at a concentration of 12.5 µg/mL, while this coumarin can inhibit 81% of *Mycobacterium avium* at the same concentration. This coumarin has a minimum inhibitory concentration (MIC) of 3.13 µg/mL or 8 µM, which represents the lowest concentration that inhibits > 99% of the bacterial population observed at the beginning of the assay.
Moreover, the coumarins: (-)-calanolide A, (-)-calanolide B, and (-)-soulattrolide exhibited 98-99% inhibition at a concentration of 12.5 µg/mL against *M. tuberculosis* strain H37Rv, with MIC values at the same level as (+)-calanolide A, as shown in **Table 4.** It may be possible to identify the main structural elements included in these pyranocoumarins and responsible for their anti-TB action. First off, compounds with the 12-OH group, like those in previous compounds, are active, but the other compounds, which all have a carbonyl group at the 12-position, are inactive. This suggests that the 12-OH group represents the most important structural element. The structure of some coumarins is summarized in **Figure 5**.
Dicoumarol [143] showed excellent activity against *Bacillus anthracis*, *Staphylococcus aureus*, *Staphylococcus albus*, *Streptococcus pyogenes*, and *Pasteurella avicida*, although it has no growth suppressant action against some microorganisms. Cavallito suggested that the predominant activity of relatively lipophilic dicoumarol against Gram-positive bacteria can be attributed to the hydrophilic properties of Gram-negative bacteria and lipophilic character of Gram-positive bacteria [144].
Ukita and co-workers [145] observed remarkable antibacterial activity against *Staphylococcus aureus* and *Mycobacterium tuberculosis* (avian type) with another synthetic coumarin, named 3-acetyl-4-hydroxycoumarin. More recently, Ukita's group [112] deduced that 3-acetyl coumarins manifest an uncoupling effect on oxidative phosphorylation when they studied their mode of action (**Figure 6**). Thus, dicoumarol was found to be a potent uncoupling agent [146].
To enhance the potency and antifungal profile of the core structure, Sardari and colleagues isolated angelicin as a

bioactive component from *Diplotaenia damavandica*, a rare Iranian native species [147]. This bioactive molecule was considered the lead structure in the present study, based on the synthesis of novel angelicin derivatives endowed with highly significant antimicrobial activity. It should be noted that these compounds' lipophilicity and antifungal activity correlate rather strongly. **Table 3** presents some coumarin products that have antibacterial properties, and **Table 4** shows their minimal inhibitory concentrations.

Recently, Xu and co-workers revealed that coumarins may prevent the adhesion and formation of biofilm by *Candida albicans* on implanted medical devices, and the research group observed that these molecules not only suppress biofilm formation but also affect the structure of the mature biofilm; moreover, the adhesion, the cell surface hydrophobicity (CSH) and the filamentous growth of *C. albicans* significantly decreased after coumarin treatment, indicating that coumarin inhibits biofilm formation by suppressing adhesion [148].

Table 3. List of some coumarins and their derivatives used as antimicrobial agents.

Compound	Bioactivity	Microbial strain	Ref
Ferulenol	Antibacterial	*Mycobacterium tuberculosis* H37Rv,	[149]
Warfarin	Antibacterial	*Mycobacterium tuberculosis* H37Rv,	[150]
(+)-Calanolide A	Antibacterial	*M. tuberculosis* H37Rv, *M. tuberculosis* H37Ra (ATCC 25177), *M. tuberculosis* H37Rv (ATCC 27294), *M. tuberculosis* CSU19, *M. tuberculosis* CSU 33, *M. tuberculosis* CSU 36, *M. tuberculosis* CSU 38, *M. tuberculosis* H37Rv-INH-R (ATCC 35822), *M. tuberculosis* H37Rv-EMB-R (ATCC 35837), *Mycobacterium avium,*	[142]
(-)-Calanolide A, (-)-Calanolide B, (-)-Soulattrolide,		*Mycobacterium tuberculosis* H37Rv,	[142]
Herniarin	Antibacterial	*Acaligenes faecalis,* *Bacillus cereus,* *Sarcina lutea,*	[151]
	Antifungal	*Aspergillus sp.,* *Byssochlamys fulva,* *Candida sp,* *Hanseniaspora melligeri,* *Hansenula anomala,* *Pichia chodati,* *Saccharomyces sp.,* *Zygosaccharomyces sp,*	[151]

Continued

Daphnetin	Antiplasmodial	*Plasmodium falciparum*, *Plasmodium yoelii*,	[152]
Scopoletin	Antibacterial	*Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Bacillus subtilis* [153],	[154]
	Antifungal	*Alternaria alternata* (IMI-305675): (IC_{50}= 305.4 in ppm µg/mL) [155], *Fusarium semitectum* (IMI-211833): (IC_{50}= 469.3 in ppm µg/mL) [155], *Fusarium fusiformis* (IMI- 211848): (IC_{50}= 822.5 in ppm µg/mL) [155], *Byssochlamys fulva* [151], *Penicillium chrysogenum* [151], *Cladosporium herbarum* [153], *Aspergillus candidus* [153],	[155]
Psoralen	Antibacterial	*Staphylococcus aureus*,	[156]
	Antifungal	*Candida albicans*,	[156]
Umckalin	Antibacterial	*Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 25923), *Streptococcus pneumoniae* (strain 78), *Klebsiella pneumoniae* (V 6089), *Proteus mirabilis* (ATCC 14153), *Pseudomonas aeruginosa* (ATCC 27853), *Beta-hemolytic streptococcus* (1451),	[154]
Angelicin	Antifungal	*Aspergillus niger* PLM 1140, *Candida albicans* (ATCC 14053) *Cryptococcus neoformans* KF-33, *Saccharomyces cerevisiae* PLM 454,	[147]

Continued

5,6,7-Trimethoxy-2*H*-chromen-2-one	Antibacterial	*Streptococcus pneumoniae*, *Haemophilus influenzae*,	[154]
6,8-Dihydroxy-5,7-dihydroxycoumarin.	Antibacterial	*Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 25923), *Streptococcus pneumoniae* (strain 78), *Klebsiella pneumoniae* V 6089, *Proteus mirabilis* (ATCC 14153), *Pseudomonas aeruginosa* (ATCC 27853), *Beta-hemolytic streptococcus* 1451,	[154]
5,8-Di (2,3-dihydroxy-3-methylbutoxy) psoralen	Antifungal	*Aspergillus sp.*	[153]
Dentatin	Antiplasmodial	*Plasmodium falciparum* : (IC_{50}= 8.5± 12.3 µg/mL)	[157]
Clausarin	Antiplasmodial	*Plasmodium falciparum* : (IC_{50}= 0.1± 0.7 µg/mL)	[157]
Byakangelicin	Antibacterial	*Bacillus subtilis*,	[153]
	Antifungal	*Cladosporium herbarum*, *Aspergillus candidus*,	[153]
Oxypeucedanin	Antifungal	*Cladosporium sp.*	[158]
Oxypeucedanin hydrate	Antifungal	*Cladosporium sp.*	[158]
Osthenol	Antibacterial	*S. aureus*, *B. cereus*,	[159]

Continued

6',7'-Dihydroxybergamottin	Antibacterial	*S. aureus,* *S. epidermidis,* *P. aeruginosa,* *E. cloacae,* *K. pneumoniae,* *E. coli,*	[165]
Crenulatin	Antibacterial	MRSA (Methicillin resistant)	[171]
	Antifungal	*C. albicans* (ATCC 10231)	
Suberosin	Antibacterial	MRSA (Methicillin resistant)	[171]
	Antifungal	*C. albicans* (ATCC 10231)	
Marmesin senesioate (-) prantschimgin	Antibacterial	MRSA (Methicillin resistant)	[171]
	Antifungal	*C. albicans* (ATCC 10231)	

Table 4. Minimum inhibitory concentrations of bioactive coumarin derivatives.

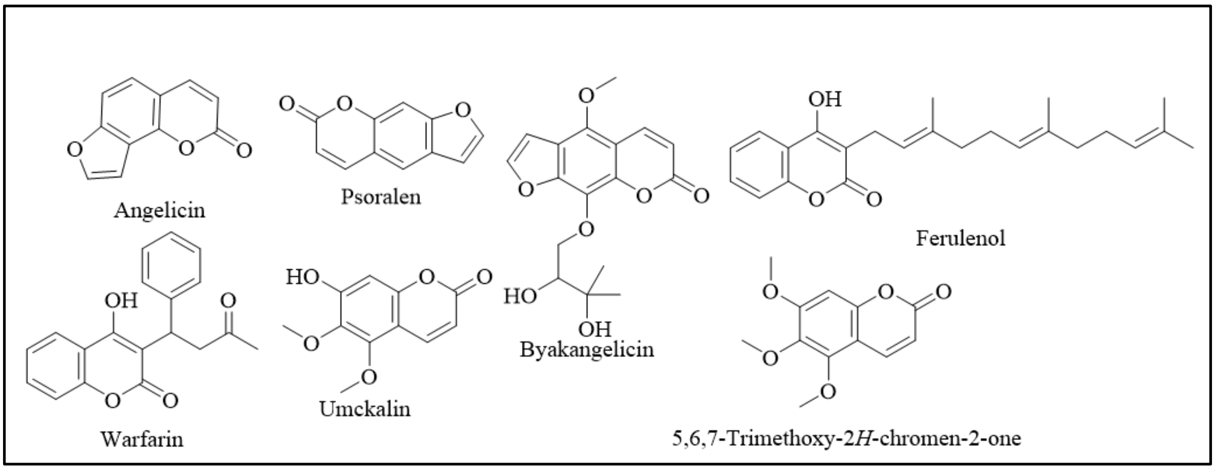
Compound	**Microbial strain**	**MIC (μg/mL)**
(+)-Calanolide A [142]	*Mycobacterium tuberculosis* (H37Rv), *M. tuberculosis* H37Ra (ATCC 25177), *M. tuberculosis* H37Rv (ATCC 27294), *M. tuberculosis* (CSU19), *M. tuberculosis* (CSU 33), *M. tuberculosis* (CSU 36), *M. tuberculosis* (CSU 38), *M. tuberculosis* H37Rv-INH-R (ATCC 35822), *M. tuberculosis* H37Rv-EMB-R (ATCC 35837),	3.13 16 8 16 16 8 8 8 8
(-)-Calanolide A, (-)-Calanolide B, (-)-Soulattrolide,	*Mycobacterium tuberculosis* (H37Rv)	6.25 6.25 3.13
Daphnetin [152]	*Plasmodium falciparum*	4.45-7.12
Scopoletin	*Staphylococcus aureus [154],* *Escherichia coli [154],* *Klebsiella pneumoniae [154],* *Proteus mirabilis [154],* *Pseudomonas aeruginosa* [154], *Bacillus subtilis* [153], *Cladosporium herbarum* [153], *Aspergillus candidus* [153],	500 500 500 400 400 250 250 > 125

Continued

Umckalin [154]	*Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 25923), *Streptococcus pneumoniae* (strain 78), *Klebsiella pneumoniae* V 6089, *Proteus mirabilis* (ATCC 14153), *Pseudomonas aeruginosa* (ATCC 27853), *Beta-hemolytic streptococcus* 1451,	200 200 500 200 200 200 500
5,6,7-Trimethoxy-2*H*-chromen-2-one [154]	*Streptococcus pneumoniae,* *Haemophilus influenzae,*	500 500
6,8-Dihydroxy-5,7-dimethoxy-2*H*-chromen-2-one [154]	*Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 25923), *Streptococcus pneumoniae* (strain 78), *Klebsiella pneumoniae* V 6089, *Proteus mirabilis* (ATCC 14153), *Pseudomonas aeruginosa* (ATCC 27853), *Beta-hemolytic streptococcus* 1451,	220 220 500 250 220 220 500
Angelicin [147]	*Candida albicans* (ATCC 14053), *Aspergillus niger* (PLM 1140), *Cryptococcus neoformans* (KF-33), *Saccharomyces cerevisiae* (PLM 454),	62.5 62.5 250 125
Byakangelicin [153]	*Bacillus subtilis ,* *Cladosporium herbarum ,* *Aspergillus candidus ,*	250 62.5 > 125
Psoralen [156]	*Staphylococcus aureus,* *Candida albicans,*	500 500
Osthenol [173]	*S. aureus,* *B. cereus,*	62.5 62.5
6',7'-Dihydroxybergamottin [165]	*S. aureus,* *S. epidermidis,* *P. aeruginosa,* *E. cloacae,* *K. pneumoniae,* *E. coli,*	1200 1350 1370 1750 2100 1450
Officinalin [165]	*S. aureus,* *S. epidermidis,* *P. aeruginosa,* *E. cloacae,* *K. pneumoniae,* *E. coli,*	4500 5500 5000 5750 4800 4900
Stenocarpin isobutyrate [165]	*S. aureus,* *S. epidermidis,* *P. aeruginosa,* *E. cloacae,* *K. pneumoniae,* *E. coli,*	5250 4000 5000 4800 3900 4500

Continued

Officinalin isobutyrate [165]	*S. aureus,* *S. epidermidis,* *P. aeruginosa,* *E. cloacae,* *K. pneumoniae,* *E. coli,*	3500 2700 3500 2750 2250 4800
8-Methoxypeucedanin [165]	*S. aureus,* *S. epidermidis,* *P. aeruginosa,* *E. cloacae,* *K. pneumoniae,* *E. coli,*	5250 4000 5000 4800 3900 4500
Peucedanin [165]	*S. aureus,* *S. epidermidis,* *P. aeruginosa,* *E. cloacae,* *K. pneumoniae,* *E. coli,*	1500 1750 1400 2100 2500 2750
Crenulatin [171]	MRSA (Methicillin resistant), *C. albicans* (ATCC 10231)	1250 625
Suberosin [171]	MRSA (Methicillin resistant), *C. albicans* (ATCC 10231)	1250 625
Marmesin senesioate (-) prantschimgin [171]	MRSA (Methicillin resistant), *C. albicans* (ATCC 10231)	1250 625



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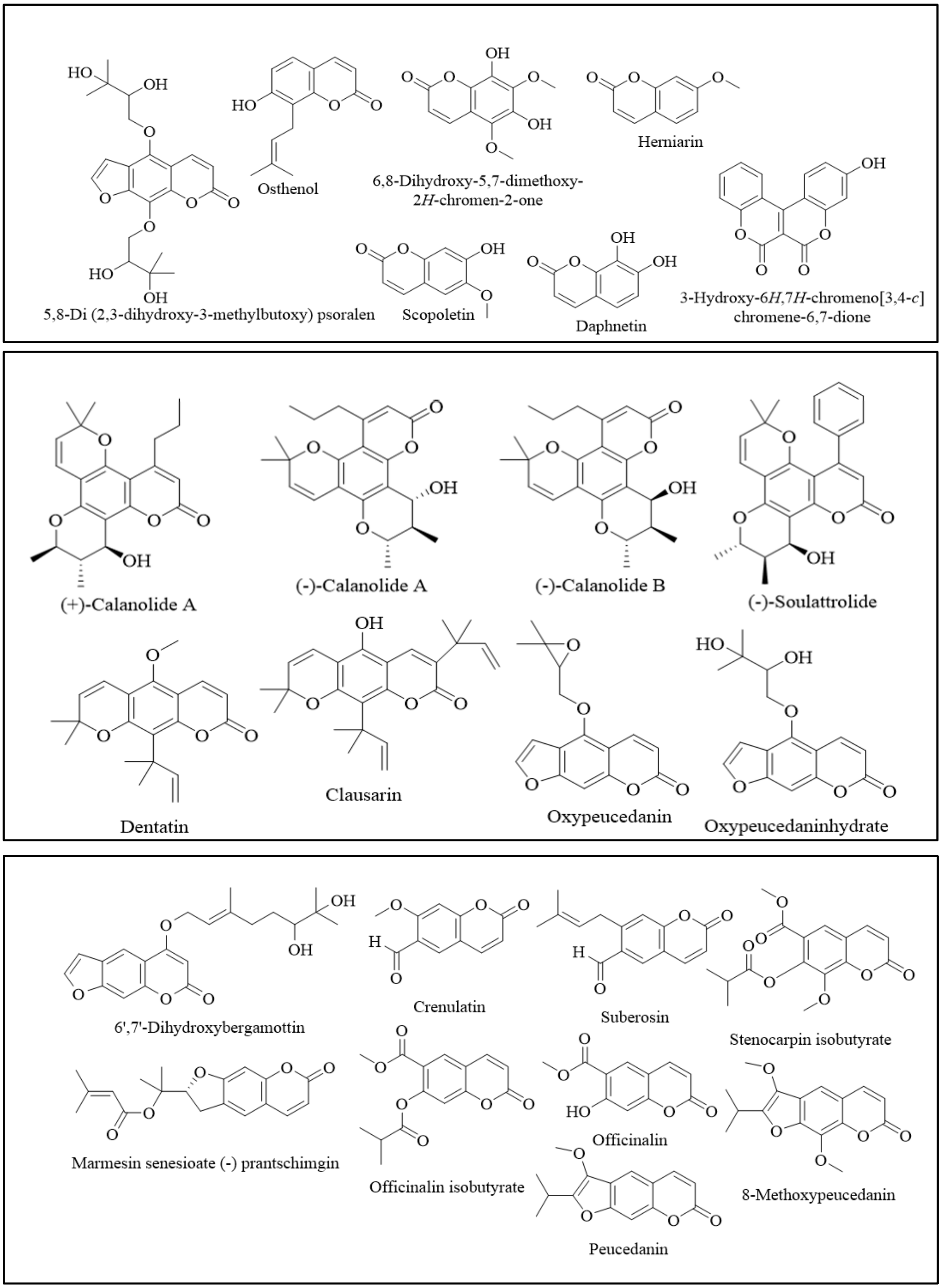


Figure 5. Chemical structures of some natural bioactive coumarins and their derivatives.

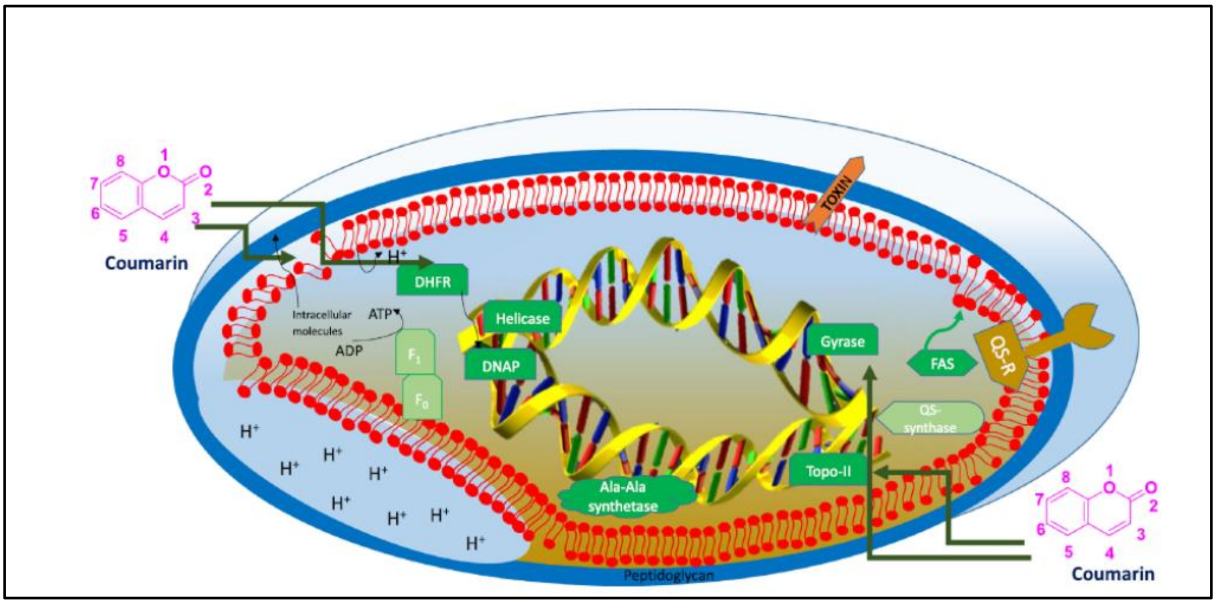


Figure 6. Schematic representation of the action mechanism of coumarins possessing antimicrobial activities [175].

2.6. Terpenes and essential oils

Terpenes are secondary metabolites produced by many plants, particularly conifers, and highly enriched with isoprene-based units, and all these units can be arranged linearly or form rings. They are therefore formed from isopentenyl pyrophosphate (IPP), which reacts with a starter molecule: dimethylallyl pyrophosphate (DMAPP), geranyl pyrophosphate (GPP), geranylgeranyl pyrophosphate (GGPP), etc. On the other hand, isoprene is easily obtained by the degradation of terpenes [176]**.** The structure f some terpenes is summarized in **Figure 7.**

Artemisinin and its *α*-artemether derivative are sesquiterpenes used as antimalarial agents [177]. In addition, these substances have shown significant activity against bacteria [178], fungi [179], viruses [120], and protozoa [180]. The mechanism of action of terpenes involves the rupture of the membrane via lipophilic compounds.

According to Chilean herbal therapy, Mendoza et *al*. [181] found that the antimicrobial activity of resinous exudates from twigs and leaves of four Chilean species: *Pseudognaphalium viravira, P. robustum, P. heterotrichium,* and *P. cheiranthifolium* against five strains: *Escherichia coli* ATCC 25922, S*almonella paratyphi* B ATCC 2659, *Proteus vulgaris* ATCC 6380, *Klebsiella pneumoniae* ATCC 13883, and *Erwinia carotovora* IC2610 is extremely correlated with the presence in these exudates of *ent*-16-kauren-19-oic and *ent*-9 (11),16-kauradien-19-oic acids, while the introduction of the *β*-OH group in position- 3 considerably reduced the antimicrobial activity of these compounds.

Another spicy-tasting diterpene, aframodial, isolated from the seeds of *Aframomum daniellii*, a Cameroonian spice, has a broad-spectrum, non-toxic antifungal effect [184].

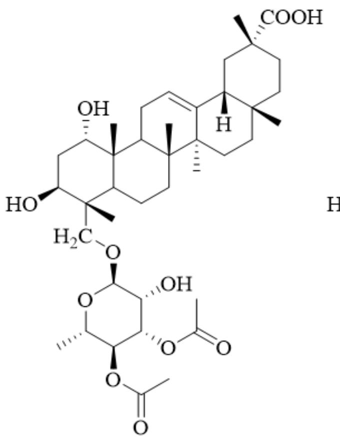
Two diterpenes: horminone and 7*α*, 12-dihydroxy-17(15→16)-*abeo*-abieta-8,12,16-triene-11, l4-dione isolated by Batista et *al*. [127], were found to be effective against *Staphylococcus aureus*, *Vibrio cholerae*, *Pseudomonas aeruginosa*, and *Candida* spp. Kadota et *al*. [186] found that trichorabdal A, a diterpene from a Japanese herb, could directly inhibit *Helicobacter pylori*. However, *S. aureus* ATCC 29213 demonstrated intermediate susceptibility at 8 mg/mL for the compounds: lupeol acetate, cycloart-23-ene-3,25-diol, and *β*-sitosterol, using the agar-well diffusion assay. Additionally, lupeol acetate exposures resulted in statistically significant increased adhesion for *E. coli* ATCC 29922, *E. coli* ATCC 35218, *S. aureus* ATCC 29213 and *S. aureus* ATCC 43300 at all concentrations tested at (2-15 mg/mL) [89].

The pentacyclic triterpenes [187] 1*α*,3,*β*-hydroxyimberbic acid **(1)**; 1*α*,3,*β*-hydroxyimberbic acid-23-*O*-*α*-*L*-4-acetylrhamnopyranoside **(2)**; 1*α*,3,*β*-hydroxyimberbic acid-23-*O*-*α*-*L*-3,4- diacetylrhamnopyranoside **(3)**;1*α*,3,*β*-

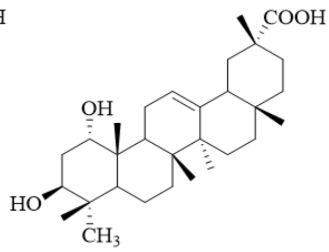
hydroxyimberbic acid-23-*α*-[*L*-3,4-diacetyl- rhamnopyranosyl]-29-*O*-*α*-rhamnopyranoside **(4)**;1*α*,3,*β* -hydroxyimberbic acid-23-*O*-*α* -[*L*-4- acetyl- rhamnopyranosyl]-29-*O*-*α*-rhamnopyranoside **(5)**, isolated from *Combretum imberbe* Engl. & Diels, and derived from imberbic acid, exhibits potent antibacterial activity, particularly against *Mycobacterium fortuitum* and *Staphylococcus aureus*, Actually, they are best known for their molluscicidal action, particularly in their monodesmosidic form [188]. Furthermore, compound **(1)** was found to be active against *Mycobacterium fortuitum* at a concentration of 1.56 mg/mL and *Staphylococcus aureus* at 3.13 mg/mL. The compound **(2)** inhibited *Staphylococcus aureus* at 12.5 mg/mL, while compound **(3)** inhibited *S. aureus* at 6.25 mg/mL and *Mycobacterium fortuitum* at 12.5 mg/mL. The compound **(4)** showed significant inhibitory activity against *Proteus vulgaris* (12.5 mg/mL) and *Staphylococcus aureus* (6.25 mg/mL), while compound **(5)** inhibited *Candida albicans* at 12.5 mg/mL and *Staphylococcus aureus* at 25 mg/mL. These terpenes are also the main constituents of essential oils from many types of plants and flowers [189]. It should be noted that the essential oils are complex mixtures of volatile compounds such as monoterpenes (*β*-citronellol, borneol), sesquiterpenes (viridiflorene, *δ*-cadinene), and other aromatic compounds derived from phenylpropane such as estragole, thymol, etc. [133]. About 60% of the essential oil derivatives examined were fungus inhibitors, while 30% prohibited bacterial growth [190]. Researchers have found that terpenoids in essential oils are useful in combating *Listeria monocytogenes* [191]. Thus, basil oils, including basil sweet linalool (BSL) and basil methyl chavicol (BMC), showed antimicrobial activity against *Aeromonas hydrophila* and *Pseudomonas fluorescens.* The results with resting cells demonstrated that BMC was bactericidal to both *Aeromonas hydrophila* and *Pseudomonas fluorescens* by virtue of the fact that the efficacy of washing fresh lettuce with 1% (v/v) BMC on the survival of natural microbial flora was comparable to that of 125 ppm chlorine [136].

The bactericidal effect of the essential oils of cloves and oregano (*Origanum vulgare*), was simultaneously examined by Rhayour [6] with two of their components, eugenol and thymol on *E.coli* and *Bacillus subtilis* species, respectively, as Gram negative and Gram positive bacteria. The antibacterial activity of both essential oils, similarly to their two major components, is specifically confined to their ability to induce cellular lysis. This action was confirmed by the release of absorbent substances at 260 nm. This release of molecules associated with rapid bacterial mortality could be the result of the envelope damage induced by antibacterial agents simultaneously attacking the membrane and cell wall (**Figure 8**) [192]. The antimicrobial power of active essential oil is involved in its interference with the lipid bi-layer of the target cell due to its hydrophobic property, resulting in permeability disruption and loss of cell constituents [7]. In addition, this reaction varies depending on the nature of the lipid bi-layer, which explains the resistance of Gram negative bacteria [193].

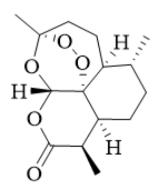
This antimicrobial effect can be explained by the destruction of certain enzymatic systems responsible for certain cellular activities, including cellular energy production and structural compound synthesis [194]. On the other hand, the essential oil obtained from the species (*Leptospermum citratum*), according to Freeman and Carel [195], caused leaks of potassium ions (K^+) in the bacterial cell membranes of *E.coli* and *S.aureus*. This leak of K^+ ions is the first evidence of irreversible damage to the bacterial membrane. Thymol and carvacrol represent the active components of this essential oil that increase the permeability of the bacterial membrane, a precursor effect of their death, indicating its bactericidal properties.



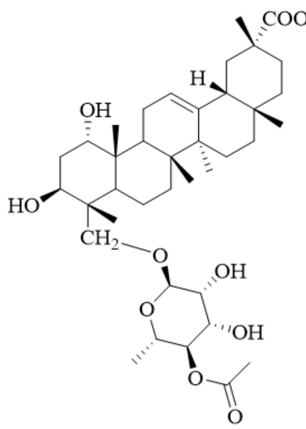
1α-3-β-23-Trihydroxy-olean-12-en-29-oate-23-O-α-L-3, 4-acetylrhamnopyranoside



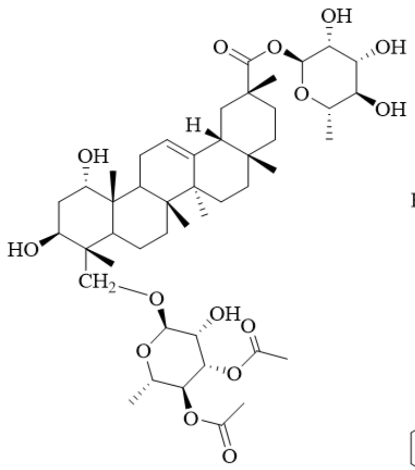
Imberbic acid



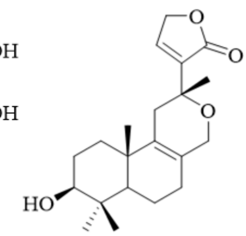
Artemisinin



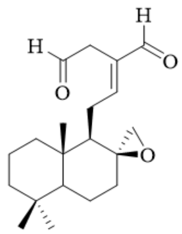
1α-3-β-23-Trihydroxv-olean-12-en-29-oate-23-O-α-L-4-acetylrhamnopyranoside



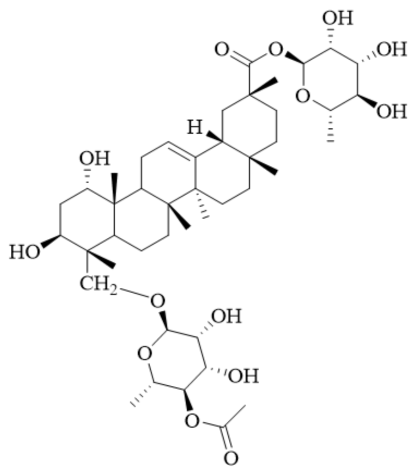
1α-3-β-23-Trihydroxy-olean-12-en-29-oate-23-O-α-L-3,4-acetyl-29-dirhamnopyranoside



Aulacocarpinolide



Aframodial



1α-3-β-23-Trihydroxy-olean-12-en-29-oate-23-O-α-L-4-acetyl-29-dirhamnopyranoside

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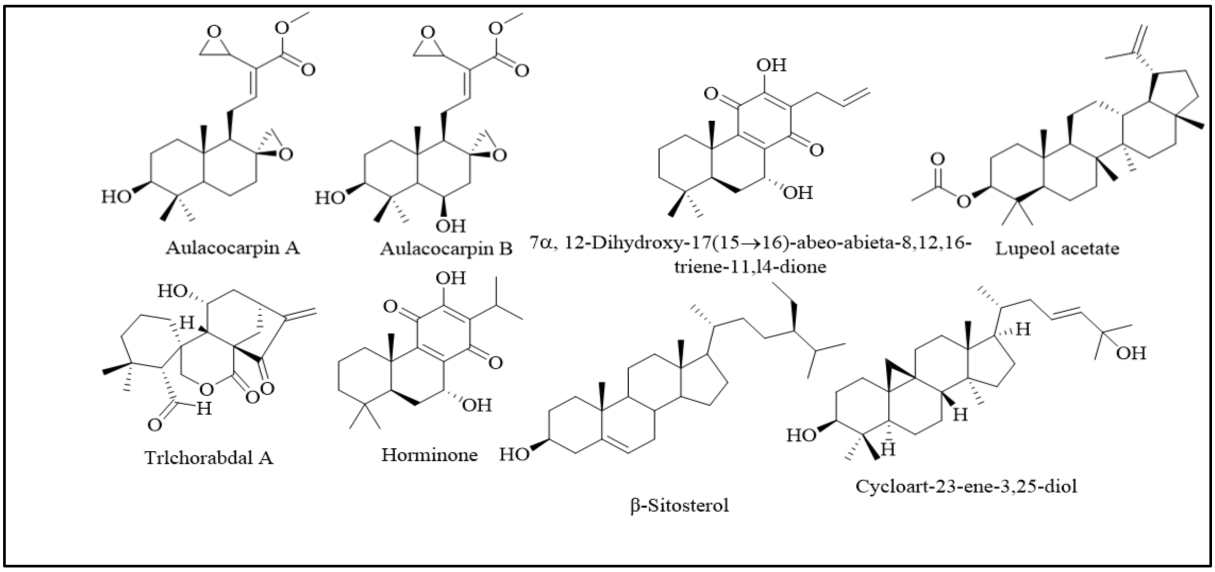


Figure 7. Chemical structures of some natural bioactive terpenes.

The antibacterial activity of these constituents can be outlined in three phases [196]:

- Attack and increase permeability of the bacterial wall by the active molecule, which leads to the loss of cellular constituents.
- Acidification of the cytoplasmic medium inside the cell, blocking the production of cellular energy and the synthesis of structural components.
- Destruction of genetic material or inhibition of protein synthesis, leading to the death of the bacterium.

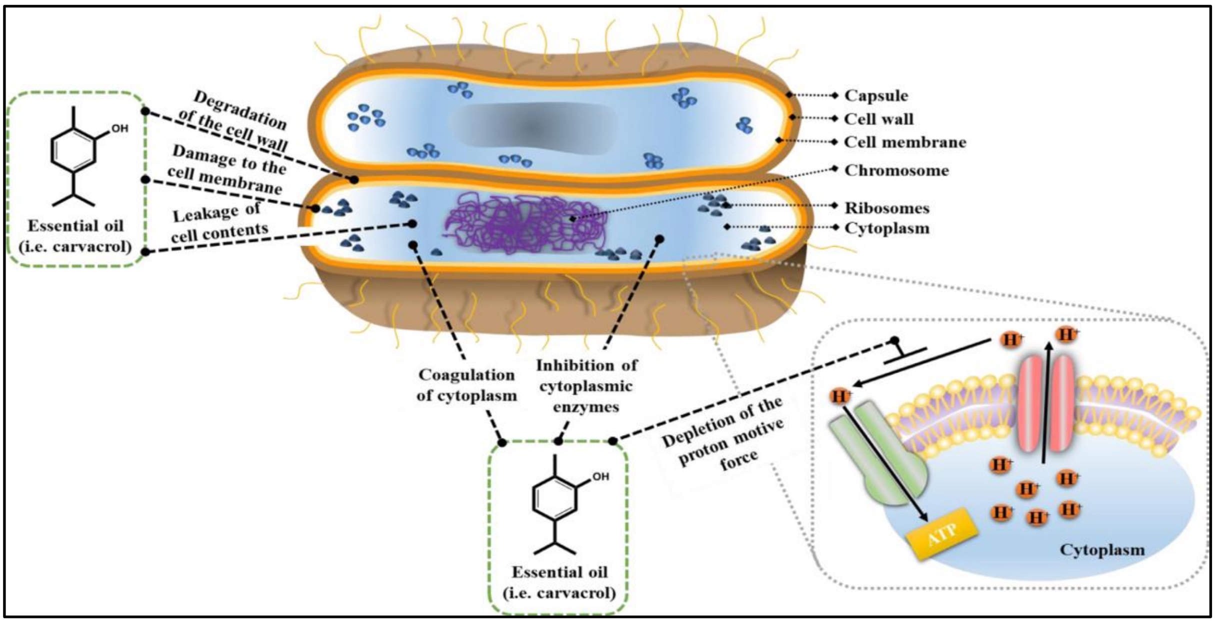


Figure 8. Targets of essential oils in bacterial cells, showing different mechanisms of antimicrobial activity: degradation of the cell wall; damage to the cell membrane; leakage of cell contents; cytoplasmic protein coagulation or inhibition; and depletion of the proton motive force [192].

2.7. Alkaloids

Alkaloid plants such as opium poppy or *Papaver somniferum* have been known and used for a very long time, but knowledge of their active substances only dates back to the beginning of the 19th century. In 1803, Charles Derosne, a French pharmacist and industrialist, was the first to isolate a plant alkali by extracting a mixture of narcotine and morphine from opium, but he initially attributed the alkaline nature of his extract to preparation residues [197]. Finally, in 1805 in Westphalia, a pharmacy assistant, Friedrich Sertürner, recognized the alkaline nature of opium's sleep-inducing principle. A decade later, he named it morphium, in reference to Morpheus, the ancient Greek divinity of dreams [198].

The elucidation of the chemical structures of alkaloids didn't begin until 1870, with Schiff's discovery of the simplest, coniine, and some didn't reveal their structure until the end of the 20th century, during which Maurice-Marie Janot and his students isolated, analysed, and synthesized over a hundred of them, establishing the structure of corynantheine in 1953, a major milestone in the progress of alkaloid chemistry [199]. Codeine and heroin, derivatives of morphine, have been used in therapeutic applications.

Alkaloids are a large and structurally diverse group of compounds that have served as scaffolds for important antibacterial drugs such as metronidazole and quinolones (**Table 5**). Diterpenoid alkaloids, isolated from plants of the *Ranunculaceae* family [200], showed generally antimicrobial properties [201]. Alkaloids have proven to be microbicidal substances against *Giardia intestinalis* and *Entamoeba histolytica* species [180]. Furthermore, they have antidiarrheal properties that are possibly due to their effects on the small intestine during transit time. The structure of some alkaloids is summarized in **Figure 9**.

Berberine is an important representative of the alkaloid family. It is potentially effective against plasmodes [201] and trypanosomes [202]. The mechanism of action of planar quaternary aromatic alkaloids such as berberine and harman [203] is strongly attributed to their ability to intercalate in the DNA molecule [204]. Cushnie et *al*. (2014) reported other natural alkaloids with development potential, focusing on those with direct antibacterial activity and those that enhance antibiotic activity. Clausenol, isolated from an alcoholic extract of *Clausena anisata* bark, proved highly active against Gram-positive (*Bacillus subtilis* ST 204, *Staphylococcus aureus* MC 27927) and Gram-negative bacteria (*Escherichia coli* ST 203, Salmonella *enterica* ST 288, *Pseudomonas aeruginosa* ST 243) and fungi (*Candida albicans* ST 388, *Trichophyton rubrum* ST 389), while clausenine from the same species showed low activity against Gram-negative bacteria and fungi [205].

Cichewicz et *al*. [18] reported that two biting compounds, capsaicin and dihydrocapsaicin, isolated from *Capsicum* species, exhibited varying degrees of inhibition against *Bacillus cereus*, *Bacillus subtilis*, *Clostridium sporogenes*, *Clostridium tetani* and *Streptococcus pyogenes*, insofar as capsaicin induces changes in the pH and properties of epithelial cells in the digestive tract, thus preventing microbial infections. These findings are corroborated by a study conducted by Tellez and colleagues, which showed that giving dietary capsaicin for longer than two weeks caused detectable morphological changes in the cecal mucosa, suggesting the possibility of capsaicin-induced alterations in host susceptibility to *Salmonella enteritidis* invasion [182].

Despite its detrimental effect on the human gastric mucosa, capsaicin was also proven to be bactericidal to *Helicobacter pylori* when incubated at a pH of up to 5.4 [183].

The antibacterial activity of some carbazole alkaloids: harmandianamines A-C, clausevatine D, clausamine A, clausamine B, clausine S, clausevatine D, girinimbine, *O*-demethylmurrayanine, clauszoline I, clausine Z, causzoline N, clausine D, clausine F, clausemine D, isolated from the twigs of *Clausena harmandiana* , was evaluated against *Escherichia coli* TISTR 780, *Salmonella typhimurium* TISTR 292, *Staphylococcus aureus* TISTR 1466 and methicillin-resistant *Staphylococcus aureus* (MRSA) SK1.

It is noteworthy that compounds clausamine F and clausamine A displayed significant activity with MIC values of 4 and 8 µg/mL, respectively, while clausamine B showed important antibacterial activity against *S. aureus* MRSA SK1 with a MIC value of 0.25 µg/mL, which is better than that of the standard drug, vancomycin with MIC (1 µg/mL).

Furthermore, clausine F was found to be active against *S. aureus* TI and have antimicrobial activity against *Bacillus cereus* and *Staphylococcus aureus* with MIC_{100} values of 6.25 and 12.5 µg/mL, respectively [208].
Another study of Ramsewak et *al.* [234], reported that (+)-mahanine is more active against Gram positive bacteria (*Staphylococcus aureus*, and *Streptococcus pyogenes*) with MIC_{100} (25 µg/mL) than against Gram negative bacteria *E. coli* with MIC_{100} (100 µg/mL). In addition, the antibacterial activity of (+)-mahanine was found to be comparable to that of the benzylisoquinoline alkaloid, anoolobine, showing significant activity against several Gram-positive bacteria with MIC_{90} values ranging from 12 to 50 µg/mL.
In vitro studies have proved that hapalindole T which is the active principle in the methanolic extract of the cyanobacterium, *Fischerella sp*. isolated from Neem (*Azadirachta indica*) tree bark, is endowed with inhibitory activity against *Mycobacterium tuberculosis*, *Enterobacter aerogenes*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Escherichia coli* and three multi-drug resistant *E. coli* strains [235].
Wang et *al.*(2013) [211] found that the length of the carbon chain and the substitution of the side chain at C-2 of the quinolone alkaloids have a considerable effect on the antibacterial activity, by virtue of the fact that compounds 1-Methyl-2-nonyl-4(1*H*)-quinolone , 1-Methyl-2-undecyl-4(1*H*)-quinolone,1-Methyl-2-dodecyl-4-(1*H*)-quinolone,1-Methyl-2-tridecyl-4(1*H*)-quinolone,1-Methyl-2-tetradecyl-4-(1*H*)-quinolone, evocarpine, evocarpine A, evocarpine B ,evocarpine C, evocarpine D, evocarpine E exhibited moderate activities against *Staphylococcus aureus* ATCC 25923, *Staphylococcus epidermidis* ATCC 12228, and *Bacillus subtilis* ATCC 6633. The 1-methyl-2-tridecyl-4(1*H*)-quinolone showed the best activity against these three strains (MIC values: 4-8 µg/mL). Dekker et *al*. [218] reported that the potencies of the quinolone compounds against *H. pylori* are affected by the side chains, insofar as the most potent is the epoxy derivative, (*E*)-2-(5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl)-1,3-dimethyl-2,3-dihydroquinolin-4(1*H*)-one. Alterations of the terpene unit, such as a double bond in place of the epoxide group as in the case of (*E*)-2-(3,7-dimethylocta-2,6-dien-1-yl)-1,3-dimethylquinolin-4(1*H*)-one, and the addition of a hydroxyl group at C-1' as in the case of (*E*)-2-(1-hydroxy-3,7-dimethylocta-2,6-dien-1-yl)-1-methylquinolin-4(1*H*)-one or C-3' as in the case of (*E*)-2-(3-hydroxy-3,7-dimethylocta-1,6-dien-1-yl)-1,3-dimethylquinolin-4(1*H*)-one reduces quinolone activity. Furthermore, the presence of *N*-methyl group makes the compounds more active than those without *N*-methyl group, as in the cases of (*E*)-2-(3,7-dimethylocta-2,6-dien-1-yl)-1,3-dimethylquinolin-4(1*H*)-one and (*E*)-2-(3,7-dimethylocta-2,6-dien-1-yl)-1-methylquinolin-4(1*H*)-one.

Table 5. Some natural alkaloids used as antimicrobial agents.

Compound	Bioactivity	Microbial strain	Ref
Clausenol, Clausenine, Clausenal,	Antibacterial	*Escherichia coli* (ST 203), *Staphylococcus aureus* (MC 27927), *Pseudomonas aeruginosa* (ST 243), *Bacillus subtilis* (ST 204), *Salmonella typhi* (ST 288),	[205] [206]
	Antifungal	*Candida albicans* (ST 388), *Trichophyton rubrum* (ST 389),	
Harmandianamine A Harmandianamine B Harmandianamine C Clausevatine D Clausevatine E Clausamine A Clausamine B Clausine S Girinimbine *O*-Demethylmurrayanine	Antibacterial	*Escherichia coli* (TISTR780), *Staphylococcus aureus* (TISTR1466), *Salmonella typhimurium* (TISTR292), Methicillin-resistant *S. aureus* (SK1),	[207]

Continued

Clauszoline I Clausine Z Causzoline N Clausine D Clausine F Clausemine D			
(+)-Mahanine Murrayanol	Antibacterial	*Bacillus cereus*, *Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (MSU strain), *Streptococcus pyogenes* MHM-1645),	[208] [234]
	Antifungal	*Candida krusei* (MSU strain), *Candida parapsilosis* (MSU strain),	
Eudistomin Y2 Eudistomin Y3 Eudistomin Y4 Eudistomin Y5 Eudistomin Y6 Eudistomin Y7	Antibacterial	*Staphylococcus aureus* (ATCC 6538p), *Bacillus subtilis* (ATCC 6633), *Micrococcus luteus* (IFO 12708), *Salmonella typhimurium* (ATCC 14028), *Proteus vulgaris* (ATCC 3851), *Escherichia coli* (ATCC 35270),	[209]
	Antifungal	*Aspergillus fumigatus* (HIC 6094), *Trichophyton rubrum* (IFO 9185), *Trichophyton mentagrophytes* (IFO 40996), *Candida albicans* (ATCC 10231).	
Hapalindole X, Deschlorohapalindole I, 13-Hydroxy-dechlorofontonamide, Hapalindole A [238], Hapalindole I [238], Hapalindole J [238], Hapalindole C [238], Hapalindole U [238], Anhydrohapaloxindole A [239], Fischerindole L [240], Fischerellin A [210], Fischerellin B [210] ,	Antibacterial	*Mycobacterium tuberculosis* , *Mycobacterium smegmatis* , *Candida albicans* , *Staphylococcus aureus* , *Escherichia coli*, *Acinetobacter baumannii*,	[210]
Hapalindole T [235]	Antibacterial	*Mycobacterium tuberculosis*, *Enterobacter aerogenes*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Escherichia coli*, multi-drug resistant *E.coli*,	[235]
Welwitindolinone A isonitrile, Welwitindolinone B isothiocyanate, *N*-Methylwelwitindolinone B isothiocyanate,	Antifungal	*Aspergillus oryzae*, *Penicillium notatum*, *Saccharomyces cerevisiae*, *Trichophyton mentagrophytes*.	[241]

Continued

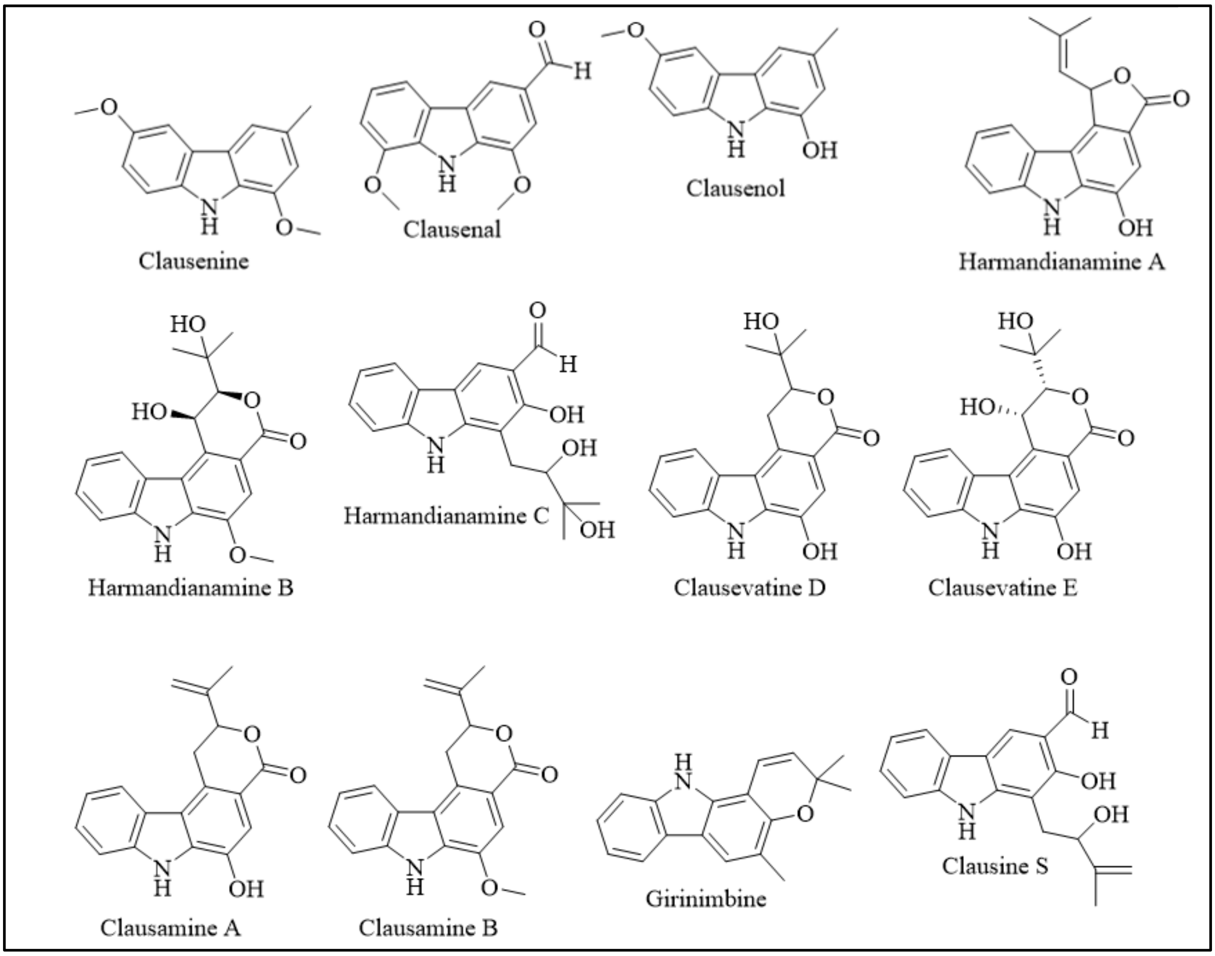
3-*epi* Welwitindolinone B isothiocyanate, Welwitindolinone C isothiocyanate, *N*-Methylwelwitindolinone C isonitrile,			
1-Methyl-2-nonyl-4(1*H*)-quinolone [242] , 1-Methyl-2-undecyl-4(1*H*)-quinolone [243], 1-Methyl-2-dodecyl-4-(1*H*)-quinolone [244], 1-Methyl-2-tetradecyl-4-(1*H*)-quinolone [246], Evocarpine [243], Evocarpine A [211], Evocarpine B [211], Evocarpine C [211], Evocarpine D [211], Evocarpine E [211],	Antibacterial	*Staphylococcus aureus* (ATCC 25923), *Staphylococcus epidermidis* (ATCC 12228), *Bacillus subtilis* (ATCC 6633),	[211]
Kokusaginine, Maculine, Kolbisine,	Antibacterial	*Escherichia coli*, *Mycobacterium smegmatis*, *Bacillus subtilis*,	[54]
Sanguinarine, Chelerythrine**,**	Antibacterial	Methicillin-resistant *staphylococcus aureus* (MRSA), Methicillin-sensitive *Staphylococcus aureus* (MSSA), Vancomycin-resistant *enterococci faecalis* (VRE), Vancomycin-sensitive *enterococci faecalis* (VSE), *Staphylococcus epidermidis* (ATCC 12228), *Staphylococcus aureus* (ATCC 25923), *Streptococcus pyogenes* (ATCC 19615), *Enterobacter aerogenes* (ATCC 13048), *Enterococcus* spp (ATCC 6589), *Escherichia coli* (ATCC 25922), *Klebsiella pneumoniae* (ATCC 13883), *Pseudomonas aeruginosa* (ATCC 27853) *Enterobacter cloacae* (ATCC 1304), *Shigella sonnei* (ATCC 25931), *Salmonella typhimurium* (ATCC14028), *Burkholderia cepacia* (ATCC 17759), *Morganella morganii* (ATCC 25829),	[213]
	Antifungal	*Candida albicans* (ATCC 10231), *Saccharomyces cerevisae* (ATCC 2601), *Cryptococcus neoformans* (ATCC 28952), *Candida tropicalis* (ATCC 18803),	[217]

Continued

		Candida krusei (ATCC 6258), *Candida parapsilosis* (ATCC 22018) , *Saccharomyces cerevisae* (ATCC 2601), *Cryptococcus gattii* (ATCC 2601).	
8-Acetonyldihydronitidine, 8-Acetonyldihydroavicine, Liriodenine,	Antibacterial	*Staphylococcus aureus,* *Escherichia coli,*	[214]
	Antifungal	*Cladosporium cladosporioides,* *Cladosporium gloeosporioides,*	
Palmatine	Antibacterial	*Helicobacter pylori,* *Brucella abortus,* *S.aureus, E.coli,*	[247] [248]
	Antileishmanial	*Leishmania donovani,*	[249] [250]
	Antitrypanosomal	*Trypanosoma brucei,*	[249] [250]
	Antiplasmodial	*Plasmodium falciparum,*	[249] [250]
Berberine	Antibacterial	Methicillin-resistant *staphylococcus aureus* (MRSA), Methicillin-sensitive *Staphylococcus aureus* (MSSA), Vancomycin-resistant *enterococci faecalis* (VRE), Vancomycin-sensitive *enterococci faecalis* (VSE), *Clostridium perfringens,* *Salmonella typhimurium,* *Vibrio parahaemolyticus,* *Fusobacterium nucleatum,* *Prevotella intermedia,*	[213] [55] [56] [215]
	Antifungal	*Trichophyton mentagrophytes,*	[55]
Jatrorrhizine	Antibacterial	*Staphylococcus aureus* MRSA,	[251] [252]
	Antifungal	*Candida albicans,* *Candida auris,* *Candida tropicalis,*	
Dihydrochelerythrine, Dihydroavicine, Bocconoline, Nitidine, 2,3-Dihydroxychelerythrine,	Antibacterial	*Staphylococcus epidermidis* (ATCC 12228), *Staphylococcus aureus* (ATCC 25923), *Streptococcus pyogenes* (ATCC 19615), *Enterobacter aerogenes* (ATCC 13048), *Enterococcus* spp (ATCC 6589), *Escherichia coli* (ATCC 25922), *Klebsiella pneumoniae* (ATCC 13883),	[217]

Continued

		Pseudomonas aeruginosa (ATCC 27853) *Enterobacter cloacae* (ATCC 1304), *Shigella sonnei* (ATCC 25931), *Salmonella typhimurium* (ATCC14028), *Burkholderia cepacia* (ATCC 17759), *Morganella morganii* (ATCC 25829),	
	Antifungal	*Candida albicans* (ATCC 10231), *Saccharomyces cerevisae* (ATCC 2601), *Cryptococcus neoformans* (ATCC 28952), *Candida tropicalis* (ATCC 18803), *Candida krusei* (ATCC 6258), *Candida parapsilosis* (ATCC 22018) , *Saccharomyces cerevisae* (ATCC 2601), *Cryptococcus gattii* (ATCC 2601).	
(*E*)-2-(5-(3,3-Dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl)-1,3-dimethyl-2,3-dihydroquinolin-4(1*H*)-one, (*E*)-2-(3,7-Dimethylocta-2,6-dien-1-yl)-1,3-dimethylquinolin-4(1*H*)-one, (*E*)-2-(3-Hydroxy-3,7-dimethylocta-1,6-dien-1-yl)-1,3-dimethylquinolin-4(1*H*)-one, (*E*)-2-(3,7-Dimethylocta-2,6-dien-1-yl)-3-methylquinolin-4(1*H*)-one, (*E*)-2-(3,7-Dimethylocta-2,6-dien-1-yl)-1-methylquinolin-4(1*H*)-one, (*E*)-2-(3,7-Dimethylocta-2,6-dien-1-yl)-3-methyl-1-((methylthio)methyl)quinolin-4(1*H*)-one,	Antibacterial	*Helicobacter pylori*,	[218]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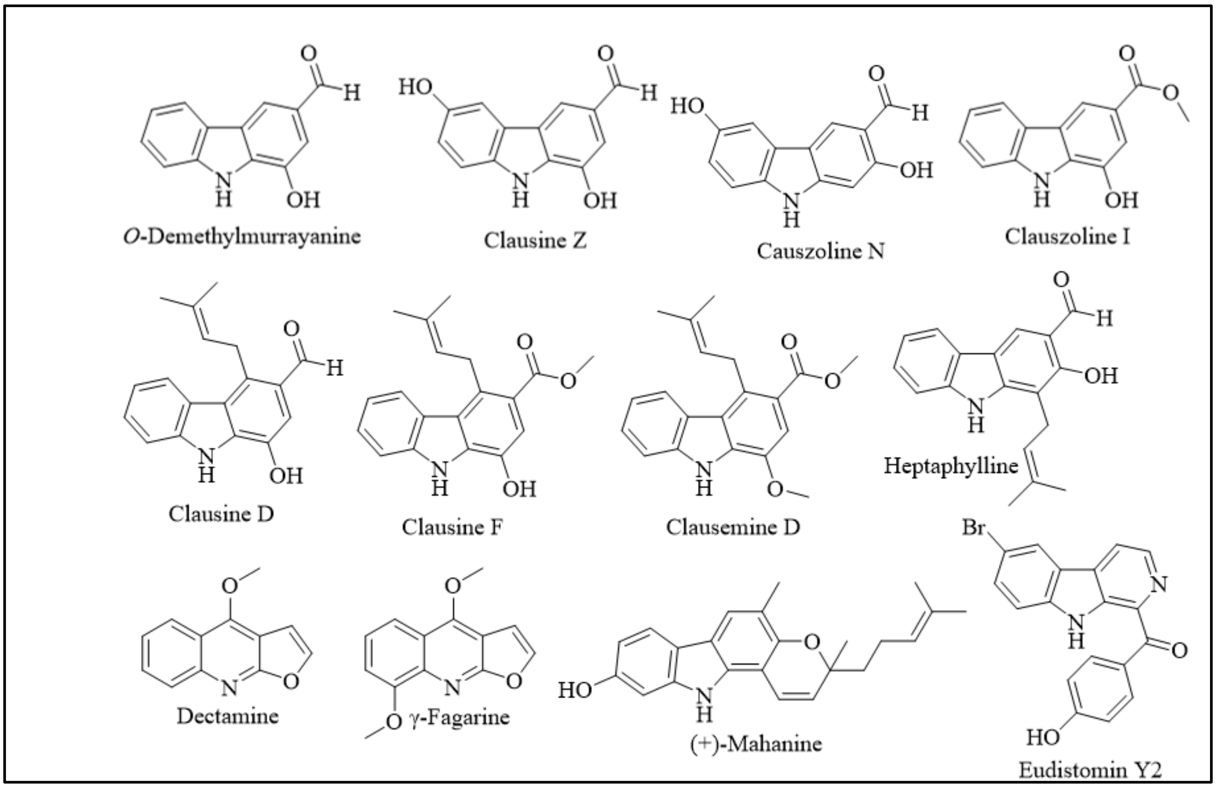
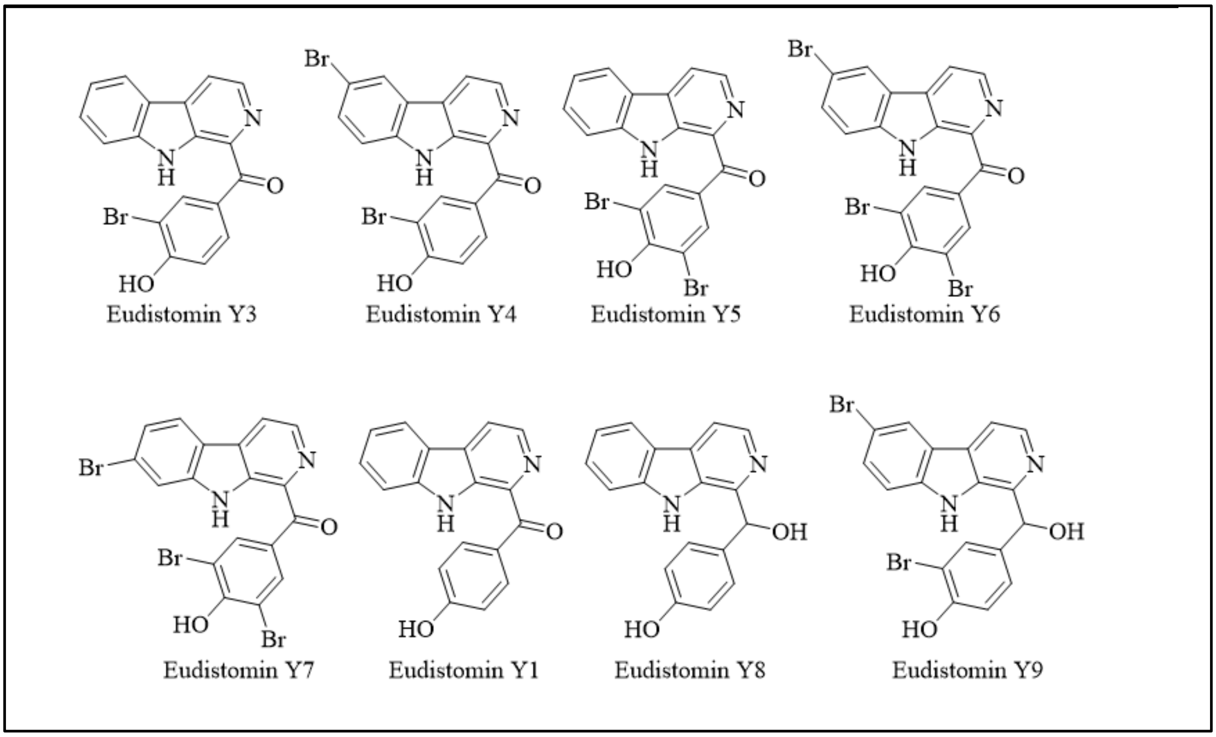
Clausenal
Clausenol
Harmandianamine A
Harmandianamine B
Harmandianamine C
Clausevatine D
Clausevatine E
Clausamine A
Clausamine B
Girinimbine
Clausine S

Continued


O-Demethylmurrayanine
Clausine Z
Causzoline N
Clauszoline I
Clausine D
Clausine F
Clausemine D
Heptaphylline
Dectamine
γ-Fagarine
(+)-Mahanine
Eudistomin Y2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Eudistomin Y4
Eudistomin Y5
Eudistomin Y6
Eudistomin Y7
Eudistomin Y1
Eudistomin Y8
Eudistomin Y9

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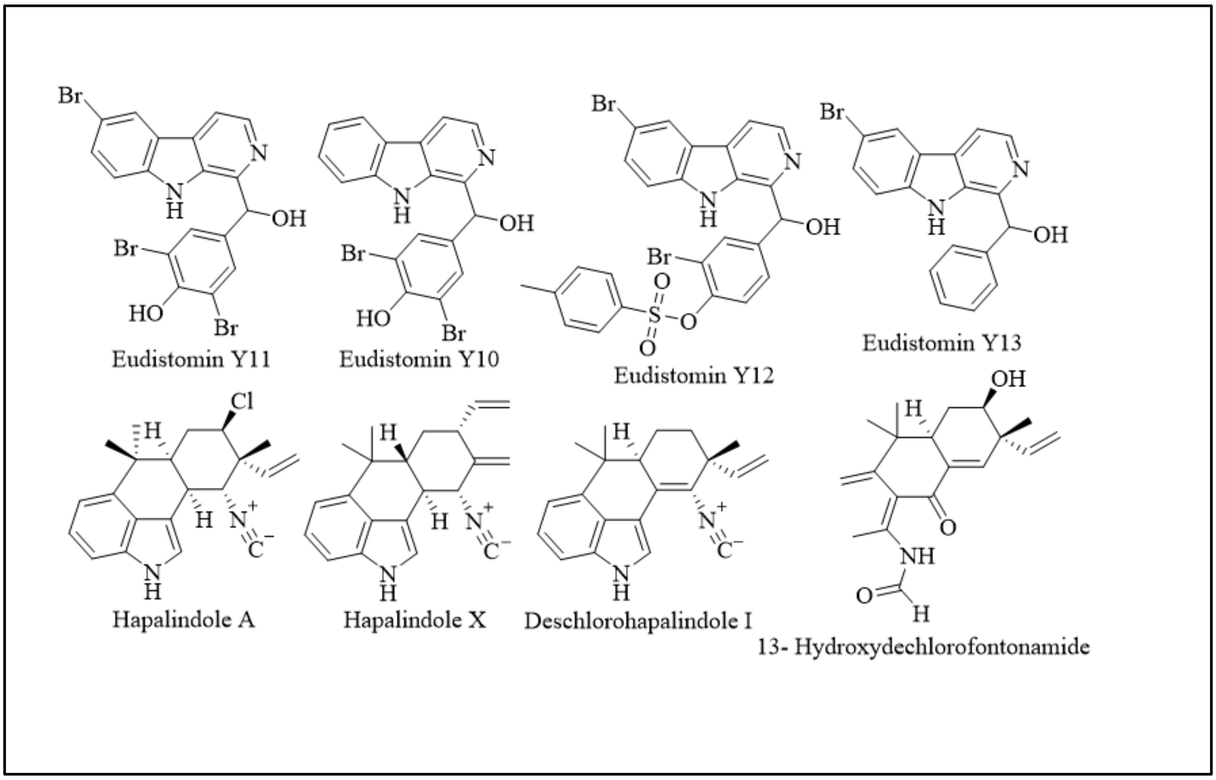
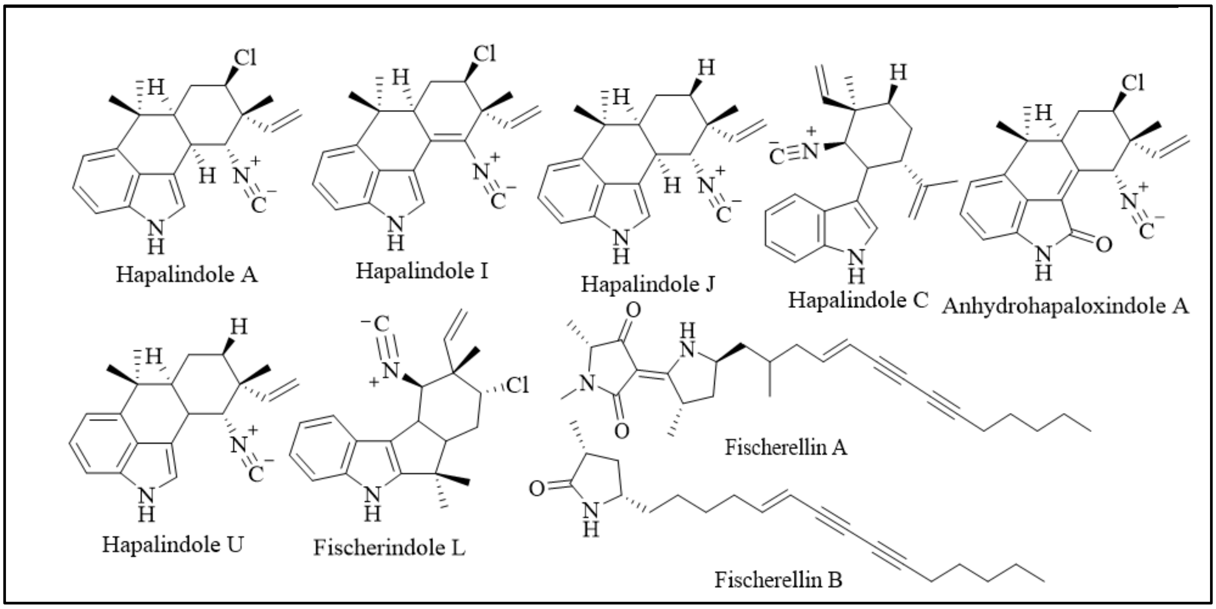

Eudistomin Y11
Eudistomin Y10
Eudistomin Y12
Eudistomin Y13
Hapalindole A
Hapalindole X
Deschlorohapalindole I
13- Hydroxydechlorofontonamide


Hapalindole A
Hapalindole I
Hapalindole J
Hapalindole C
Anhydrohapaloxindole A
Hapalindole U
Fischerindole L
Fischerellin A
Fischerellin B

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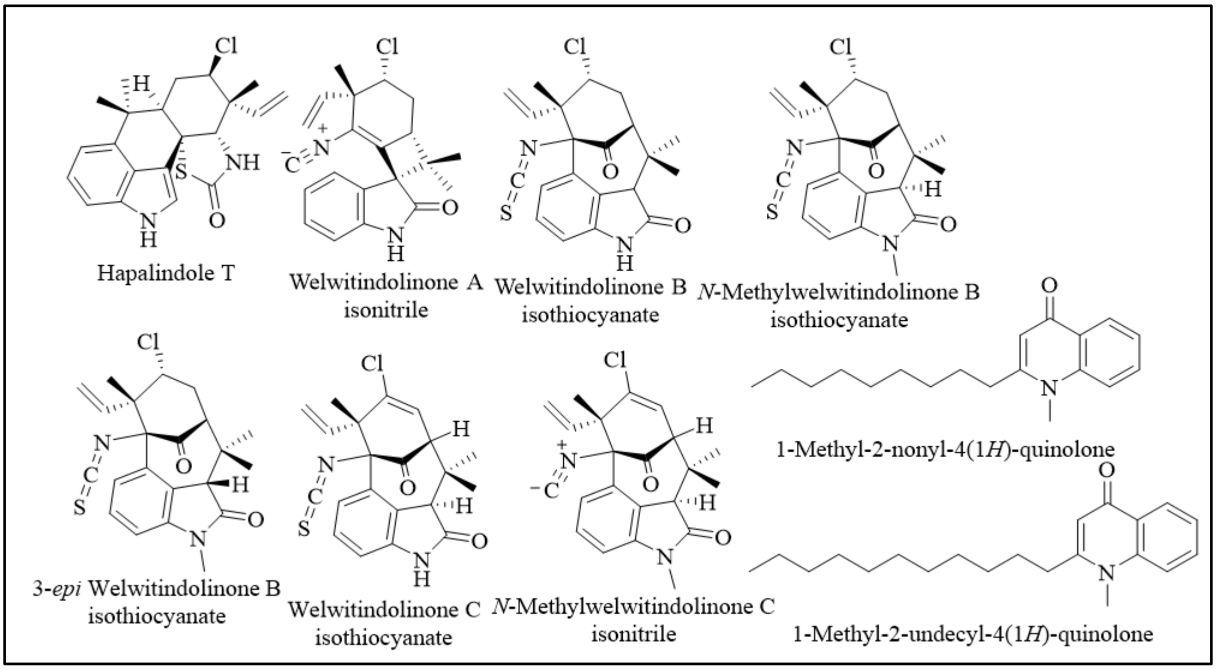
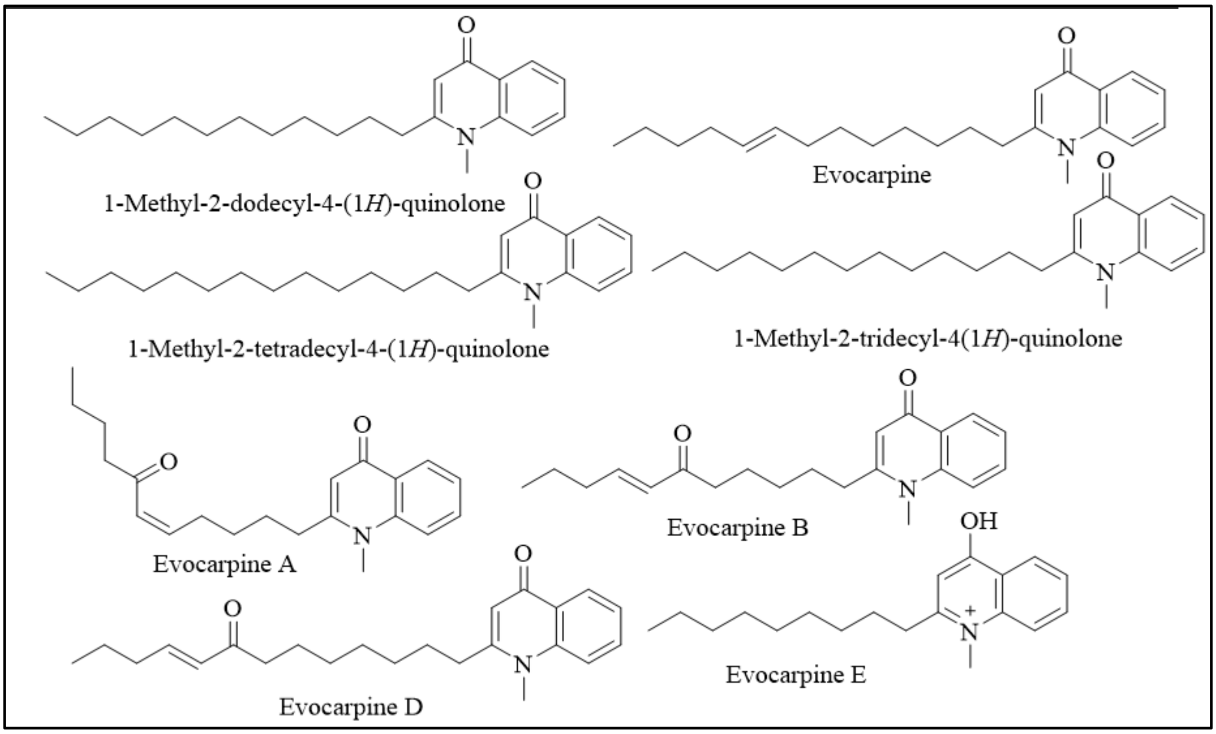

Hapalindole T
Welwitindolinone A isonitrile
Welwitindolinone B isothiocyanate
N-Methylwelwitindolinone B isothiocyanate
1-Methyl-2-nonyl-4(1*H*)-quinolone
3-*epi* Welwitindolinone B isothiocyanate
Welwitindolinone C isothiocyanate
N-Methylwelwitindolinone C isonitrile
1-Methyl-2-undecyl-4(1*H*)-quinolone


1-Methyl-2-dodecyl-4-(1*H*)-quinolone
Evocarpine
1-Methyl-2-tetradecyl-4-(1*H*)-quinolone
1-Methyl-2-tridecyl-4(1*H*)-quinolone
Evocarpine A
Evocarpine B
Evocarpine D
Evocarpine E

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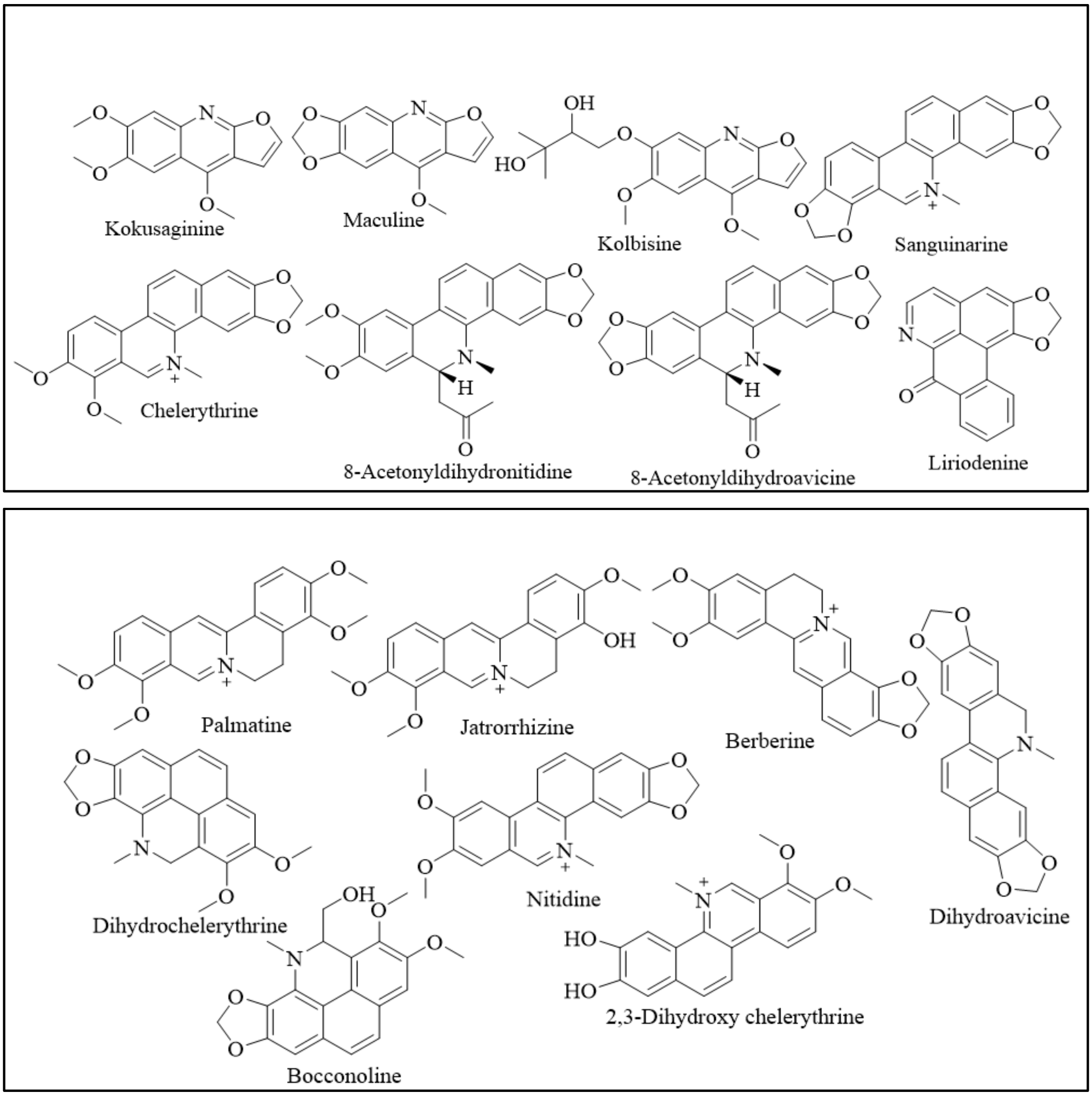

Figure 9. Chemical structures of some natural alkaloids used as antimicrobial agents.

Mechanism of action

- The activation and regulation of many bacterial phenotypes depend on the mode of communication and perception phenotypes depend on the mode of communication and perception called quorum sensing (QS) used by bacteria. It is based on the production of small auto-inducers (AIs), which can diffuse across the membrane or be transported outside the cell (**Figure 10**). These autoinducers, whose concentration is proportional to the number of bacteria, serve as a molecular indicator of bacterial density [253]. Above certain concentration of these molecules, a cellular response is triggered by the activation and repression of genes that are implemented only when cell density is high, to set up particular phenotypes, such as biofilm formation, virulence, production of exo-polysaccharides, exo-proteases and siderophores, etc. Many quorums sensing-induced factors are of global interest to the bacterial community, either to supply nutrients to the population or for the transition from a planktonic (i.e. suspended) mode of life to a sessile mode, called biofilm, more frequently encountered in the natural environment [254]. Various strategies have therefore been developed to inhibit these QS-regulated behaviors by blocking communication between bacteria, among which QS inhibition, which is called quorum quenching (QQ), can interfere with this system in different ways, either intracellularly or extracellularly.

The use of inhibitor molecules, known as QS inhibitors (QSI), which mimic auto-inducers (AIs), makes it possible to intervene at the level of bacterial cells to inhibit the production or perception of AIs. Many (QS) inhibitors have been isolated from natural products such as tea, mushrooms, honey, garlic, cloves, and marine organisms. Others have been synthesized in the laboratory, mimicking the structure of AIs to create similar but inactive molecules (antagonists) [255].

Quorum quenching could also limit biofouling on boat hulls by acting on the first stage in the appearance of fouling, which is the development of a bacterial biofilm.

Alkaloids represent quorum sensing (QS) inhibitors due to their effects on QS-regulated virulence factors and processes and/or their interactions with specific QS targets [256].

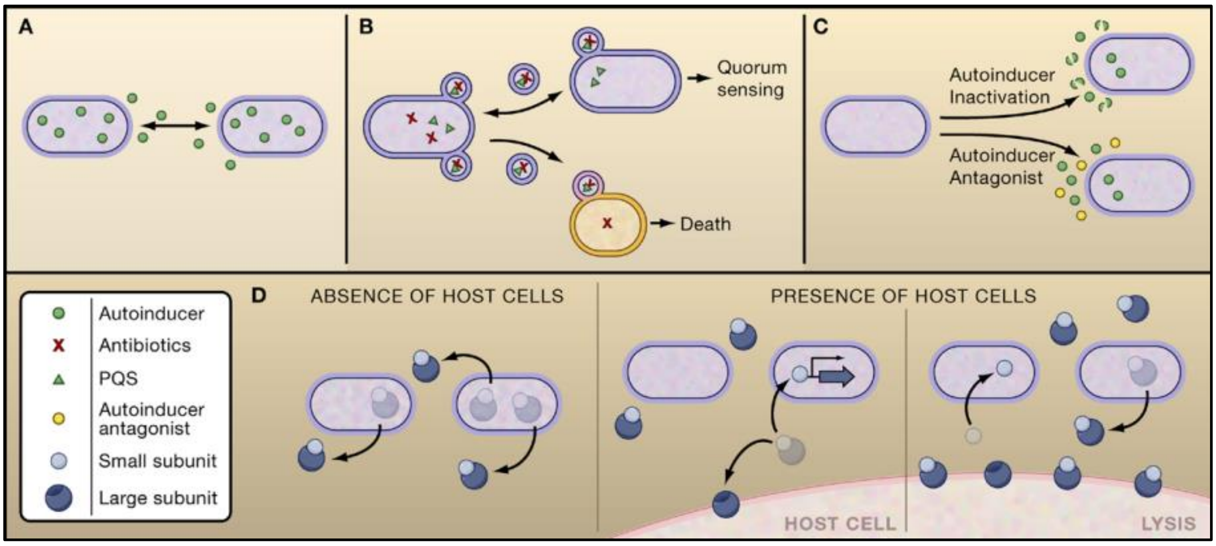

Figure 10. Mechanisms of bacterial quorum sensing and different quorum quenching strategies. **(**A) Quorum sensing. Quorum-sensing bacteria produce and respond to the extracellular accumulation of signal molecules called autoinducers (depicted as green spheres). (B) Mixed messaging. Membrane vesicles traffic the *Pseudomonas aeruginosa* quinolone signal (PQS; depicted as green triangles) between cells. PQS facilitates group behavior when delivered to other *P. aeruginosa* cells, but other quinolones (X), also contained in the vesicles, are antibiotics that kill other bacterial species. (C) Quorum quenching. Quorum-sensing bacteria are vulnerable to a variety of quorum-quenching mechanisms, such as the enzymatic inactivation of autoinducers or the presence of autoinducer antagonists (yellow spheres), molecules with structures similar to those of autoinducers that prevent autoinducer detection and response. (D) Conversations across kingdoms. *Enterococcus faecalis* produces a cytolysin composed of two subunits. The small cytolysin subunit acts as an autoinducer that monitors the environment for other *E. faecalis* cells. The large cytolysin subunit monitors the vicinity of eukaryotic host cells. Left: If no host cells are present, the two subunits form an inactive complex, and production of the subunits is held at a low basal level. Right: If host cells are present, the large subunit binds to the surface of the host cells, leaving the small subunit free to induce high-level production of both subunits, which together bind to target cells and cause them to lyse.

- Some alkaloids such as isoquinolines, pyrrolidines, imidazoles and pyrrole-imidazoles inhibit the formation and dispersal of bacterial biofilms [257].
- Other studies have shown that certain alkaloids, such as berberine and its derivatives, can inhibit bacterial hydrolysis of the connective tissue component collagen, preventing bacteria from producing the destructive proteolytic and glycolytic enzymes responsible for invading host tissue barriers and extending to deeper tissues in terms of inflammation [258].
- In addition to their ability to increase bacterial sensitivity to the host immune system by disrupting sortase-dependent immune evasion proteins, the thiazole alkaloid, 3-hydroxypropyl-3-((*Z*)-5-((5-(2-chlorophenyl)furan-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl) benzoate was shown to inhibit dihydrolipoamide acyltransferase, an enzyme used by *M. tuberculosis* to detoxify reactive nitrogen intermediates in host macrophages, thereby promoting cell destruction in infected macrophages [259].
- *In vivo t*ests of berberine's effects on the heat-labile enterotoxin secretory responses of *Vibrio cholerae* and *Escherichia coli* revealed that this alkaloid acts at a biochemical step after cyclase activation [260].
- The inhibitory action of sanguinarine against methicillin-resistant *Staphylococcus aureus* (MRSA) was induced by the release of autolytic enzymes from the membrane-bound cell wall, causing cell lysis and changes in bacterial morphology.
- The bacterial secretion system represents one of the main targets for antibiotic development, used to assemble the surface structures that promote adherence and export toxins and virulence proteins to host cells. Some thiazole alkaloids such as 2-imino-5- arylidene thiazolidinone have broad-spectrum activity, inhibiting secretion in multiple bacterial species, and protecting macrophages against *S. Typhimurium* cytotoxicity. Based on its activity profile and molecular studies aimed at excluding any interference with protein transcription or translation, this alkaloid inhibited type III secretion-dependent functions, except for flagellar motility, and type II secretion-dependent functions, suggesting that its target may be secretin, which is an outer membrane protein conserved in both secretion systems [261] .
- Recent research shows that virstatin can prevent the production of virulence factors by disrupting the regulation of virulence genes. Microarray and mutant studies identified ToxT as a likely target, and it was found to be the best protector against *V. cholerae* colonization [262] .
- The emergence of multi-drug resistant bacteria has created an urgent need for antibiotics with new mechanisms of action. The bacterial cell division protein FtsZ is an attractive target for the development of new antibiotics.

3. Conclusion

In response to pharmaceutical and agricultural antimicrobial treatments, disease resistance has increased dramatically. It is therefore necessary to create new chemical prototypes. In order to detect small quantities of biologically active chemicals - which should be sufficiently selective to identify the most targeted pathogens and lend themselves to the analysis of complex mixtures - new bioassay techniques and protocols have had to be developed as part of the successful discovery of new natural antimicrobial products.

Since natural products are widely available, inexpensive, less harmful, and easy to extract from plants, they represent the main precursors of antimicrobial leads and thus cover a wide range of spaces not yet available in synthetic libraries.

According to recent research, these bioactive molecules showed strong microbial growth inhibitory properties against several species. Iron chelation, inhibition of cell wall production, and membrane damage are among the possible mechanisms of action. Furthermore, they can target microbial virulence factors, such as biofilms, enzymes, adhesion, and motility, as well as the phytochemicals and antibiotics that work together to prevent the growth of germs.

It should be noted that several design strategies have been used to build natural product libraries. Using large-scale organic synthesis techniques in the matrix synthesis of these libraries increases the possibility of identifying and optimizing a desired therapeutic profile of antimicrobial compounds.

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