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REVIEW ARTICLE

Antimicrobial Capacity of Plant Polyphenols against Gram-positive Bacteria: A Comprehensive Review

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Abstract: ***Background*:** Multi-drug-resistant bacteria such as Methicillin-resistant *Staphylococcus aureus* (MRSA) disseminate rapidly amongst patients in healthcare facilities and suppose an increasingly important cause of community-associated infections and associated mortality. The development of effective therapeutic options against resistant bacteria is a public health priority. Plant polyphenols are structurally diverse compounds that have been used for centuries for medicinal purposes, including infections treatment and possess, not only antimicrobial activity, but also antioxidant, anti-inflammatory and anticancer activities among others. Based on the existing evidence on the polyphenols' antibacterial capacity, polyphenols may be postulated as an alternative or complementary therapy for infectious diseases.

***Objective*:** To review the antimicrobial activity of plant polyphenols against Gram-positive bacteria, especially against *S. aureus* and its resistant strains. Determine the main bacterial molecular targets of polyphenols and their potential mechanism of action.

***Methodology*:** The most relevant reports on plant polyphenols' antibacterial activity and their putative molecular targets were studied. We also performed virtual screening of thousand different polyphenols against proteins involved in the peptidoglycan biosynthesis to find potential valuable bioactive compounds. The bibliographic information used in this review was obtained from MEDLINE via PubMed.

***Results*:** Several polyphenols: phenolic acids, flavonoids (especially flavonols), tannins, lignans, stilbenes and combinations of these in botanical mixtures, have exhibited significant antibacterial activity against resistant and non-resistant Gram-positive bacteria at low µg/mL range MIC values. Their mechanism of action is quite diverse, targeting cell wall, lipid membrane, membrane receptors and ion channels, bacteria metabolites, and biofilm formation. Synergic effects were also demonstrated for some combinations of polyphenols and antibiotics.

***Conclusion*:** Plant polyphenols mean a promising source of antibacterial agents, either alone or in combination with existing antibiotics, for the development of new antibiotic therapies.

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1. INTRODUCTION

1.1. Increase of Antibiotic Resistance. The Gram-positive *Staphylococcus aureus* Case

Antibiotic resistance is a significant public health problem nowadays with a tendency to increase worldwide. Worse still, very few therapeutic alternatives are available in the management of some serious infectious diseases. Therefore, many international institutions are urging to find new treatments for these infections, in particular agents that suppress or abrogate the emergence of drug resistance [1, 2]. The causes for antibiotic resistance increase are very varied and distributed in different areas: the massive use in human health, veterinary medicine and in agriculture, tourism and emigration. In fact, the World Health Organization

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(WHO) has pointed out the need to develop a global plan of action called "One health" as a way to indicate the need for the involvement of many actors in different fields [3, 4]. These actions include the prevention of hospital infections, the recommendation of the discriminated use of antibiotics or the promotion of research and development of new drugs [5].

Strategies to combat this phenomenon should start with the prudent use of antibiotics and must implement multidisciplinary stewardship groups that address the infectious processes in an integrated manner. This includes improving microbiological diagnosis, studying the influence of antibiotics in the microbiome and in the environment, controlling the use of antibiotics in animals destined for human consumption, implementing measures of education to the users of antibiotics and to health professionals and promoting measures for infection control in the sanitary field, including the promotion of hand washing of staff. Also, the need to promote basic and clinical research that helps the development of new antibiotics has repeatedly been reported, since the number of drugs available to treat these multiresistant bacteria is extremely low [6-8].

At present, there are numerous bacterial species (both Gram-positive such as *Enterococcus faecium*, *Enterococcus faecalis* or *Staphylococcus aureus* and Gram-negative such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Helicobacter pylori*; among others), that cause infections whose treatment with the usual antibiotic drugs is not effective, that is, they have developed phenomena of resistance to one or several drugs.

Within Gram-positive bacteria, *S. aureus* is a microorganism with high rates of resistance to multiple antibiotics and is frequently associated with very serious infections. Resistant *S. aureus* is viewed as a public health priority. Besides being a risk for patients, it supposes a global health burden due to the additional cost for the health systems. Then, specific plans have been designed and implemented to control these infections [9-11]. In addition to the resistance problems presented by this pathogen, some strains have virulence factors that cause serious infectious processes, such as Panton-Valentine Leucocidin (PVL) that has frequently been associated with necrotizing pneumonia in the out-of-hospital setting [12].

Resistance to methicillin, which affects the activity of most beta-lactam drugs, is the most prominent problem in this strain and results in methicillin-resistant *S. aureus* (MRSA). MRSA is frequently associated with infections in hospital environments, disseminates rapidly amongst patients in healthcare facilities and is an increasingly important cause of community-associated infections, which leads to high mortality and morbidity rates. In hospitals, there is also the risk of horizontal transmission of this pathogen, both among patients and with the participation of health personnel since this microorganism can colonize the nasal mucosa asymptomatically [13]. MRSA affects more than 150,000 patients hospitalized annually in the EU, resulting in extra in-hospital costs of EUR 380 million for EU healthcare systems.

Methicillin resistance is associated with the presence of the penicillin-binding protein 2a (PBP2a) protein, with lower affinity to the beta-lactam antibiotics encoded in the mecA gene and in some cases by mecC [14]. Much less frequently, borderline oxacillin-resistant *S. aureus* (BORSA) is isolated with borderline resistance to methicillin (oxacillin MICs equal to 1-8 μg/mL) and without alterations in the penicillin-binding protein; these strains show hyperproduction of beta-lactamases or some mutations in PBP genes. Treatment of severe infections caused by BORSA may be ineffective, even with larger doses of oxacillin [15]. In addition, the existence of strains with mutations in PBP4 that cause high resistance to beta-lactams has recently been reported [16].

The treatment of these MRSA strains implies vancomycin as the drug of choice, but this drug is associated with risk of renal toxicity for the patients. In addition, the existence of heteroresistant strains with a high minimum inhibitory concentration has been reported in recent years, although within the range considered sensitive (MIC of 1.5 mg/L), so there is much controversy about the most appropriate treatment [17].

Another therapeutic alternative for MRSA are oxazolidinones, such as linezolid and tedizolid. These antibiotics inhibit protein synthesis by binding to the peptidyl transferase center of the 50S bacterial ribosomal subunit and have very low rates of antibiotic resistance, although some clinical isolates have recently been described resistant by mutations in the V domain of 23S rRNA or by cfr plasmids [18-20].

Daptomycin, a cyclic lipopeptide, is also a therapeutic alternative in some of these infectious processes. It is 4-8-fold as active as vancomycin against methicillin-susceptible *S. aureus* (MSSA) and MRSA and retains most of this activity against *S. aureus* with reduced susceptibility to vancomycin. Daptomycin binds to the bacterial cytoplasmic membrane, leading to membrane depolarization due to the loss of potassium ions from the cytoplasm. Resistant strains are rarely described,

and resistance mechanisms are often associated with changes in composition, charge, and fluidity of the cell wall [21].

Recently, some new drugs have appeared that improve the perspective in the treatment of this pathogen, such as ceftaroline and ceftobiprole, the only active cephalosporins against MRSA strains and therefore, with great clinical utility in the treatment of some of these infectious processes [22].

Two new lipoglycopeptides have also been commercialized, called oritavancin and dalbavancin. They work as classic glycopeptide drugs (vancomycin and teicoplanin) binding the terminal carboxyl of the d-alanyl-d-alanine residue of the growing peptide chains but differ from their parent glycopeptides by the addition of lipophilic tails. This addition allows these agents to have prolonged half-lives, giving them unique dosing profiles [23, 24].

Despite the above mentioned recent advances, the treatment of *S. aureus* infections and especially if it is resistant to methicillin (MRSA) is a public health problem of the first magnitude that requires a coordinated effort to control it and an urgent need for new more active therapeutic tools with low toxicity for patients.

2. EVOLUTIONARY BASIS OF THE PHARMACOLOGY OF PLANT POLYPHENOLS. MOLECULAR PROMISCUITY

Humans have been using plants as medicinal resources for thousands of years. There are many records from Traditional Chinese Medicine, Ayurvedic medicine, Kampo medicine, European medicine and African medicine among others using herbal products as a crucial medicinal system [25].

Plants are sessile organisms, which cannot escape from environmental stress situations (radiation, climate, predators, *etc.*). They do not possess an immune system to fight microbial infections neither. For these reasons, plants have developed some static defense systems to respond to the environmental stress and survive. These mechanisms include mechanical ones, as spines, thorns, and barks. On the other hand, plants have developed an extensive chemical arsenal of secondary metabolites which serves, among other uses, as an antimicrobial defense system [26, 27].

Plants produce a remarkably diverse array of more than 100,000 different low-molecular-mass secondary metabolites. These metabolites are distinct from the components of primary metabolism because they are generally nonessential for the underlying metabolic processes (photosynthesis, protein synthesis, tissue differentiation, *etc.*) of the plant. This significant molecular diversity results in part from an evolutionary process driven by selection for the acquisition of improved defense against microbial attack or insect/animal predation [28]. In tissues subjected to these stressful situations, high concentrations of various polyphenolic compounds can be observed [29].

Among plant secondary metabolites, polyphenols represent a broad class of natural products, which present a wide biological activity such as anticancer, antioxidant, anti-inflammatory, antiaging, cardioprotective and antimicrobial. This review focuses only on their antimicrobial capacity.

Polyphenolic compounds present a significant structural variability but share common phenolic moieties in their structure (Fig. **1**). In addition, polyphenols usually show conjugated forms with carbohydrates or form esters with organic acids. This phenomenon contributes to the enormous increase in the variety of the chemical forms of polyphenols. These compounds have modulated their diversity throughout evolution to act as ligands of many different molecular targets generating high molecular promiscuity [30, 31]. This multi-target trait is vital in the antimicrobial capacity of plant polyphenols and their synergistic effects with traditional antibiotics too [32].

Polyphenols are well tolerated by the human body. Dietary polyphenols are mostly present in plants as glycosides. After ingestion, these compounds are transformed in the gastrointestinal tract by the microbiota and digestive enzymes. They are usually deglycosylated at the digestive tract becoming aglycones, which exhibit higher bioactivity than their respective glycosides. If not absorbed, they may reach the large intestine where microbial transformation may occur yielding a diversity of bioavailable phenolic acids and lactones. When absorbed in the small intestine, they pass through portal vein towards the liver, where suffer further transformations [33, 34]. *In vivo* intestinal metabolism studies in rats suggested that main metabolic transformation involved were glucuronidation and sulfation, whereas *in vitro* studies highlighted hydrolysis of polyphenols [35]. After these processes, transformed polyphenols circulate towards different tissues and organs, exerting their antimicrobial and other bioactive activities [36]. The digestive and microbiota driven transformations are crucial for polyphenols to become bioactive molecules. For this reason, the administration route of polyphenols has to be optimized to obtain the desired biological activity.

3. MAJOR POLYPHENOLS WITH ANTIMICROBIAL CAPACITY.

In this section, the antimicrobial capacity of the most representative polyphenols classified by families against different bacteria is reviewed.

3.1. Phenolic Acids

Phenolic or phenol carboxylic acids are substances that contain a phenolic ring and an organic carboxylic acid function in their chemical structure (Fig. **1**). Among the most common phenolic acids present in plants are p-hydroxybenzoic, 3,4-dihydroxybenzoic, caffeic, vanillic, ferulic, *p*-coumaric, syringic and sinapic acids.

Phenolic acids have demonstrated antimicrobial activity against several Gram-positive bacterial species. The antibacterial activity of phenolic acids-enriched peanut extracts against *S. aureus* (ATCC 13565) has been reported with MIC values between 24 – 301 μg/mL, depending on the type of extract [37, 38]. *Bacillus subtilis* (8649) was also sensitive to phenolic acids with MICs of 2 mM when using *p*-coumaric acid, ferulic acid or sinapic acid and a MIC of 4 mM when using caffeic acid [39]. Pure *p*-coumaric acid also inhibited *Bacillus cereus* (MTCC 1272) growth with a MIC value of 41 μg/mL [40].

3.2. Ellagitannins and Gallotannins

Both ellagitannins and gallotannins belong to the group of hydrolyzable tannins (Fig. **1**). Ellagitannins derive from ellagic acid, while gallotannins derive from gallic acid. Ellagitannins have a common monomeric moiety called hexahydroxydiphenoyl (HHDP) which is esterified to a polyol and a galloyl residue. Ellagitannins are present in wood-aged wine, walnuts, pecans, berries and fruits, especially abundant in pomegranates, guavas and tropical highland blackberries [41, 42]. Oligomeric ellagitannins have vast structural diversity and varied biological activities depending on their structures. One of the largest groups of oligomeric ellagitannins contains a valoneoyl group that is produced through oxidative C−O coupling between a galloyl group of one monomer and an HHDP group of the other [43]. Some of the most representative ellagitannins commonly found in seeds, leaves, and fruits of plants are punicalagin, punicalin, corilagin, tellimagrandin I, geraniin and furosan. Examples of studied gallotannins are pentagalloylglucose, trigalloylglucose and tannic acid. Gallotannins are often found as complex mixtures [44]. Gallotannins are abundant in bean coats and nuts, especially in red sword bean (*Canavalia gladiata*) coat and witch hazel (*Hamamelis virginiana*) [45, 46].

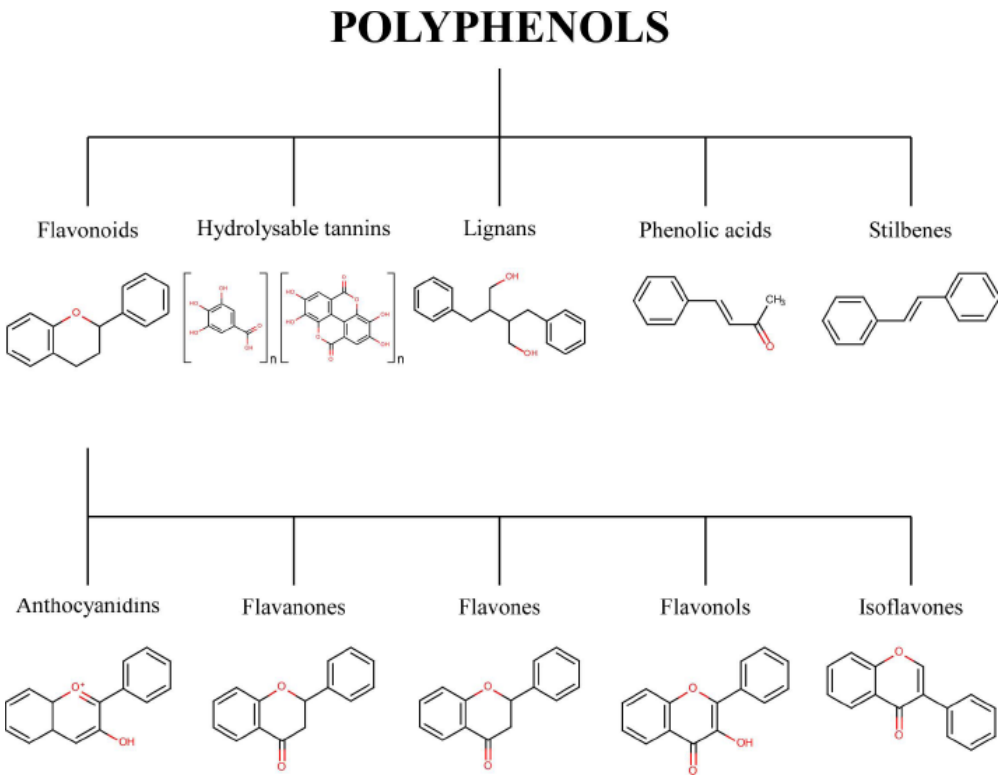


Fig. (1). Families and subfamilies of polyphenols with their core chemical structures.

It is known that ellagitannins extracted from botanical sources such as *Cistaceae* possess antibacterial activity within micromolar values [47, 48]. As examples, the ellagitannins davidiin and 3-O-galloylgranatin A have shown antibacterial activity against MRSA (OM481 and OM584) with a MIC of 64 μg/mL. They also had activity against VRE (*E. faecium* FN-1 and *E. faecalis* NCTC 12201) with MICs between 16 and 64 μg/mL [49]. Isorugosins are a subclass of ellagitannins that also present antibacterial activity against both MSSA (209P) and MRSA (OM481 and OM505) at MIC concentrations between 23 and 91 μM [43]. Ellagic acid and punicalagin have also demonstrated antimicrobial activity against *S. aureus* (CECT 59) with MIC values of 12.35 and 42.11 μg/mL, respectively [50]. Other study estimated at 12.5 μg/mL the MIC of both punicalagin and punicalin against *S. aureus* (BCRC 10781) [51].

Regarding gallotannins, penta-, hexa-, hepta-, octa-, nona- and deca-O-galloylglucose exhibited antibacterial activity against the Gram-positive *S. aureus*, *B. cereus*, *L. monocytogenes* and *B. subtilis* with MICs between 100 and 600 μg/mL. The degree of galloylation did not seem to affect the antibacterial activity. In general Gram-positive bacteria were generally more susceptible to tannins than Gram-negative [52]. Tannic acid also demonstrated antibacterial activity against *B. subtilis* with a MIC of 30 μg/mL [53].

3.3. Flavonoids

Flavonoids are a group of polyphenolic compounds found ubiquitously in plants. Until now, more than 9000 different flavonoid compounds have been described in plants, where they play important biological roles by affecting several developmental processes. They are structurally composed of a 15C backbone with at least two aromatic rings, which are tailored with diverse hydroxyl, methoxy or glycosyl groups (Fig. **1**) [36]. They form a wide molecular class with interesting antimicrobial properties. Next, the antimicrobial activity of the different sub-classes of flavonoids will be described.

3.3.1. Flavanols (Catechins, Procyanidins and Proanthocyanidins)

Flavanols (sometimes referred to as flavan-3-ols) are derivatives of flavans that bear the 2-phenyl-3,4-dihydro-2H-chromen-3-ol skeleton. Flavanols exist in monomeric and polymeric forms, may be substituted with gallic acid and present different isomers, so these compounds constitute one of the most numerous subclasses of polyphenols. On the contrary, they do not exist in the glycosylated form in nature. The most representative compounds of this class include the monomeric forms catechin, epicatechin gallate, epigallocatechin, epigallocatechin gallate, theaflavins and the polymeric forms proanthocyanidins and thearubigins.

Flavanols are most abundant in brewed black and green tea and dark chocolate, with more than 100 mg per 100g of foodstuff. Other significant flavanol sources are blackberries, cooked broad beans and pecan nuts [54]. Monomeric catechins are the most abundant polyphenols in green tea extracts. Their antimicrobial activity has been intensely studied, especially against Gram-positive bacteria, either isolated or in synergy with traditional antibiotics [36]. For instance, MICs between 62.5 and 125 μg/mL have been reported for epigallocatechin (EGC) and epigallocatechin gallate (EGCG) against five different clinical isolate strains of *S. aureus* [55]. Besides the positive interaction with classical antibiotics, researchers have found that EGCG antibacterial effects against *S. aureus* are enhanced by other organic molecules such as ascorbic acid and decreased by others such as casein [56]. Green tea catechins have also shown activity against *B. subtilis* (MTCC1427) with a MIC of 156 μg/mL and a large decrease of its adhesion potential to host cells [57].

Polymeric procyanidins and proanthocyanidins have shown moderate antimicrobial activity against clinical isolates of MRSA (OM481, OM505, OM584, and OM623), but exhibited strong synergic effects and resistance reversion when used with oxacillin or penicillin G [58].

3.3.2. Anthocyanins

Anthocyanins are colored water-soluble molecules belonging to the flavonoid subfamily of polyphenols. Anthocyanins are responsible for the red, purple, and blue colors in fruits and vegetables, being very common in berries, currants, and grapes. Among the anthocyanin pigments, cyanidin-3-glucoside is the major anthocyanin found in most of the plants [59].

Anthocyanins are very abundant in bilberries (285.21 mg/100 g foodstuff), aronia (349.79 mg/100 g foodstuff) and elderberry juice concentrate (411.40 mg/100 g foodstuff) [54].

Anthocyanin enriched extracts from bilberry and blueberry have shown antimicrobial activity against some Gram-positive bacteria: *Listeria monocytogenes*, *S. aureus*, *B. subtilis*, and *E. faecalis* [36]. These molecules can cause localized disintegration of bacterial

outer membrane causing leaking of cytoplasm [60]. Anthocyanins may also difficult the bacterial uptake of certain oligoelements, inhibiting diverse physiological functions [61, 62].

3.3.3. Flavonols, Flavanones, Flavones and Isoflavones

These subgroup of flavonoids include well-known flavonols such as kaempferol, quercetin, and myricetin; the flavanones naringenin, eriodyctiol and hesperidin [63]; the flavones luteolin, apigenin and baicalein and the isoflavones genistein and daidzein as isoflavones [36, 64].

Flavonols are mainly present in fresh capers, dried parsley, and elderberry juice, with concentration over 100 mg per 100 g of foodstuff, but are also widely distributed in many other plants. Flavanones are mainly present in oregano, grapefruit, lemon, and oranges. Flavones are extremely abundant in dried parsley and oregano, with concentrations of 4.5 g and 1.0 g per 100 g of foodstuff, respectively [54].

The flavonols quercetin and kaempferol have demonstrated to have high antimicrobial activities with reported MIC values as low as 1.95 μg/mL and 7.8 μg/mL respectively against *S. aureus* (ATCC 6538) and MRSA clinical isolates [65, 66]. Glycosylated forms of these flavonols also showed antimicrobial activity against *S. aureus* with MICs of 250 μg/mL for quercetin-3-O-arabinofuranoside and 130 μg/mL for kaempferol-3-O-rhamnoside. Myricetin has shown a MIC value of 15.76 μg/mL against *S. aureus* (CECT 59) [50]. Glycosylated myricetin derivatives also showed antibacterial activity with MICs of 250 μg/mL against *S. aureus* (ATCC 12600) [67]. Quercetin-3-glucoside obtained a MIC value of 14.37 μg/mL against *S. aureus* (CECT 59) [50].

The flavanone naringenin exhibited antibacterial activity against several *S. aureus* strains (ATCC 29213, ATCC 10832, BAA-1717, 8325-4 and DU 1090) with MIC values between 256 and 512 μg/mL. Moreover, staphylococcal expression of α-toxin was significantly reduced when the organism was treated with 16 μg/mL of naringenin, reducing *S. aureus* virulence [68]. Naringenin derivatives have also proven to be especially effective against Gram-positive bacteria. Concentrations of 0.25 mM of alkyl prunin esters with 10-12C chain lengths diminished viable *S. aureus* (ATCC 29213) with about 6 log orders and *L. monocytogenes* (01 / 155, 99 / 287 and 99 / 287RB6, strains obtained from Dr. Carlos Malbran Microbiology Institute, Buenos Aires, Argentina) with about 3 log orders after two hours [69].

Flavones has shown a remarkable antibacterial capacity against Gram-positive bacteria. Luteolin inhibited clinically isolated *S. aureus* growth with MICs between 31.2 and 125 μg/mL. Apigenin demonstrated MICs ranging 3.9 – 15.6 μg/mL against 15 MRSA and 5 MSSA strains [66, 70]. The flavone baicalein exhibited weak antimicrobial activity against clinically isolated vancomycin-resistant *Enterococcus* (VRE). Nevertheless, baicalein demonstrated great synergy effectiveness with the antibiotic gentamicin against Gram-positive VREs [71] and also synergy with tetracycline against MRSA (OM481 and OM584) [72].

A group of nine isoflavones (2′-hydroxyerythrin A, daidzein-7-O-butenoyl glycoside, 7,4'-dihydroxy-6-methoxyisoflavone, daidzein, daidzin, genistein, formononetin, ononin, and isoerythrinin A) was tested against *S. aureus* (ATCC 26112) and *E. faecium* (ATCC 35667). Among them, only 2′-hydroxyerythrin A inhibited bacterial growth significantly with MICs of 13.1 μg/mL for *S. aureus* and 16.5 μg/mL for *E. faecium,* followed by isoerythrinin A with MICs of 18.3 μg/mL for *S. aureus* and 22.6 μg/mL for *E. faecium* [73].

3.4. Lignans

Plant lignans are a polyphenol subclass, which a chemical structure consisting of two phenylpropanoid moieties connected via C8-C8′ at their side chain or by additional ether, lactone, or carbon bonds (Fig. **1**) [74]. Some examples of lignans are enterodiol, magnolol, and honokiol. The most abundant natural sources of lignans are flax and sesame seeds. Other secondary sources are grains, fruits and vegetables [75].

The norlignans hyposoxide (HYP) and rooperol (RO), derived from *Hypoxis rooperi* T. Moore, demonstrated antimicrobial activity against *S. aureus*, showing MIC values of 20 μg/mL and 800 μg/mL for RO and HYP, respectively. These values were lower than their respective MIC values for *E. coli*. A stronger antibacterial effect was also observed against the Gram-positive bacteria when the whole *Hypoxis rooperi* extract was utilized. RO showed a 5 times lower MIC value than the positive control neomycin [76].

Magnolol and honokiol have shown remarkable antimicrobial activity against both methicillin-sensible *S. aureus* (MSSA ATCC 25923) and ten clinical isolates of MRSA. Magnolol showed a MIC of 32 μg/mL against MSSA and a MIC range between 8 and 64

μg/mL against the MRSA clinical isolates. On the other hand, honokiol demonstrated a MIC of 16 μg/mL against MSSA and a range between 16 and 32 μg/mL against MRSA [77].

The antimicrobial activity of some lignans has been proposed to be related to their multidrug-resistant reversal activity (MDR). This is the case of dibenzylbutane, furofuran, and tetrahydrofuran lignans, which have exhibited comparable or stronger MDR activity than verapamil. Arylnaphtalene lignans exhibited additional moderate antimicrobial activity against *S. aureus* [78]. Melaleucin A and melaleucin C are recently discovered lignans showing a potent antimicrobial activity against MSSA (ATCC 6538) and MRSA (JCSC4788) with MICs of 8 μg/mL and 16 μg/mL, respectively [79].

Virgatusin, a tetra-substituted tetrahydrofuran lignan, has shown stereoselective anti-Gram-positive bactericidal activity in disc-plate assays, affecting *B. subtilis*, *S. aureus* and *Listeria denitrificans*. This compound seemed to damage the cytoplasmic membrane, leading to membrane-related cell death [80].

3.5. Stilbenes

Stilbenes chemical structure consists of two aromatic rings and phenolic hydroxyl groups with double bonds that makes two *cis*- and *trans*- forms of isomers (Fig. **1**) [81]. Stilbenes are typically present in wine, grapes, tree nuts and berries. Resveratrol is the most famous integrant of this polyphenol subclass [82].

Resveratrol has demonstrated a significant antibacterial activity against some Gram-positive bacteria. Resveratrol exhibited MICs of 16.5 μg/mL against *B. subtilis* and 32 μg/mL against *S. aureus* [83]. The resveratrol efficacy has been also proven against MRSA clinical isolates with MICs between 250 μg/mL and 1000 μg/mL [66]. The chemical stilbene backbone has been proven to reduce *S. aureus* virulence factors, *e.g.* hemolysis [84]. It also inhibits *Mycobacterium tuberculosis* (H37Rv) and *E. faecalis* (ATCC 29212) growth with a MIC of 100 μg/mL each [85].

Other stilbenes such as pterostilbene have shown strong antibacterial activity against *S. aureus* (ATCC 25923) with a MIC of 25 μg/mL [86]. It is also reported that prenylation of stilbenes enhance their antibacterial activity against MRSA (18HN) and *L. monocytogenes* (EGD-e) [87].

3.6. Herbal Mixtures and Botanical Extracts

There is a great deal of research related to the antibacterial properties of herbal mixtures and plant extracts. Botanical extracts can be obtained in many ways, such as infusion, fractioning, ultrasound-assisted extraction, using supercritical fluids, *etc.* There is extensive literature reporting the antimicrobial activity of plant extracts, however, in this review, only data derived from well characterized extracts, with clear evidences on their putative correlation between their composition and their antimicrobial activity have been included. One of the most widely studied botanical extracts worldwide is the green tea extract derived from *Camellia sinensis* [88].

Green tea extract is well known for its traditional therapeutic properties: antioxidative, anti-inflammatory or antimicrobial among others. The chemical composition of green tea is complex and varies depending on variety and extraction procedure. The most abundant phytochemicals present in green tea are polyphenols, and flavonoids in particular: catechins, catechin gallates and proanthocyanidins [89]. Green tea extract has shown antimicrobial activity against *S. aureus* (ATCC 6538p and four clinical isolates) with MICs ranging from 250 to 1000 μg/mL [55]**.** Green tea extract also demonstrated antibacterial activity against other Gram-positive bacteria with MIC values of 156 μg/mL against both *B. subtilis* (MTCC1427) and *Staphylococcus epidermis* (MTCC435) and a MIC of 313 μg/mL against *Brevibacterium linens* (MTCC268). Moreover, skin pathogens such as *S. epidermidis, Micrococcus luteus, Brevibacterium linens, Pseudomonas fluorescens* and *B. subtilis* were found to be sensitive to green tea extract via disc diffusion assay [57]. MRSA growth was also especially sensitive to green tea extract, being inhibited by the equivalent of a 1:10 dilution of a cup of tea [89].

Cistaceae extracts have demonstrated antimicrobial activity against *S. aureus* (CECT 59). Aqueous extracts from *Cistus ladanifer* and *Cistus populifolius* have shown MIC values of 154 and 344 μg/mL, respectively [47]. Hydroalcoholic extract of *C. ladanifer* showed a MIC value of 144 μg/mL. Aqueous spray-dried extracts of *Cistus albidus* and *Cistus clusii* showed MIC values of 60 μg/mL and 91 μg/mL, respectively. The most active extract was the hydroalcoholic spray-dried *Cistus salviifolius* one after column fractionation, with a MIC value of 11 μg/mL [48]. Several botanical extracts from *Hibiscus sabdariffa*, *Hibiscus arnottatianus*, *Lippia citriodora*, *C. albidus*, *C. ladanifer*, *C. clusii* and *Hypooxis rooperi* were tested against three pathogenic model microorganisms: *E. coli*, *S. aureus* and *C. albicans* [90]. At the lowest concentrations tested, *i.e.* 1 mg/mL, only *C. salviifolius* extract re-

tained significant growth inhibitory activity against *S. aureus* (533R4 Serovar 3) among the extracts tested. At higher concentrations, 1 and 2 mg/mL, most extracts showed significant antimicrobial activity against *S. aureus*. The results suggest that extracts enriched in ellagitannins and flavonols revealed promising antibacterial activity agents both against Gram-positive and Gram-negative bacteria. Phenolic acids, anthocyanidins, and flavonols are plausibly more related to the antifungal activity.

3.7. Synergic Mixtures

3.7.1. Combination of Polyphenols

There is wide evidence of the synergistic effects of the combination of different polyphenols with traditional antibiotics. Pharmacological synergic interactions are often expressed as FICI (fraction inhibitory concentration index) value for a certain pair of substances in combination. For a paired combinations of antimicrobial agents, a FICI value ≤ 0.5 represents synergy, $0.5 \leq \text{FICI} \leq 1$ represents additivity, $1 \leq \text{FICI} \leq 2$ represents indifference and $\text{FICI} \geq 2$ represents antagonism [99]. The FICI value is calculated by adding up the FIC (fraction inhibitory concentration) values of both antimicrobial agents. The FIC value of a compound in a combination is calculated by dividing the MIC value of the whole combination between the MIC value of the compound alone [100].

Several studies have proposed that different polyphenolic compounds may have synergic antibacterial capacity in complex botanical mixtures. In many cases, complex polyphenolic mixture loses its efficacy after purification. This loss of functionality has been attributed to the decrease in the synergistic interactions between the phytochemicals previously present in the sample [93, 101]. The possible explanation to this behavior may be due to the capacity of polyphenols to interact with multiple molecular targets such as lipid membranes, membrane receptors, enzymes, ion channels, transport proteins and others [102].

Several examples of the synergy between a pair of polyphenols have been reported. Combinations of rutin with quercetin, morin, kaempferol, myricetin or eriodictiol strongly decreased MIC values against *B. cereus*, even when rutin had no antibacterial activity by itself [103, 104]. Two-drug combinations between luteolin, quercetin and resveratrol have shown synergistic effects against two MRSA strains (SA0929, SA1056) [66]. The flavonols quercetin and kaempferol have shown synergy when applied together or in combination with caffeic acid against *S. aureus* (ATCC 6538). The strongest synergistic effect was observed for the combination containing 7.8 μg/mL of quercetin and 31 μg/mL of caffeic acid with a FICI value of 0.37 [65].

The proportions of each polyphenol in the combination seem of key importance in synergy. Strong synergy against *S. aureus* (CECT 59) has been also found between the combinations punicalagin + ellagic acid (FICI value of 0.038), quercetin-3-glucoside (FICI of 0.31) or myricetin (FICI of 0.17). Quercetin-3-glucoside also showed synergy when paired with ellagic acid (FICI of 0.21) or myricetin (FICI of 0.05). The synergy of all these mixtures depended directly on the ratio of each component [50].

Due to the vast variety of polyphenolic structures present in nature, it is difficult to propose specific synergistic mechanisms. Nevertheless, some mechanisms have been proposed for some polyphenolic mixtures, in which partially hydrophobic phenolics interact with bacterial membranes, disrupting them to the point that small phenolic acids can enter the cells and trigger hyperacidification and electronic quenching, leading to cell death. That is the proposed mechanism for the synergy found between rosmarinic acid, a partially hydrophobic biphenyl and small phenolic acids such as gallic or caffeic acid [105, 106].

3.7.2. Interaction between Polyphenols and Antibiotics

Isolated plant polyphenols and whole extracts are currently being used to sensitize multidrug-resistant bacterial strains (MRSA, VRE, *etc.*) to traditional antibiotics with promising results [58, 107]. Green tea catechins have shown synergistic activities with gentamycin against *S. aureus* standard strains (ATCC 6538p) and a clinical isolate with FICI values of 0.56 and 0.75, respectively [55]. Baicalein has also shown strong synergy with gentamycin against VRE (VRE-70, VRE-940, VRE-096, and VRE-721) [71]. EGCG has also demonstrated powerful synergy with tetracycline to revert resistance in both resistant and sensitive *S. aureus* and *S. epidermis* via inhibiting specific Tet(K) efflux pump [108].

Some green tea catechins have demonstrated high MRSA sensitizing capacity towards methicillin, oxacillin and other β-lactam antibiotics in addition to its intrinsic antimicrobial capacity. For instance, galloyl catechins at concentrations between 6.25 and 25 μg/mL have reduced MIC of β-lactams against *S. aureus* (BB568, EMRSA-16, and EMRSA-15) from high resistance levels to below the common resistance break-

point [109]. Moreover, EGCG and especially EGC at concentrations of 25 μg/mL can heavily reduce the resistance of *S. aureus* clinical isolates towards other β-lactam antibiotics besides oxacillin: flucloxacillin, cefotaxime, cefepime, imipenem and meropenem [110].

The lignans magnolol and honokiol have demonstrated antimicrobial synergy with a broad spectrum of antibiotics: amikacin, gentamycin, fosfomycin, levofloxacin, etimicin, piperacillin, ciprofloxacin, and norfloxacin, against several clinically isolated MRSA strains with FICI values ranging between 0.25 and 0.5. These polyphenols were especially effective in reversing resistance against amikacin and gentamycin. Moreover, magnolol and honokiol have shown great synergy with oxacillin, chloramphenicol, cefoxitin and other traditional antibiotics [77, 111].

The ellagitannins corilagin and tellimagradin I have proven to inhibit the activity of PBP2a in MRSA, allowing β-lactam antibiotics to increase their activity [112]. Anti-VRE activity of tannins have also been recently reported [49]. Isoflavones isolated from *Lupinus argenteus* have potentiated the activity of norfloxacin and berberine via *NorA* multidrug resistance pump inhibition [113]. Pterostilbene has shown great synergy with the antibiotic gentamicin with a FICI value of 0.125 [86].

Extracts from guaco (*Mikania glomerata*), guava (*Psidium guajava*), clove (*Syzygium aromaticum*), garlic (*Allium sativum*), lemongrass (*Cymbopogon citratus*), ginger (*Zingiber officinale*), "carqueja" (*Baccharis trimera*), and mint (*Mentha piperita*) were tested in combination with thirteen antibiotics for antimicrobial synergism against clinically isolated *S. aureus*. All of them showed synergy with tetracycline and each extract showed synergy between two and eleven antibiotics [107]. Other study showed that a fraction of an extract from *Duabanga grandiflora* had synergy with ampicillin against MRSA (ATCC 43300) via PBP2a inhibition [114].

4. FOOD PRESERVATION

Besides being an important human pathogen, *S. aureus* is also one of the largest producers of foodborne illnesses. Because of its resistance, this bacterium can grow in many different types of foods, producing problematic heat-resistant toxins that can severely affect human health [115]. To avoid this, several studies have assessed the possibility of using polyphenols enriched formulations as natural biopreservatives of food due to its antimicrobial properties and low toxicity in humans. Besides their antimicrobial action, polyphenols can be used in new trends of active packaging, edible films, fortification of products to extend shelf life or even turn some traditional foods into functional foods [116].

Nowadays, there exist many compounds to preserve food, but not all are equally effective. A recent study compared the *S. aureus* enterotoxin I production, bacterial growth and toxin gene expression in the presence of four different food preservatives: sodium nitrite, polylysine, chitosan, and tea catechin. Results showed that tea catechins were the most efficient among the four preservatives studied exhibiting a higher antimicrobial activity and toxin suppression [117].

Researchers studied the effect of several polyphenol-derived food additives against the production of toxins and biofilms by foodborne pathogens. They found that many polyphenols such as gallic, rosmarinic and ellagic acids, catechins and epigallocatechin gallate, had strong biofilm inhibition capacity against *S. aureus* at growth sub-inhibitory concentrations. It is important to notice that polyphenols could also affect organoleptic properties in food, especially the flavor. Nevertheless, the effective concentrations proposed in the study did not affect any food properties while protecting it against staphylococcal toxins and biofilms [118].

Polyphenols like catechin or tannic acid have also demonstrated quality and organoleptic improvements when added to fish and seafood. In addition to protecting food from bacterial attack, some polyphenols have the ability to retard food browning and texture degradation via antioxidant capacity and protein cross-linking, respectively [119].

5. MOLECULAR TARGETS AND POTENTIAL MECHANISM OF POLYPHENOLS

In this section, the main molecular targets of polyphenols and the proposed mechanisms of action are reviewed and discussed.

5.1. Cell Wall Components and Synthesis

The development of antimicrobial drugs is a transcendental fact in modern medicine that saves the lives of many people infected by pathogenic bacteria. Most of these drugs have molecular targets enzymes involved in the biosynthesis of the bacterial cell wall and cellular proteins and DNA. Since the bacterial cell wall is for these microorganisms unique, using drugs that prevent their biosynthesis will have an enormous therapeutic value. In fact, more than 60% of antimicrobial drugs for clinical use prevent the formation of the bacterial cell wall [120].

The primary component of the bacterial cell wall is a highly cross-linked polysaccharide (alternating ß-1,4-linked N-acetylmuramic acid (MurNAc) and N-acetylglucosamine) with a pentapeptide that includes D-amino acids: the peptidoglycan. Peptidoglycan maintains the shape of the bacterial cell, acts as an anchoring point to extracellular structures such as flagella and allows the bacterial cell not to explode as a consequence of the greater osmolarity of its interior with respect to the hypoosmotic external environment. In Gram-negative bacteria, peptidoglycan resides in the periplasm between the cytoplasmic and external membranes, whereas in Gram-positive bacteria is a thicker layer interconnected with other polymers such as teichoic acids [121, 122]. The main difference between Gram-positive and Gram-negative bacterial cell wall is the presence of an additional polysaccharide outer membrane in the Gram-negative ones [123].

The different localization of the peptidoglycan biosynthesis machinery has allowed distinguishing three phases in this process. Most drugs for clinical use target enzymes involved in Phase III, in which the cross-linking and final maturation of this biopolymer occurs [124]. In the so-called Phase I, nucleotide-activated precursors (UDP-N-acetylglucosamine and UDP-N-acetylmuramyl pentapeptide) are synthesized in the bacterial cytoplasm. During Phase II, which occurs in the inner half of the inner membrane, the precursors are assembled with undecaprenyl phosphate to form the lipid-anchored disaccharide-pentapeptide (Lipid II), which must be flipped across the inner membrane to polymerize with other disaccharide-peptide units [121, 124]. Most of the enzymes involved in Phases I and II have not been validated as therapeutic targets, perhaps except for glutamate racemase (coded by the MurI gene) for which several inhibitors have been developed.

Polyphenols can target multiple bacterial locations and structures. However, the bacterial cell wall seems to be the main molecular target for the antimicrobial action of most polyphenols. Gram-positive bacteria seem to be more susceptible to the antimicrobial action of phenolic compounds as the outer membrane of Gram-negative bacteria acts as a permeability barrier, reducing the uptake of the phenolic compounds [61].

Polyphenols can cause morphological damage to bacterial cells or destroy the structural integrity of the cell wall and intracellular matrix. Phenolic compounds may cause cell deformation, breakage of the cell wall, and membrane condensation of cellular material with the presence of cytoplasmic material and membrane debris outside affected cells [125, 126]. Leakage is explained by the increase of the bacterial membrane and cell wall permeability caused by polyphenols [127, 128]. Some specific polyphenols such as ellagitannins, catechins or nor-lignans have demonstrated high affinity for bacterial membranes and great disruption capacity [49, 76, 129]. It is stated that catechins have a high affinity for bacterial membranes, specifically for the membranes of Gram-positive bacteria [88]. Other polyphenols such as the norlignans rooperol and hyposoxide have been proposed to perturb bacterial membranes enriched in negatively charged phospholipids (phosphatidylglycerol or cardiolipin), such as those of Gram-positive bacteria [76].

One potential mechanism involved in the degradation of the bacterial wall could be the inactivation by aggregation of certain essential surface proteins. Galloylated catechins seem to bind and cause the aggregation of at least 73 different proteins, including PBPs (penicillin-binding proteins), which are key in the wall formation, transporter proteins including ABC transporter (Oppa), PTS system transporter and phosphate ABC transporter and others [130]. It is also proposed that catechins can intimately interact with lipids in biological membranes, modifying their physical properties and causing membrane phase separations [129]. Moreover, this ability to interact and the eventual penetration of membranes may be potentially linked to apoptosis mechanisms and other cellular responses [131]. Studies demonstrated that ECG binds the MRSA cell membrane reducing its fluidity by penetrating deep into the hydrophobic region. To overcome these changes, the MRSA cell membrane undergoes molecular lipid transformations that affect peptidoglycan biosynthetic machinery, affecting also to the cooperation between PBP2 and PBP2a to overcome β-lactam antibiotics, decreasing the bacterial viability and antibiotic resistance [132].

Due to the discovery and usage of β-lactam antibiotics such as penicillin, which targets cell wall formation, bacteria developed β-lactamases to avoid the action of this antibiotic. Polyphenolic compounds have demonstrated interesting β-lactamase inhibitory properties. For instance, epicatechin, tannic acid, epigallocatechin gallate and quercetin showed significant β -lactamase inhibitory activity. Interestingly, the high antibacterial performance of tannic acid was predicted computationally based on the favorable docking assays between the polyphenol and TEM-1, a β-lactamase [133].

MRSA is a very important β-lactamase producer, conferring it with an annoying antibiotic resistance.

MRSA produces PBP2a (penicillin-binding protein 2A) which has a low affinity for β-lactam antibiotics enabling transpeptidase activity in the presence of β-lactams, preventing them from inhibiting cell wall synthesis. Nevertheless, some polyphenols such as kaempferol and quercetin have demonstrated high β-lactamase inhibition capacity and a great synergy with antibiotics like ciprofloxacin and rifampicin [134]. Natural polymeric proanthocyanidins strongly suppressed MRSA resistance to β-lactam antibiotics against MRSA and reduced cell membrane stability and β-lactamase activity at sub-MIC concentrations [135]. Other polyphenolic compounds such as epicatechin gallate, licoricidin, corilagin and tellimagrandin I have also demonstrated β-lactam antibiotic activity potentiation through PBP2a inhibition in MRSA. These findings could lead to alternative pharmaceutical treatments for resistant infections. Nonetheless, it is worth to notice that polyphenols bind to serum proteins and others, which limits their intravenous use. For this reason, polyphenolic therapy would be preferably indicated for skin, digestive tract and lung infections [136].

All of the mechanisms described above can modify the properties of bacterial membranes, facilitating other small polyphenols or antibiotics to enter the cytoplasm and cause metabolic damage [106].

5.1.1. Virtual Screening of Polyphenols on Bacterial Putative Protein Targets

If we consider that the development of a new antibiotic drug can take ten or more years and therefore is very costly economically, we can understand that the search for antimicrobial substances from products of natural origin, such as polyphenols, is gaining both scientist and medical interest. In this regard, it is necessary to clarify that the interest for phytochemical compounds does not completely lie in its use as an alternative therapy to conventional antibiotics since phytochemicals show inhibitory effects at concentrations of several orders of magnitude higher than antibiotics of current clinical use. However, there is abundant scientific evidence that adequate combinations of phytochemicals and antibiotics modify the mechanisms of resistance in pathogenic bacteria, playing a synergistic role (as we have shown earlier in this review) that allows reducing the dose of antibiotics.

In this context, we have considered opportune trying to look for possible polyphenolic phytochemicals that can modulate the activity of enzymes involved in Phases I and II of peptidoglycan biosynthesis. For this purpose, we have selected several enzymes: MraY, MurA, MurB, MurC, MurD, MurE, MurF, MurG, and MurI (see Fig. **1** of the Supplementary Information available on the website http://dockingfiles.umh.es/bcwall/) and with them we have performed molecular docking experiments with the phenolic compounds stored in the base of data Phenol Explorer 3.6 [137].

Molecular docking calculations allow us to predict the structure of ligand-receptor complexes based on calculations that estimate the variation of Gibbs free energy (Kcal/mol) [138, 139] of the binding process of a given ligand (phenolic compounds in this case) to a known binding site of a protein of our interest. For the enzymes selected above, information on their structure is available at atomic resolution, and its catalytic site is known. Thus, we have carried out the screening of those phenolic compounds that could bind with high affinity to the catalytic site and, therefore, behave as competitive inhibitors of these enzymes.

Molecular docking calculations have been carried out with the Autodock/Vina software [140] executed in a high performance computing cluster under a Linux operating system belonging to the Research, Technological Innovation, and Supercomputing Center of Extremadura [CenitS] (http://www.cenits.en/cenits/ lusitania-II/lusitania-ii-specifications). For those enzymes without high-resolution structures available at Protein Data Bank (see Table **1** of the Supplementary Information) we have carried out a homology modeling [141] using the amino acid sequences found in the UniProt database (http://www.uniprot.org/). All this information about the amino acid sequences and the generated 3D models is also available at http:// dockingfiles.umh.es/bcwall/.

After carrying out the molecular docking experiments, we made the first selection of compounds that had a free energy variation (ΔG, Kcal/mol) threshold less than or equal to the corresponding value for the co-crystallized inhibitor in each type of enzyme. Fig. (**2**) shows an example of the molecular architecture of several enzymes involved in the biosynthesis of peptidoglycan with some of the polyphenols coupled in the catalytic center that have the highest affinity. The Gibbs free energy variation values of the 931 compounds stored in the Phenol-Explorer 3.6 database docked to the nine enzymes analyzed for the six selected bacterial species are available at http://dockingfiles.umh.es/bcwall/phenol/.

Panels A) and B) of (Fig. **3**) show the phenolic compounds with ΔG values less than or equal to the inhibitor compound co-crystallized with the enzyme

Table 1. Reported MIC values for selected polyphenols against different *S. aureus* strains.

Polyphenolic Agent	Class	Source	*S. aureus* Strain	MIC µg/mL	References
Davidiin	Ellagitannin	*Davidia involucrata*	OM481	64	Y. Shimozu *et al.* / Molecules 22 (2017) 470-479
			OM584	64	
			OM481	64	
			OM584	64	
3-O-galloylgranatin A	Gallotannin	Mango kernels	ATCC 6538	< 100	C. Engels *et al.* / Appl Environ Microbiol 77 (7) (2011) 2215-2223
hexa-O-galloylglucose					
hepta-O-galloylglucose			ATCC 6538	< 100	
octa-O-galloylglucose			ATCC 6538	< 100	
nona-O-galloylglucose			ATCC 6538	< 100	
EGC	Catechin	Purchased from Sigma	ATCC 6538p	62.5	B. Bazzaz *et al.* / Journal of Pharmacopuncture 19 (4) (2016) 312-318
			Clinical isolate 1	62.5	
			Clinical isolate 2	125	
			Clinical isolate 3	125	
			Clinical isolate 4	62.5	
EGCG	Catechin	Purchased from Sigma	ATCC 6538p	125	
			Clinical isolate 1	62.5	
			Clinical isolate 2	62.5	
			Clinical isolate 3	62.5	
			Clinical isolate 4	62.5	
Punicalagin	Ellagitannin	Purchased from Phytolab	CECT59	42.1	L. Tomás-Menor *et al.* / Phytother Res 29 (2015) 466-473
		Pomegranate dried peels	BCRC 10781	12.5	C.J. Lee *et al.* / Int J Mol Sci 18 (1) (2017)
Punicalin			BCRC 10781	12.5	
Quercetin	Flavonol	Purchased from Sigma	ATCC 6538	31	M. Mokhtar *et al.* / Curr Microbiol 74 (11) (2017) 1253-1260
			Clinical isolate 8	3.9	
			Clinical isolate 14	3.9	
			Clinical isolate 26	125	
			Clinical isolate 32	1.95	
			Clinical isolate 319	3.9	
			Clinical isolate 550	7.8	
			MRSA ATCC 43300	125	Y. Su *et al.* / Molecules 19 (2014) 12630-12639
			MSSA ATCC 29213	125	
			Clinical isolate SA1053	31.2	
Kaempferol			ATCC 6538	15.6	M. Mokhtar *et al.* / Curr Microbiol 74 (11) (2017) 1253-1260
			Clinical isolate 8	15.6	
			Clinical isolate 14	15.6	

(Table 1) contd….

Polyphenolic Agent	Class	Source	*S. aureus* Strain	MIC µg/mL	References
			Clinical isolate 26	15.6	
			Clinical isolate 32	15.6	
			Clinical isolate 319	7.8	
			Clinical isolate 550	15.6	
Myricetin			CECT59	15.76	L. Tomás-Menor *et al.* / Phytother Res 29 (2015) 466-473
Quercetin-3-glucoside	Glycosylated flavonol	Purchased from Sigma	CECT59	14.37	
Quercetin-3-O-arabinofuranoside		Isolated from *Searsia chirindensis*	ATCC 12600	250	B. Madikizelaetal *et al.* /Journal of Ethnopharmacology 150 (2013) 609–613
Kaempferol-3-O-rhamnoside			ATCC 12600	130	
Myricetin-3-O-rhamnoside			ATCC 12600	250	
Myricetin-3-O-arabinopyranoside			ATCC 12600	250	
Naringenin	Flavanone	Purchased from NICPBP	ATCC 29213	256	Y. Zhang *et al.* / Fitoterapia 86 (2013) 92–99
			ATCC 10832	256	
			BAA-1717	512	
			8325-4	256	
			DU 1090	256	
Luteolin	Flavone	Purchased from Sigma	MRSA ATCC 43300	125	Y. Su *et al.* / Molecules 19 (2014) 12630-12639
			MSSA ATCC 29213	125	
			Clinical isolate SA0922	31.2	
Apigenin	Flavone	*Scutellaria barbata*	15 MRSA and 5 MSSA laboratory strains	62.5 - 125	Y. Sato *et al.* / Journal of Ethnopharmacology 72 (2000) 483-488
2′-hydroxyerythrin A	Isoflavone	Soya beans	ATCC 26112	13.1	T. Wang *et al.* / In publication process doi: 10.1002/jsfa.8663
Isoerythrinin A			ATCC 26112	18.3	
Magnolol	Lignan	Purchased from XXST	ATCC 25923	32	Zuo *et al.* / BMC Complementary and Alternative Medicine 15 (2015) 425
			10 MRSA clinical isolates	8 - 64	
Honokiol			ATCC 25923	16	
			10 MRSA clinical isolates	16 - 32	
Hypoxoside		Provided by Monteloeder SL	CECT59	20	O. Laporta *et al.* / Arch Biochem Biophys 467 (1) (2007) 119-131
Rooperol			CECT59	800	
Melaleucin A	Neolignan	Isolated from *Mucuna bracteata*	ATCC 6538	8	C. Li *et al.* / Fitoterapia 120 (2017) 171–176
			MRSA (JCSC4788)	8	
Melaleucin C			ATCC 6538	16	
			MRSA (JCSC4788)	16	
Resveratrol	Stilbene	Isolated from *Bacillus cereus*	MTCC 902	32	S. Kumar *et al.* / Letters in Applied Microbiology 54 (2012) 410-417

(Table 1) contd….

Polyphenolic Agent	Class	Source	*S. aureus* Strain	MIC µg/mL	References
		Purchased from Sigma	MRSA ATCC 43300	1000	Y. Su *et al.* / Molecules 19 (2014) 12630-12639
			MSSA ATCC 29213	1000	
			Clinical isolate SA1056	250	
Pterostilbene		Purchased	ATCC 25923	25	W. Lee *et al.* / Molecules 22 (2017) 463
Eupomatenoid-5	Neolignan	Extracted from *Piper regnellii*	MRSA (32 clinical strains)	1 - 8	F. J. Marçal *et al.* / Molecules 15 (2010) 2060-2069
			MSSA (32 clinical strains)	1 - 8	

Table 2. Reported MIC values for selected botanical extracts against different *S. aureus* strains.

Polyphenolic Agent	Extraction Type / SolvenT	Vegetal Source	*S. aureus* Strain	MIC µg/mL	References
Green tea extract	Water	*Camelia sinensis* leaves	ATCC 6538p	500	B. S. Bazzaz *et al.* / Journal of Pharmacopuncture 19 (4) (2016) 312-318
			Clinical isolate 1	250	
			Clinical isolate 2	1000	
			Clinical isolate 3	500	
			Clinical isolate 4	500	
Cistus populifolius extract	Water	Flowers and leaves	CECT 59	344	E. Barrajon-Catalan *et al.* / Food and Chemical Toxicology 48 (2010) 2273–2282
Cistus ladanifer extract			CECT 59	154	
	Hydroalcoholic		CECT 59	144	L. Tomás-Menor *et al.* / Food and Chemical Toxicology 55 (2013) 313–322
Cistus albidus extract	Water		CECT 59	60	
	Hydroalcoholic		CECT 59	292	
Cistus clusii extract	Water		CECT 59	91	
	Hydroalcoholic		CECT 59	304	
Cistus salviifolius extract	Water		CECT 59	50	
	Hydroalcoholic		CECT 59	45	

MraY. It should be noted that most of these compounds have been selected for *S. aureus* (121 compounds), while for the other species only 30 to 40 have been selected, except for *E. faecalis*, for which there are only 7 compounds. We can find several examples of compounds that show a high affinity for the catalytic site of the MraY enzyme for all six bacterial species, and that could, therefore, be considered as potential broad-spectrum inhibitors. This is the case of flavanols PE000133, PE000134, PE000136, PE000143, PE000149, PE000157, PE000161, PE000169, PE000170, PE000174, PE000189, PE000198, PE000322, and PE000450.

Several studies have shown the antibacterial activity of several theaflavins against *S. aureus* [142], *P. aeruginosa* [143], *H. pylori* [144] or *E. faecalis* [145]. As we can see in (Fig. **3A**), only some polyphenols show high affinity for the catalytic site of the enzyme MurA for the six bacterial species studied, including several theaflavins PE000143, PE000149, and PE000151. Numerous compounds show high affinity to the binding site studied, especially for the enzymes of the species *A. baumannii* and *P. aeruginosa*, and with ΔG values lower than -12 Kcal/mol. Likewise, several proanthocyanidins show high affinity for MurA, as is the case of PE000150, PE000151, PE000152, PE000153, PE000154, and PE000155. Except for the case of *H. pylori*, numerous compounds show high affinity against the catalytic site of the MurB enzyme (Fig. **3D**), with values lower than -11 Kcal/mol.

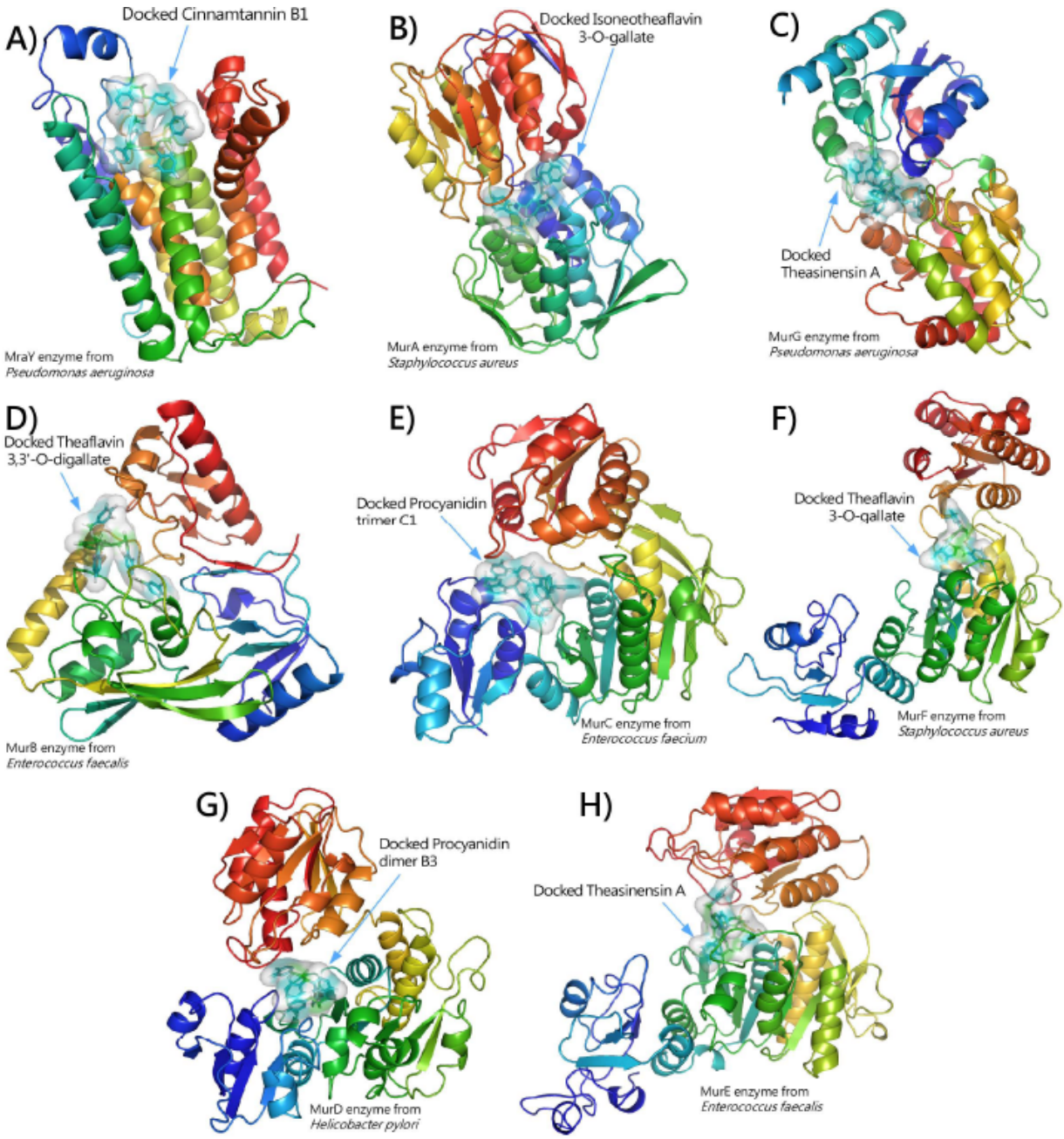


Fig. (2). Secondary structure model of eight enzymes involved in Phases I and II of peptidoglycan biosynthesis with some of the phenolic compounds resulting from molecular docking experiments at the catalytic site of the enzyme. Each panel includes the name of the enzyme, the bacterial species, and the docked compound.

Among these compounds are several theaflavins again. Also, theaflavins (PE000134, PE000136, PE000143) and proanthocyanidins (PE000157, PE000161, PE0174) show high affinity for the catalytic site of the MurC enzyme (Fig. **3E**). In the case of the MurD enzyme (Fig. **3F**), in addition to theaflavins and proanthocyanidins, the high affinity shown by several epicatechins is noteworthy (PE000193, PE000194, and PE000175). Against the catalytic site of MurE enzyme (Fig. **3G** and **3H**) abundant phenolic compounds show lower ΔG than the crystallographic ligands ($NADP^+$ and FAD), especially for the species *E. faecium*, *E. faecalis* and *Acinetobacter baumannii*; although these compounds are usually different in the three species. In the same way as against MurD, also proanthocyanidins (PE000174, PE000176, PE000188, and PE000189) and epicatechins (PE000193, PE000194) show a high affinity towards the catalytic site of Mur E of all six analyzed species. Theaflavins (PE000133, PE000134, PE000136, PE000143, PE000149) and proanthocyanidins (PE000157, PE000174, PE000189, PE000198) also show high affinity against MurF enzyme for several of

the bacterial species analyzed (Fig. **3I**). Up to 90 phenolic compounds show high affinity compared to the crystallographic ligand against the catalytic site of the MurG enzyme (Figs. **3J** and **3K**) of *P. aeruginosa*. As compared to other enzymes, proanthocyanidins are remarkable for their affinity to this enzyme in most of the selected species.

As we can see in (Fig. **2**), the enzymes MurC, MurD, MurE, and MurF show an identical pattern of secondary structure; probably this explains why several phenolic compounds show similar affinity to the four enzymes. Similarly, the MurA and MurG enzymes also have high similarity in their secondary structure (Fig. **2B** and **2H**, respectively).

Finally, we analyzed the data of the molecular docking of polyphenols against the catalytic and regulatory site of the glutamate racemase (MurI); an amino acid racemase that has been widely studied as a pharmacological target (Fig. **4**), in whose active center there are two thiol groups. This enzyme shows a different quaternary structure in *H. pylori* (head-head dimer, Fig. **4A**) of the remaining species analyzed in this study, which forms a tail-tail dimer (Fig. **4B**). This enzyme, in addition to catalyzing the conversion of L-Glu to D-Glu, has been shown to be a potent inhibitor of DNA gyrase [146]. Both glutamate analogs [147, 148] and allosteric inhibitors with affinity in the nanomolar range against *H. pylor*i have been designed against this enzyme [149-151]. The ΔG values calculated from molecular docking data of different polyphenols against the catalytic and allosteric sites of the glutamate racemase are shown in (Figs. **4C** and **4D**), and we can observe that many polyphenols show better affinity than the reference inhibitor compounds, especially against the *E. faecium* enzyme (Fig. **4C**). It must be highlighted the high affinity of various catechins (PE000780, PE000786, PE000787, PE000788, and PE000789) against the glutamate racemase of *E. faecium*, *E. faecalis* and *A. baumannii*. Again, certain theaflavins (PE000143, PE000144, PE000149) have a high affinity for the catalytic site of this enzyme. In the case of the *H. pylori* racemase there are also numerous phenolic compounds that show lower ΔG than the experimentally tested inhibitors. Such is the case of the daidzeins (PE000857, PE000859) and the lithospermic (PE001041) and salvianolic acid (PE001044).

5.2. Other Bacterial Protein Targets of Polyphenols

Besides their capability of forming non-covalent multiple hydrogen bonds, hydrophobic interactions and van der Waals attractions with proteins and other molecules, polyphenols can also bind covalently to proteins. The sulfhydryl groups of cysteine and the ε-amino groups of lysine, as well as α-terminal amino groups, appear to combine most readily with quinones derived from polyphenols [152]. Possible targets for polyphenols are cell surface adhesion proteins, membrane-bound enzymes, and cell wall polypeptides [61].

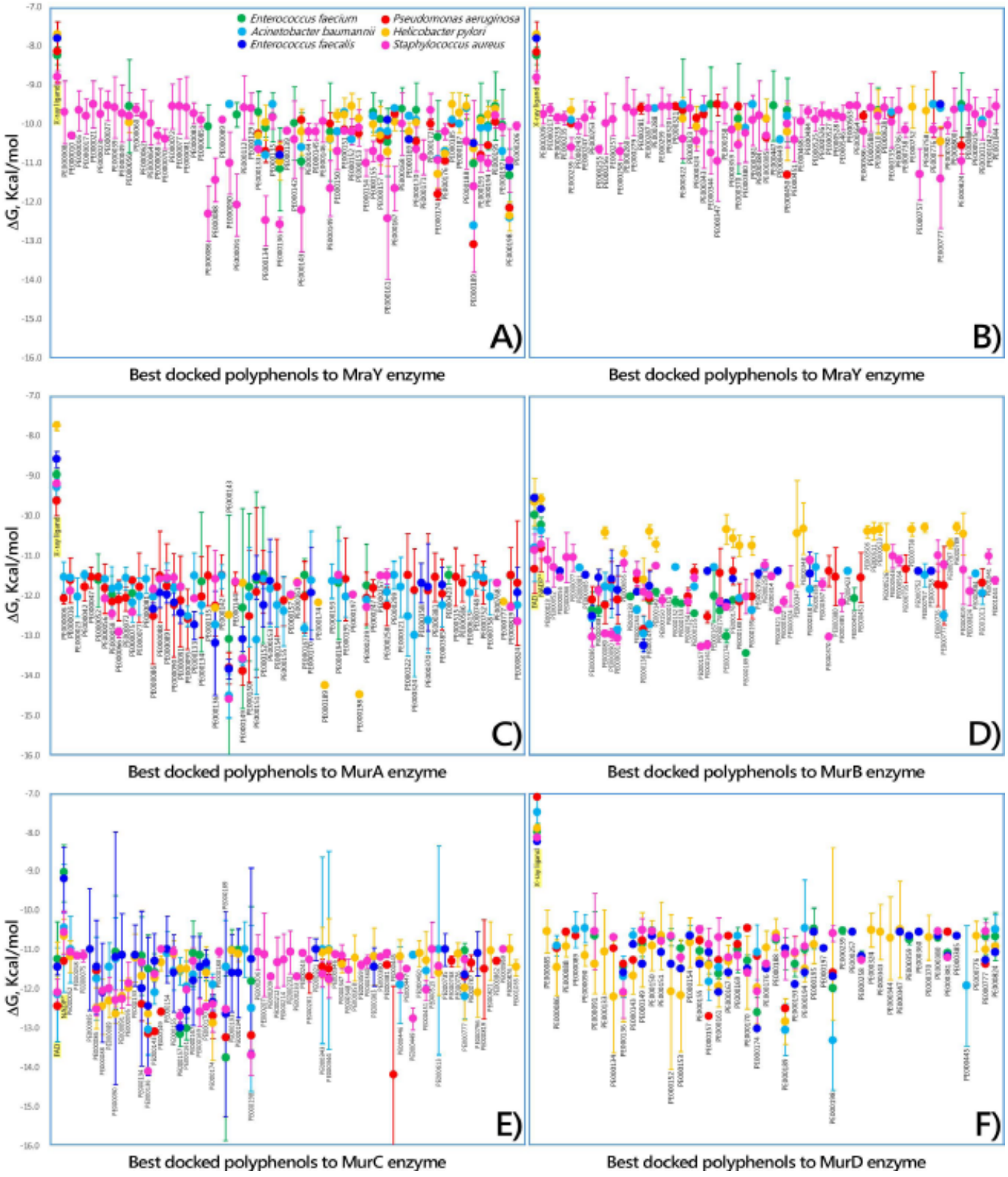
PBPs are critical molecular targets for antibiotics. These proteins are part of the peptidoglycan synthesis machinery, key in the cell wall formation [153]. Changes in these proteins allow bacteria to avoid antibiotic effects, *e.g.*, PBP2a in *S. aureus* that confers resistance to methicillin, penicillin and other penicillin-like antibiotics [154]. Some polyphenols such as flavonoids and tannins have been proposed to form non-specific interaction with PBPs (including PBP2a) eventually leading to MRSA growth inhibition [114].

The lignan 3′-demethoxy-6-O-demethylisoguaiacin from *Larrea tridentate* has been shown to interact with the cellular membrane where this polyphenol represses the activity of some proteins of the ABC transport system of MRSA. As a consequence, the bacteria could not release the phytochemical causing bacteria death [155]. This is proposed as a novel target mechanism for the development of novel antibacterial agents. Other related target protein is the oligopeptide ABC transporter binding lipoprotein (Oppa), a component of the oligopeptide permease that capture peptides ranging in size from 2 to 18 amino acids from the environment and pass them on to the other components of the oligopeptide transport system for internalization [156]. It has been reported that the galloylated catechin EGCG binds Oppa at the bacterial inner wall and inhibits its function in *B. subtilis*. EGCG strongly binds Oppa in its open conformation and prevents it from changing to closed conformation [130].

5.3. Gene Expression Regulation

Certain polyphenols are able to modify gene expression leading to major metabolic changes in resistant bacteria. Although the mechanism of this activity is unknown, it may be presumed that the multiple targets reached by polyphenols may indirectly modulate the activity of transcription factors that result in gene expression regulation. Nevertheless, either direct interaction with DNA or epigenetic regulation by polyphenols through the modulation of the activity of DNA methyltransferases cannot be discarded [157].

The lignan magnolol has shown the ability to significantly reduce the expression of the antibiotic resistance genes *mecA*, *mecI*, *femA* and *femB* in mRNA


Enterococcus faecium
Acinetobacter baumannii
Enterococcus faecalis
Pseudomonas aeruginosa
Helicobacter pylori
Staphylococcus aureus
ΔG, Kcal/mol
A)
B)
Best docked polyphenols to MraY enzyme
Best docked polyphenols to MraY enzyme
C)
D)
Best docked polyphenols to MurA enzyme
Best docked polyphenols to MurB enzyme
E)
F)
Best docked polyphenols to MurC enzyme
Best docked polyphenols to MurD enzyme

(Fig. 3) contd….

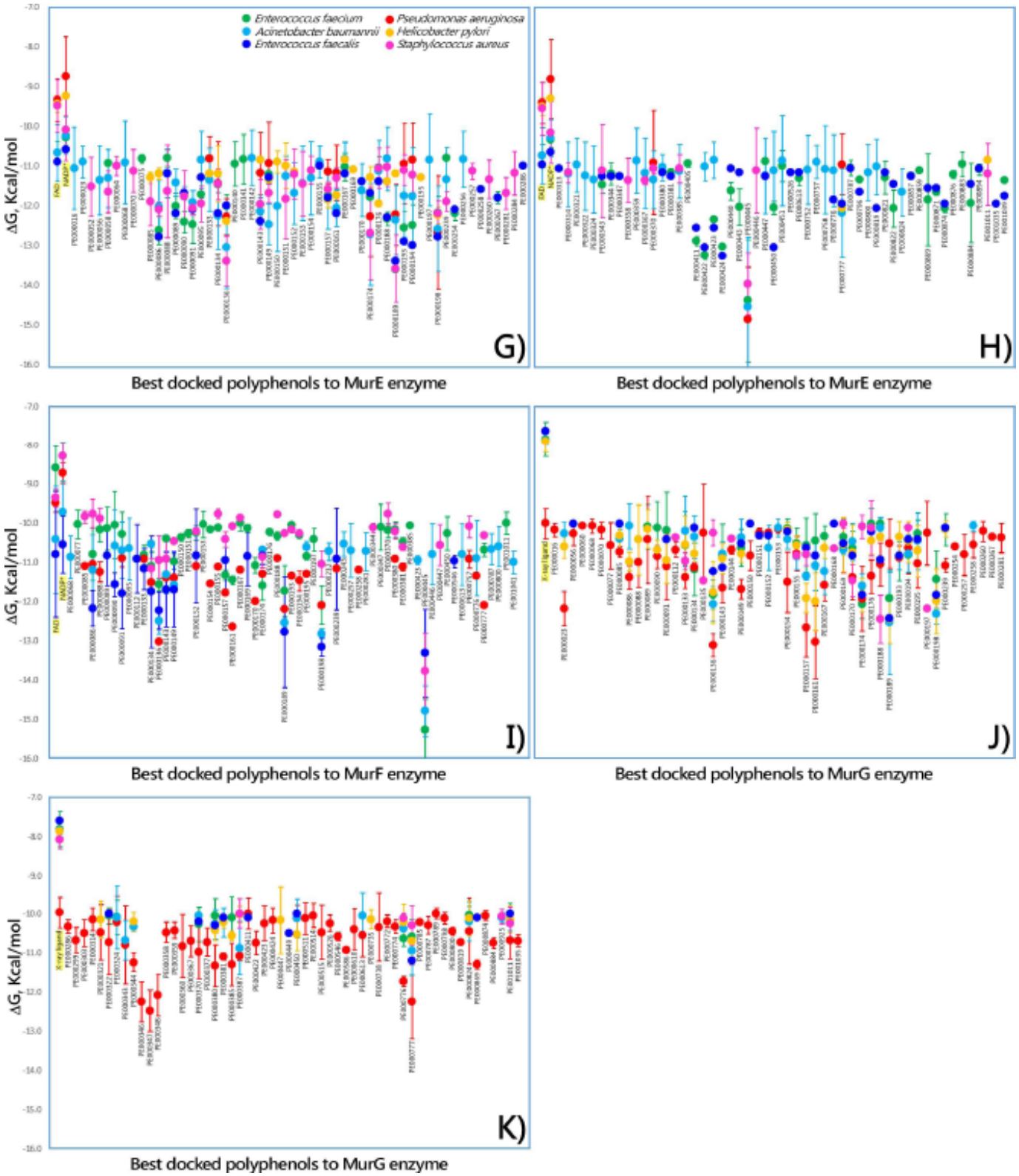


Fig. (3). Comparison of the free energy variation of the selected Phenol-Explorer database 3.6 polyphenols with ΔG less than or equal to the corresponding value for the crystallographic ligands for each bacterial species. In each panel, the enzyme is indicated, below each calculated value the name of each phenolic compound is included with the terminology used by the Phenol-Explorer 3.6 database. The color code is the same in all panels: green, *Enterococcus faecium*; red, *Pseudomonas aeruginosa*; light blue, *Acinetobacter baumannii*; orange, *Helicobacter pylori*; dark blue, *Enterococcus faecalis*, and pink, *Staphylococcus aureus*.

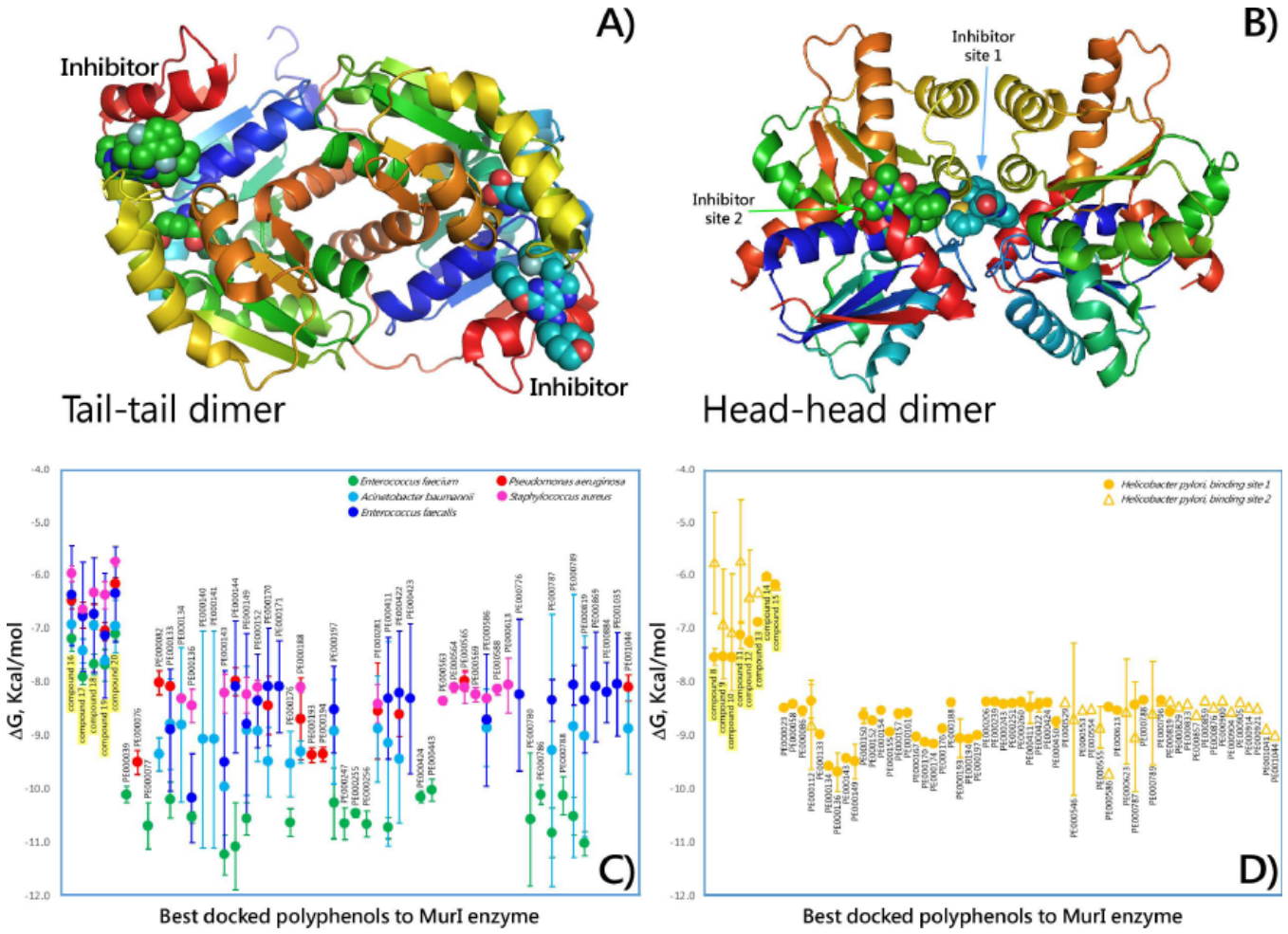


Fig. (4). Quaternary structure of the glutamate racemase with tail-tail dimers for *E. faecalis* (Panel A) and head-head dimers for *H. pylori* (Panel B). Comparison of calculated free energy variation (Panels C and D) of phenolic compounds with some known compounds inhibitors (yellow name).

[111]. Other lignan, 3′-demethoxy-6-O-demethylisoguaiacin have been proven to modulate MRSA (ATCC BAA-44) genetic expression, affecting more than 200 genes. From this pull, it downregulated 6 key genes involved in antibiotic resistance making MRSA unable to pump out antibiotic molecules [155].

Galloyl catechins, especially (-)-epicatechin gallate (ECg), are able to abrogate beta-lactam resistance in MRSA and prevent biofilm formation with profound changes in cell morphology. ECg binds to the bacterial membrane eliciting major alteration in the structure and the thermotropic behavior of the bilayer. All these changes induce the up-regulation of genes responsible for protection against cell wall stress and maintenance of membrane integrity and function and reverse the MRSA resistant phenotype [158]. The antibacterial activity of caffeic acid phenethyl ester (CAPE) against *E. faecalis*, *L. monocytogenes*, and *S. aureus* has been also related to its capacity to target RNA and DNA related molecules [159].

The flavonoid naringenin can bind A-T base pairs regions of the DNA of *S. aureus* (ATCC 6538) via groove mode, provoking changes on its molecular conformation and altering its secondary structure [128]. Certain flavonoids such as quercetin, dihydrorobinetin and epigallocatechin (EGC) inhibited RNA synthesis in *S. aureus* (FDA 209 PJC-1). These activities are explained because of the structure of the flavonoid 3’,4’,5’-trihydroxy B-ring coupled with the 3-OH may interrupt the intercalation or hydrogen bonding with the stacking of nucleic acid bases [160]. This fact was corroborated later in structure-activity relationship studies by the finding that the presence of at least one hydroxyl group in rings A or B in flavonoids at C-3,5,7 was crucial for their antibacterial activity. Compounds without hydroxyl groups in ring B (pinocembrin, chrysin, galangin) or compounds in which the hydroxyl group was replaced with a methoxy group (kaempferide, tamarixetin) turned out to be inactive against MRSA and VRE [161].

Last, it is worth to mention that is possible to enhance the antimicrobial properties of plant extracts using molecular genetics technology. It has been reported that plants overexpressing the γ-tocopherol methyltransferase gene (γ-tmt) showed larger concentrations of polyphenolic compounds (phenolic acids and flavonoids) leading to an increased antimicrobial activity against *B. subtilis* (KCTC 3728) [162].

5.4. Biofilm Formation

Most of the bacteria live as biofilms in their natural habitats, so this feature is crucial for their survival. Furthermore, most of the staphylococcal diseases are related to biofilm formation. In this regard, many polyphenols have demonstrated to have anti-biofilm properties against *S. aureus* [163], even when biofilms can be much more resistant to antimicrobial than planktonic cells [164].

Biofilm producing Gram-positive bacteria usually cause urinary-tract infections (UTIs) in people with high-risk factors, such as elderly or pregnant. Even if some UTIs are polymicrobial, the main bacteria isolated in these cases are *Staphylococcus saprophyticus*, *E. faecalis*, and *Streptococcus agalactiae* [165]**.** To treat UTIs is essential that the antimicrobial agents penetrate biofilms and cellular membranes to act into the infecting cells. For these reasons, polyphenols and plant extracts with antimicrobial and antibiofilm capacity can be effective tools for improving medical treatments against UTIs.

Recent studies point out that many polyphenols can inhibit the formation of streptococcal biofilms. This capacity is important for preventing human pharyngitis, which is caused by well-organized attached bacterial biofilms. After the polyphenol application, the target *Streptococcus pyogenes* bacteria appeared less aggregated and showed morphological changes when observed by scanning electron microscope. The generation of reactive oxygen species (ROS) by polyphenols has been proposed as the underlying mechanism that affects cell wall integrity, adhesion molecules and quorum sensitivity [166].

The choice of delivery system is essential for the polyphenols in order to exert their antibacterial and anti-biofilm activity. For example, curcumin is known to have high antibacterial and anti-quorum sensing activity, but its use is very limited because of its poor aqueous solubility and quick degradation. To overcome these problems, researchers have created curcumin quantum dots using acetone as a solvent, which are hundreds of times smaller than regular curcumin particles. Consequently, they significantly improved its durability and efficacy. These particles show better penetration and interaction with cells and biofilm matrix, resulting in increased uptake by the bacteria [167].

5.5. Bacterial Metabolites, Proton and Ion Equilibrium

Polyphenols can also exert their antibacterial activity by modulating the level of some essential metabolites or by impairing ionic strength equilibrium or proton gradient leading to cell death. Nevertheless, most of these effects may derive from the capability of polyphenols to interact with phospholipid membranes or directly with the receptors and ion pumps on the cell membrane. For example, the inhibitory effect of the gallotannins on bacterial growth is in part associated with its role as iron chelators with high affinity, besides their capacity to inactivate membrane proteins of bacterial cells [52].

A synergistic effect in a combination of oregano and cranberry extracts has been proposed against *Helicobacter pylori*, exerting a stronger antibacterial capacity compared to the isolated extracts. The authors postulate that, in a first stage, some polyphenols of the combination damage cell membrane or affect ion pumps, making cells more sensitive to other compounds [168]. As a consequence, hyperacidification takes place at the bacterial plasma membrane interface and cytosol, due to proton donation of acidic polyphenols and cell membrane disruption, inhibiting ATP synthesis. Moreover, it is stated that soluble polyphenols can also quench free electrons from the electron transport chain at the bacterial membrane. All these effects could reduce cytochrome activity and thus the oxidative phosphorylation, inhibiting bacterial growth. Some evidences point out that these effects may be mediated through the modulation of proline dehydrogenase by polyphenols at the plasma membrane. Polyphenolic moieties may mimic proline structure and can cause enzyme inhibition, which can be reverted by proline. This mechanism is proposed for the antibacterial activity against *S. aureus* of small soluble polyphenols such as gallic or caffeic acid [106, 169].

Researchers have found that oolong tea extract (semifermented tea leaves of *Camellia sinensis*) and isolated polymeric catechins have an inhibitory action on the insoluble glucan synthesis from sucrose by the glucosyltransferases (GTFs) of *Streptococcus mutans* (MT8148R) and *Streptococcus sobrinus* (6715). This activity leads to inhibition of sucrose-dependent cell adherence of these bacteria, avoiding caries formation

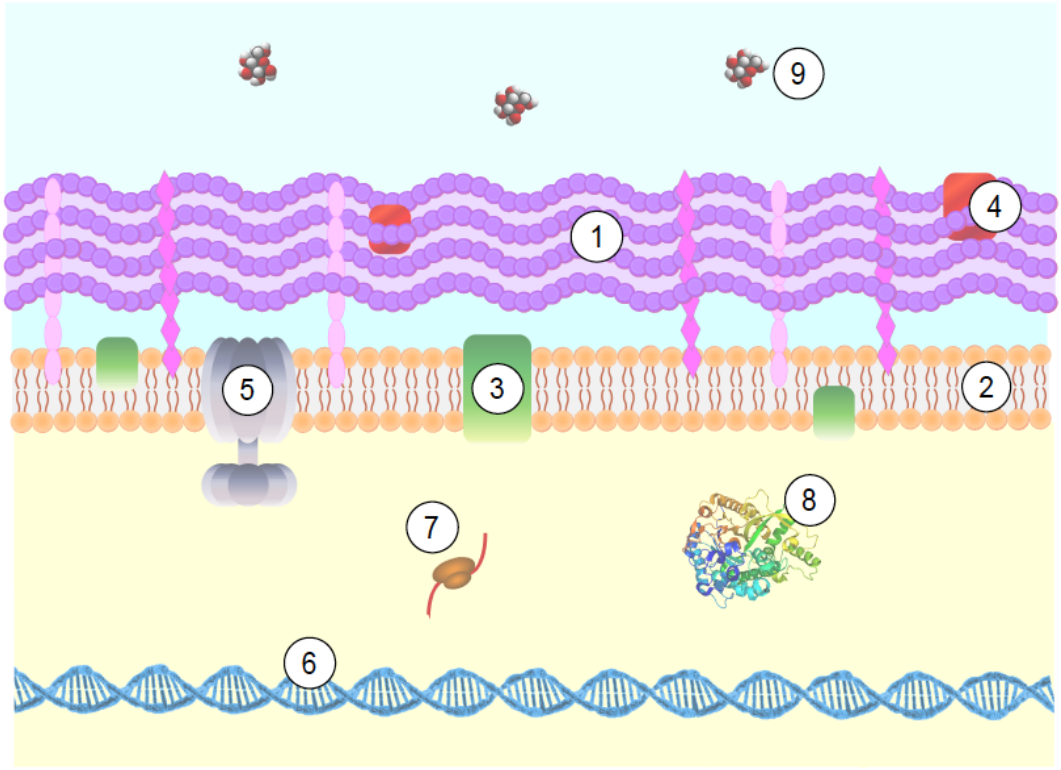


Fig. (5). Scheme of a bacteria and the putative molecular target of polyphenols. 1: Cell wall, 2: Cell membrane, 3: Membrane proteins, 4: Cell wall proteins, 5: ATPase, 6: DNA, 7: RNA related molecules, 8: Cytoplasmic proteins, 9: Soluble nutrients and ions.

in animal models [170]. Some polyphenols from cranberry have also shown GTFs inhibitory capacity against *S. mutans* (UA159), such as quercetin-3-arabinofuranoside, myricetin, and procyanidin A2. Furthermore, these polyphenols reduced biofilm formation and surface adsorption by inhibiting F-ATPases and acid production [171, 172]. Catechins have also demonstrated to neutralize staphylococcal enterotoxin B (SEB), a superantigen that aggravates atopic dermatitis [173].

Other flavonoids such as rutin, naringenin, quercetin and sophoraflavanone G can affect the fluidity of both internal and external bacterial membranes. This activity results in a membrane potential nullification decreased ATP production and cell motility [162, 174, 175]. Polymeric tannins are also capable of making complexes with certain nutrients and minerals rendering them unavailable for bacteria to intake, and affecting their metabolism [176].

5.6. Resistance to Natural Antimicrobials

To date, literature about bacteria acquiring resistance to botanicals is limited. One example is a study that relates genetic changes (deletion of *sigB* gene) in *L. monocytogenes* with enhanced resistance to carvacrol [177]. It may be possible for bacteria to develop resistance against specific polyphenols with a specific molecular target involved. However, it seems less likely to develop resistance when complex mixtures of polyphenols that affect several molecular targets at the bacterial cell are utilized [178, 179]. Since plant extracts are a complex mixture of numerous phytoactive components, development of bacterial resistance to such synergistic combinations may be much slower than those for single chemical compounds.

A “tannin-resistant” Gram-positive bacteria (*Streptococcus sp.*) has been identified in places with high exposure to this kind of polyphenols, such as goat, sheep and deer rumens [180]. This kind of bacteria is supposed to protect ruminants from anti-nutritional effects. The proposed mechanisms by which bacteria can overcome growth inhibition by tannins include modification of the substrate, dissociation of tannin–substrate complexes, extracellular polysaccharide formation, cell membrane modifications and metal ion chelation [181]. It is worth to highlight that bacteria, which are pre-

dominant in tannin-rich mediums of the gastrointestinal tract of ruminants, may not be resistant *per se*. Likely, this resistance may be more related to higher nutrient accessibility of the bacteria in the particular microenvironment of the ruminant stomach [176].

CONCLUDING REMARKS AND PERSPECTIVES

Resistance to antibiotics has now become a public health problem worldwide. Drug-resistant infections kill around 700,000 people worldwide each year, and this figure could increase to several million by 2050, according to experts. If at the individual level it causes loss of human lives, at a collective level it can lead to the collapse of public health systems, since it involves high-cost therapies (if they exist) due to the more extended hospitalization of the patients compared to treatments of non-resistant strains. Poor sanitary conditions together with deficient diet in developing countries and the indiscriminate and inappropriate use of beta-lactam antibiotics (both for human and veterinary use) in the developed countries make it possible to understand the emergence of resistance phenomena to antimicrobial drugs.

Although research is continuously increasing our knowledge and adding new therapeutic alternatives, no new effective antibiotics against resistant strains have been developed in nearly 30 years. Only five of top fifty pharmaceutical companies are developing new antibiotics, and only a few projects for drug discovery are based on antibiotics development among more than five hundred. In this context of peremptory need of new treatments and therapeutic solutions, natural compounds have been underestimated since pharma companies are mostly focused on more profitable synthetic compounds. Evolution has selected these natural compounds along millennials providing them with molecular promiscuity and polypharmacological properties.

Among plant compounds, polyphenols are probably the most important family of natural compounds, both in number and relevance. Throughout this review, we have highlighted a number of polyphenolic compounds (phenolic acids, flavonoids, tannins, lignans, stilbenes and combinations of these in botanical mixtures) that have exhibited significant antibacterial activity against resistant and non-resistant Gram-positive bacteria at low microg/mL range MIC values. Interestingly, the synergic interaction of some of these polyphenols with selected antibiotics that allows diminishing resistance to the antibiotic deserves further research.

The mechanism of action of the antibacterial capacity of polyphenols is quite diverse in agreement to their multitargeted character. Bacterial membrane and cell wall seem to be one of the main targets of polyphenols. Some polyphenols have exhibited the capacity to interact or even integrate into the phospholipid bilayer causing membrane disruption or lipid phase separation affecting the activity of several protein receptors and channels and cell wall assembly machinery. Alternatively, some of these small molecules can interact directly with proton or ion pumps causing the impairment of membrane-related processes such as proton gradient, ATP synthesis or oxidative phosphorylation leading to bacteria cell death. Alternatively, polyphenols may interact with bacteria nucleic acids either directly or through epigenetic regulation leading to compromised bacteria cell viability. Some polyphenols have also exhibited the capacity to affect cell wall integrity and/or adhesion molecules that are essential for microbial surface colonization and biofilm formation.

Other putative molecular targets for polyphenols may be those proteins involved in the peptidoglycan biosynthesis such as PBP, Mra or Mur protein families. To this respect, the results of virtual screening techniques for the docking of the 931 compounds of the Phenol-Explorer 3.6 database against nine enzymes for six selected bacterial species are fully available. Among all the compounds tested, some theaflavins, proanthocyanidins, and catechins showed promising results that may deserve further attention. This is just an example of the power of *in silico* drug screening, as a complementary technique, to accelerate the discovery of novel antibiotics.

To date, just a few *in vivo* experiments using polyphenols as antibiotics have been clinically relevant, thus much work needs to be done. One of the major tasks will be to find the right polyphenolic combinations or combinations polyphenol-antibiotic that enable to reduce resistance in resistant strains. For that purpose, a pharmacological approach will be required in order to look for synergistic therapeutic effects.

Bioavailability, administration route, delivery and galenic formulation are still significant issues. Due to the metabolism of polyphenols both in the gastrointestinal tract and in the liver, polyphenolic antibacterial therapy would be preferably indicated for skin, digestive tract and lung infections. Anyway, based on the existing evidence, plant polyphenols suppose a promising source of antibacterial agents, either alone or in combination with existing antibiotics, for the development of new antibiotic therapies.

LIST OF ABBREVIATIONS

μg/mL	=	Micrograms per milliliter
ABC	=	ATP-binding cassette
ATCC	=	American Type Culture Collection
ATP	=	Adenosine triphosphate
B. cereus	=	*Bacillus cereus*
B. subtilis	=	*Bacillus subtilis*
C. albidus	=	*Cistus albidus*
C. clusii	=	*Cistus clusii*
C. ladanifer	=	*Cistus ladanifer*
C. salviifolius	=	*Cistus salviifolius*
CECT	=	Colección Española de Cultivos Tipo
CFU	=	Colony-forming unit
DNA	=	Deoxyribonucleic acid
E. faecalis	=	*Enterococcus faecalis*
E. faecium	=	*Enterococcus faecium*
EGC	=	Epigallocatechin
EGCG	=	Epigallocatechin gallate
FICI	=	Fractional Inhibitory Concentration Index
GTFs	=	Glucosyltransferases
KCCM	=	Korean Culture Center of Microorganisms
KCTC	=	Korean Collection for Type Cultures
L. monocytogenes	=	*Listeria monocytogenes*
LPS	=	Lipopolysaccharide
MDR	=	Multi-drug resistance
MIC	=	Minimum inhibitory concentration
MRSA	=	Methicillin-resistant *Staphylococcus aureus*
MSSA	=	Methicillin-sensitive *Staphylococcus aureus*
MTTC	=	Microbial Type Culture Collection
NCTC	=	National Collection of Type Cultures
PBP	=	Penicillin-binding protein
PTS	=	Phosphotransferase system
RNA	=	Ribonucleic acid
ROS	=	Reactive oxygen species
S. aureus	=	*Staphylococcus aureus*
VRE	=	Vancomycin-resistant *Enterococcus*

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL.

Functional and structural information of selected enzymes involved in the peptidoglycan biosynthesis (Phase I and II) of the cell wall of some medically relevant bacteria available at http://dockingfiles.umh.es/bcwall/.

The Gibbs free energy variation values of the 931 compounds stored in the Phenol-Explorer 3.6 database docked to the nine enzymes analyzed for the six selected bacterial species are available at http://dockingfiles.umh.es/bcwall/phenol/.

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