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Phytochemicals for human disease: An update on plant-derived compounds antibacterial activity

Ramona Barbieri[a], Erika Coppo[a], Anna Marchese[b,**], Maria Daglia[c], Eduardo Sobarzo-Sánchez[d,e], Seyed Fazel Nabavi[f], Seyed Mohammad Nabavi[f,*]

[a] Sezione di Microbiologia DISC University of Genoa, Italy
[b] Sezione di Microbiologia DISC-IRCCS San Martino-IST University of Genoa, Italy
[c] Department of Drug Sciences, Medicinal Chemistry and Pharmaceutical Technology Section, University of Pavia, Italy
[d] Laboratory of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Santiago de Compostela, 15782, Spain
[e] Dirección de Investigación, Universidad Central de Chile, Santiago, Chile
[f] Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran

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ABSTRACT

In recent years, many studies have shown that phytochemicals exert their antibacterial activity through different mechanisms of action, such as damage to the bacterial membrane and suppression of virulence factors, including inhibition of the activity of enzymes and toxins, and bacterial biofilm formation. In this review, we summarise data from the available literature regarding the antibacterial effects of the main phytochemicals belonging to different chemical classes, alkaloids, sulfur-containing phytochemicals, terpenoids, and polyphenols. Some phytochemicals, besides having direct antimicrobial activity, showed an *in vitro* synergistic effect when tested in combination with conventional antibiotics, modifying antibiotic resistance. Review of the literature showed that phytochemicals represent a possible source of effective, cheap and safe antimicrobial agents, though much work must still be carried out, especially in *in vivo* conditions to ensure the selection of effective antimicrobial substances with low side and adverse effects.

Contents

Abbreviations: MDR, multi-drug resistant; MIC, minimum inhibitory concentration; MRSA, methicillin resistant *Staphylococcus aureus*; MBC, minimum bactericidal concentration; MRSE, methicillin resistant *Staphylococcus epidermidis*; MSSE, methicillin susceptible *Staphylococcus epidermidis*; MSSA, methicillin susceptible *Staphylococcus aureus*; QS, quorum-sensing; IZ, inhibition zone; FIC, fractional inhibitory concentration; EC, epicatechin; EGC, epigallocatechin; ECG, epicatechin gallate; EGCG, epigallocatechin gallate; NDM-1, New Delhi metallo-beta-lactamase-1; ATP, adenosine triphosphate; VRE, vancomycin-resistant *Enterococcus faecalis*; PACs, proanthocyanidins; PPC, purple prairie clover.

* Corresponding author at: Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran, P.O. Box 19395-5487, Iran.
** Corresponding author.
E-mail addresses: anna.marchese@unige.it (A. Marchese), Nabavi208@gmail.com (S.M. Nabavi).

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1. Introduction

Since earliest times, many plants have been known to exert healing properties against human infections due to their content of secondary metabolites, which in more recent times have been found to act as antimicrobial agents against human pathogens. Over the past decade, much attention has been placed on the study of phytochemicals for their antibacterial activity, especially against multidrug-resistant Gram-negative and Gram-positive bacteria (Borges et al., 2015b).

Antibacterial resistance is defined as the resistance of bacteria to treatment with antibiotic drugs that was originally found to be effective for the treatment of infection caused by that microorganism. This means that antibiotics become ineffective against resistant bacteria allowing infections to persist in patients, putting them at increased risk of worse clinical outcomes and death. In fact, on average, the mortality rate for patients with infections caused by non-resistant bacteria is less than half of that of people with a resistant form of the same infection. Antibiotic resistance is present worldwide and new resistance mechanisms are continuing to emerge, strongly increasing the risk of spread of resistant strains. Thus, antibiotic resistance represents a threat to global public health and represents an important economic issue, due to the higher health care costs of necessary therapies and the increased duration of illness, treatment, and potential hospitalisation when compared with non-resistant, common infections. It has been scientifically proven that the indiscriminate and inappropriate use of antibiotics has accelerated the emergence of drug-resistant strains. In addition, poor sanitary conditions and inadequate food-handling encourage the further spread of antimicrobial resistance. Considering that antibacterial resistance is a multifactorial problem, driven by many interconnected factors, the World Health Organization suggests a series of concerted and coordinated actions. These actions range from the prevention of infection transmission, especially in hospitals and clinics, to promotion of research and development of new treatments for infection (http://www.who.int/mediacentre/factsheets/fs194/en/ Updated April 2015). Nevertheless, the discovery of new antibiotics is very expensive and time consuming, requiring about ten years to bring a new antibiotic to market. Therefore the search for antibacterial substances derived from natural products, such as phytochemicals, has gained increasing importance alongside the discovery of new synthetic chemical compounds with antibiotic and bacteriophage properties (Mandal et al., 2014).

In the last three decades, thousands of phytochemicals with different mechanisms of action have been listed as antibacterial compounds, thanks to a number of studies on their activity performed worldwide, especially in Latin America. For instance, in the early 1990s in Argentina, Anesini and Perez (1993) tested 132 plant species with known uses as therapeutic treatments, against penicillin G resistant strains of *Staphylococcus aureus*, *Escherichia coli* and *Aspergillus niger*, using cephazolin, ampicillin, and miconazole as standard antibiotics with the agar-well diffusion method. They found that boiling water extracts of *Tabebuia impetiginosa* bark, Achyrocline sp. aerial parts, *Larrea divaricata* leaves, *Rosa borboniana* flowers, *Punica granatum* fruit pericarp, *Psidium guineense* fruit pericarp, *Lithrea ternifolia* leaves and *Allium sativum* bulbs produce very active extracts.

Since then, hundreds of research articles have been published on this subject (Cruz et al., 1996; Daglia, 2012; Erdem et al., 2015; Hannan et al., 2008; Izzo et al., 1995; Mahmoud et al., 2016; Nabavi et al., 2015a,b; Pawar and Pal, 2002).

In addition, since phytochemicals cannot be used in monotherapy due to their higher minimum inhibitory concentrations (MIC) (100–5000 μg/ml) when compared with antibiotics (0.031–512 μg/ml), in the past few years the effects of combinations of antibiotics and phytochemicals have been studied. The results of these investigations show that phytochemicals modulate or modify resistance mechanisms in bacteria, suggesting that phytochemicals can be used in combination with antibiotics to increase the activity and decrease the doses of antibiotics (Santiago et al., 2015; Touani et al., 2014).

In view of the potential of phytochemicals in providing effective antimicrobial drugs in the near future, the present paper is aimed at critically reviewing the scientific reports that demonstrate the *in vitro* antibacterial effects of different types of phytochemicals belonging to different chemical classes: alkaloids, sulfur-containing phytochemicals, terpenoids, and polyphenols. In addition, we discuss their chemical structure, traditional uses and sources.

2. Phytochemicals

Phytochemicals are a large group of chemical compounds naturally occurring in plants, conferring color, flavor, aroma and texture. These compounds have been developed over thousands of years of evolution to defend organisms from the effects of free radicals, viruses, bacteria and fungi. They are widely distributed in fruits, vegetables, legumes, whole grains, nuts, seeds, fungi, herbs and spices and in plant-based beverages such as wine and tea. Phytochemicals can be classified into several major groups based on their chemical structure: alkaloids, sulfur-containing phytochemicals, terpenoids and polyphenols.

2.1. Alkaloids

Alkaloids are organic nitrogenous bases. Their chemical structures are extremely variable. In 1819 the German chemist W. Meissner introduced the concept of alkaloids to indicate natural compounds which react as bases. These molecules have diverse and important physiological effects on humans and other animals. In the nineteenth century morphine was the first isolated alkaloid, derived from opium (Lesch, 1981), subsequently, two French researchers (P.J. Pelletier and J.B. Caventou) isolated other alkaloids including strychnine (1817), emetine (1817), brucine (1819), piperine (1819), caffeine (1819), quinine (1820), colchicine (1820) and coniine (1826). The latter compound was the first alkaloid to have its structure established (Schiff, 1870) and to be synthesized (Ladenburg, 1889). Alkaloids are produced by a large variety of organisms such as plants, bacteria, fungi and animals and have been used in medicine since ancient times. They have many effects including antimalarial (quinine), antiasthma (ephedrine), vasodilatator (vincamine), anti-hypertensive (reserpine), anti-tumor (vinblastine and vincristine) and anti-arrhythmic (quinidine) effects. Also alkaloids possess psychotropic and stimulant activities (cocaine, caffeine and nicotine) and can exert an analgesic effect, such as in morphine. Last, but not least, are the antibacterial and anti-virulence effects of alkaloids (Table 1). Regarding the antibacterial activity of alkaloids, many studies through the years have shown that many of these compounds could play a role in the treatment of many infectious diseases. An alkaloid which exhibits antibacterial activity is sanguinarine. It has long been known that sanguinarine, a benzophenanthridine alkaloid derived from the rhizomes of *Sanguinaria canadensis*, has broad antimicrobial activity and anti-inflammatory properties. In fact, *in vitro* studies have shown that sanguinarine is able to inhibit bacterial adherence to the surface of teeth, exerting an anti-plaque action (Godowski, 1988; Hannah et al., 1989). This alkaloid exerts its antibacterial activity by perturbing bacterial FtsZ Z-ring formation and inhibiting bacterial cytokinesis (Beuria et al., 2005; Kelley et al., 2012). The Authors of two recent studies

Table 1
List of alkaloids active against Gram-negative and Gram-positive bacteria.

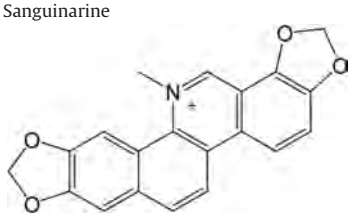
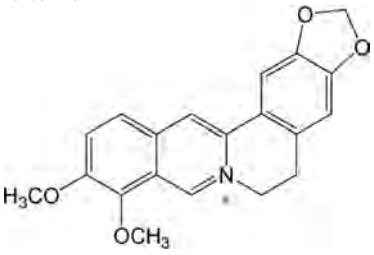
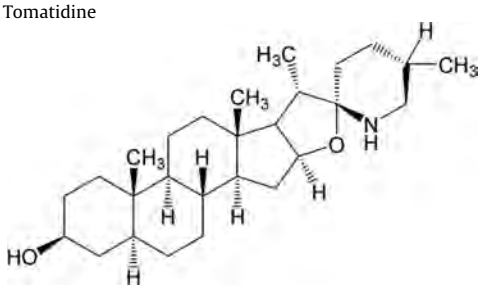
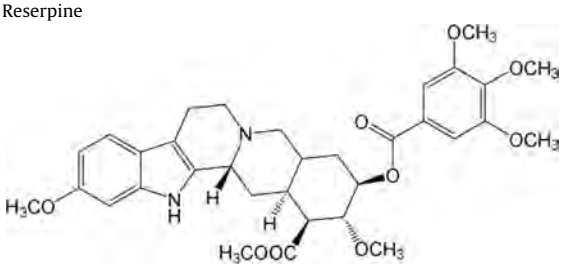
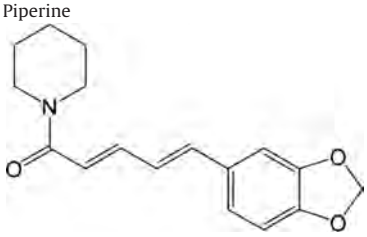
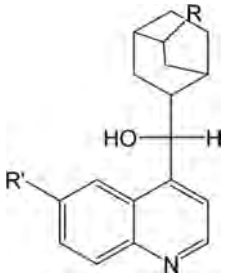
Compound	Bacteria	Ref.
Sanguinarine 	gram-positive and gram-negative bacteria	(Godowski, 1988; Hannah et al., 1989)
	Escherichia coli and *Bacillus subtilis*	(Beuria et al., 2005)
	Staphylococcus aureus and *Enterococcus faecalis* (MRSA and VRE)	(Kelley et al., 2012)
	gram-positive and gram-negative bacteria	(Hamoud et al., 2014)
	gram-positive and gram-negative bacteria	(Hamoud et al., 2015)
Berberine 	*S. sanguinis*	(Dziedzic et al., 2015)
	A. pleuropneumoniae	(Xie et al., 2012)
	S. epidermidis	(Kang et al., 2015; Wang et al., 2009)
	K. pneumoniae	(Magesh et al., 2013)
	S. typhimurium	(Liu et al., 2015)
	L. monocytogenes	
Tomatidine 	*S. aureus*	(Mitchell et al., 2011)
		(Mitchell et al., 2012)
		(Chagnon et al., 2014)
		(Boulanger et al., 2015)
Reserpine 	*K. pneumoniae*	(Magesh et al., 2013)
	E. coli	(Dusane et al., 2014)

Table 1 (*Continued*)

Compound	Bacteria	Ref.
Piperine 	*E. coli*	(Dusane et al., 2014)
Cinchona alkaloids (and synthetic derivatives) 	*S. aureus* (strain ATCC 25923)	(Skogman et al., 2012)

(Hamoud et al., 2014, 2015) tested a combination of sanguinarine, EDTA and vancomycin and a combination of sanguinarine, EDTA and streptomycin against gram-positive and gram-negative bacteria, including Multi-Drug Resistant (MDR) bacteria. The results of these studies showed that sanguinarine has strong activity against all the strains tested (Minimum Inhibitory Concentration (MIC): 0.5–128 μg/ml); additive and synergistic effects were recorded for all sanguinarine + EDTA and sanguinarine + EDTA + vancomycin associations against gram-negative bacteria. The combination of sanguinarine + EDTA + streptomycin also showed synergistic activity against almost all the strains with the exception of Methicillin Resistant *Staphylococcus aureus* (MRSA). Berberine, an isoquinoline-type alkaloid, contributes to oral health benefits. Several studies have demonstrated the efficacy of berberine against oral streptococcal growth and selected endodontic pathogens using a multispecies biofilm tooth model (Dziedzic et al., 2015; Xie et al., 2012). The most remarkable antibacterial effect was observed against *Streptococcus sanguinis* (MIC: 512 μg/ml) and the most significant synergistic effect was found in combination with penicillin, clindamycin and erythromycin (Dziedzic et al., 2015). Moreover Xie et al. (2012), demonstrated that berberine is more effective than saline as an endodontic irrigant against selected endodontic pathogens *in vitro* and, when combined with chlorhexidine 1%, is comparable with NaOCl in its bactericidal efficacy. In 2015 Kang et al. (2015), showed that berberine has an inhibitory effect on the growth of *Actinobacillus pleuropneumoniae* with a MIC value of 0.3125 mg/ml. Several studies (Boulanger et al., 2015; Chagnon et al., 2014; Mitchell et al., 2011, 2012) examined tomatidine, a steroid alkaloid isolated from tomato plants, as an alternative virulence attenuator compound for *S. aureus* and for *S. aureus* small-colony variant phenotypes, a phenomenon that may be involved in the establishment of chronic infections. The results of these studies underline that tomatidine possesses anti-virulence activity against typical *S. aureus* strains and in addition operates in synergy with aminoglycoside antibiotics. Moreover, Boulanger et al. (2015) investigated the antibacterial activity of tomatidine against *S. aureus* growth in the presence of *Pseudomonas aeruginosa*. These two pathogens frequently co-exist in cystic fibrosis diseases and the effects of these co-infections are already known (Hubert et al., 2013). Tomatidine shows a strong bactericidal effect against *S. aureus* when grown in presence of *P. aeruginosa*. Moreover, several alkaloids inhibit the formation of bacterial biofilms. 6-gingerol, a pungent oil of fresh ginger, reduces biofilm formation in *P. aeruginosa*, repressing the production of virulence factors such as elastase, pyocyanin and rhamnolipid (Kim et al., 2015).

A study conducted by Wang et al. (2009), in 2009 examined the effect of berberine on *S. epidermidis* adhesion and biofilm formation on disks of titanium alloy. The results of this study showed that berberine was able to inhibit adhesion of *S. epidermidis* onto the titanium surface, inhibiting biofilm formation. Berberine at a concentration of 63.5 μg/ml was also able to decrease biofilm growth in many *Klebsiella pneumoniae* clinical isolates (Magesh et al., 2013). In the same study reserpine, an alkaloid isolated from *Rauwolfia* spp., showed inhibitory activity against *K. pneumoniae* biofilms and a MIC value of 15.6 μg/ml. The effect of reserpine and piperine from *Piper nigrum* or black pepper was investigated against *Escherichia coli* responsible for urinary tract infections in humans by Dusane et al. (2014) Sub-inhibitory concentrations (0.5–10 μg/ml) of both compounds decreased bacterial swarming and swimming motilities and increased biofilm formation. In addition, piperine increased penetration of the antibiotics azithromycin and ciprofloxacin into *E. coli* biofilms, and promoted the effect of these antibiotics in dispersing biofilms.

More recently Skongman and colleagues (Skogman et al., 2012) evaluated the activity of cinchona alkaloids (naturally occurring compounds such as cinchonidine and cinchonine and synthetic derivatives) against biofilm producing *S. aureus* (strain ATCC 25923). Cinchonidine was found to be ineffective, whereas a synthetic derivative was effective in preventing biofilm formation of planktonic bacteria. High concentrations were needed to eradicate mature biofilms.

2.2. Sulfur-containing phytochemicals

Organosulfur compounds such as allicin, ajoene and isothiocyanates have shown antibacterial activity against both gram-positive and gram-negative bacteria (Table 2). Isothiocyanates are plant secondary metabolites known as glucosinolates, found in the *Brassicaceae* family such as broccoli, cauliflowers, and cabbage. The glucosinolates are present in plants with an enzyme (myrosinase) which hydrolyzes the glucosinolates into active compounds such as isothiocyanates after tissue disruption. The antibacterial activ-

Table 2
List of sulfur-containing phytochemicals active against Gram-negative and Gram-positive bacteria.

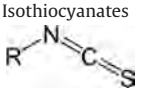
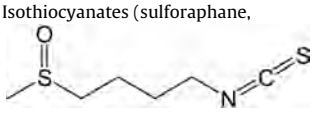
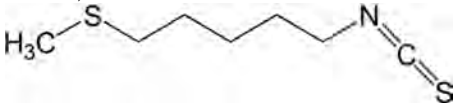
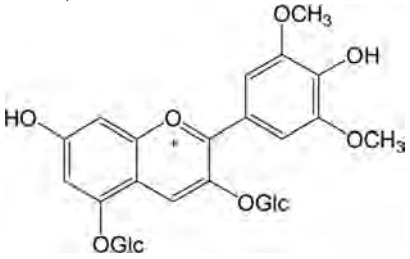
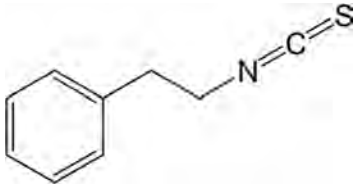
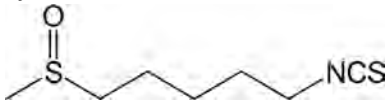
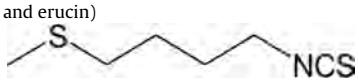
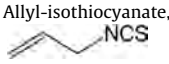
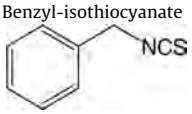
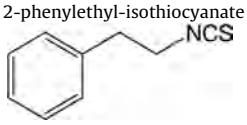
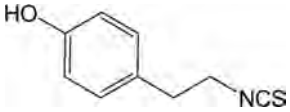
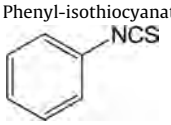
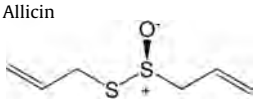
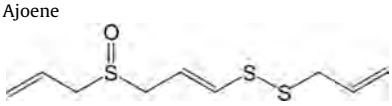
Compound	Bacteria	Ref.
Isothiocyanates 	*S. mutans* *S. sobrinus* *L. casei* *S. aureus* *E. faecalis* *A. actinomycetemcomitans F. nucleatum* *P. nigrescens* *C. perfrigens* *C. albicans* *E. coli* *E. faecalis* *L. monocytogenes* *S. aureus*	(Dias et al., 2012; Park et al., 2013)
Isothiocyanates (sulforaphane, 	*H. pylori*	(Fahey et al., 2013; Moon et al., 2010)
berteroin, 		
hirsutin, 		
phenethyl-isothiocyanate, 		
Alyssin 		
and erucin) 		
Allyl-isothiocyanate, 	MRSA *C. jejuni* *E. coli* O157:H7 *E. coli,* *P. aeruginosa,* *S. aureus* *L. monocytogenes* *S. pyogenes*	(Baysse, 2012; Cordeiro et al., 2014; Dias et al., 2012; Palaniappan and Holley, 2010; Saavedra et al., 2010)
Benzyl-isothiocyanate 	MRSA *E. casseliflavus* *S. aureus* *C. jejuni*	(Baysse, 2012; Dias et al., 2012; Galuppo et al., 2013)
2-phenylethyl-isothiocyanate 	MRSA *E. coli,* *P. aeruginosa,* *S. aureus* *L. monocytogenes*	(Dias et al., 2012; Saavedra et al., 2010)

Table 2 (*Continued*)

Compound	Bacteria	Ref.
2-(4-hydroxyphenyl) ethyl-isothiocyanate 	*E. coli* *S. aureus*	(Tajima et al., 2001)
Phenyl-isothiocyanate 	*E. coli* *S. aureus*	(Abreu et al., 2013)
Allicin 	*H. pylori*	(Aydin et al., 2000; Cañizares et al., 2004; Jonkers et al., 1999; Kockar et al., 2000)
	S. epidermidis	(Pérez-Giraldo et al., 2003)
	P. aeruginosa	(Cai et al., 2008; Ta et al., 2014)
	S. epidermidis	(Zhai et al., 2014)
	S. agalactiae	(Cutler et al., 2009)
	B. cepacia	(Wallock-Richards et al., 2014)
	S. aureus	(Cutler and Wilson, 2004; Leng et al., 2011; Pérez-Köhler et al., 2015a,b)
	Fungi	(An et al., 2009; Kim et al., 2012; Ogita et al., 2006)
Ajoene 	*P. aeruginosa*	(Jakobsen et al., 2012)

ity of these compounds has been reported since 1995 (Brabban and Edwards, 1995). Several studies have shown that isothiocyanates possess antibacterial activity against a large number of pathogenic bacteria. Park et al. (2013) examined the antimicrobial activity of isothiacyanates extracted from horseradish root against oral microorganisms (*S. mutans*, *S. sobrinus*, *Lactobacillus casei*, *S. aureus*, *Enterococcus faecalis*, *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum*, *Prevotella nigrescens*, *Clostridium perfrigens* and *Candida albicans*). The isothiocyanates showed the strongest antimicrobial activity against *C. albicans* (MIC: 0.52 mg/ml; Minimum Bactericidal Concentration (MBC): 1.25 mg/ml). Among facultative anaerobic oral bacteria, *L. casei* was the most inhibited by isothiocyanates (MIC: 0.84 mg/ml and MBC: 1.67 mg/ml). The MICs of isothiocyanates extracted from horseradish root ranged from 1.67 to 6.67 mg/ml, while the MBCs ranged from 4.17 mg/ml to 16.67 mg/ml against the anaerobic bacteria tested. Isothiocyanate compounds such as sulforaphane were bactericidal against *Helicobacter pylori*, acting by inhibiting urease (Fahey et al., 2013; Moon et al., 2010). Other natural isothiocyanates (berteroin, hirsutin, phenethyl-isothiocyanate, alyssin and erucin) possessed antimicrobial activity against *H. pylori*, but were unable to inactivate urease activity. On the other hand benzoyl-isothiocyanate was able to inactivate urease but did not show bactericidal activity (Fahey et al., 2013). The antimicrobial activity of allyl-isothiocyanate, benzyl-isothiocyanate and 2-phenylethyl-isothiocyanate was evaluated against MRSA by Dias et al. (2012) In this study benzyl-isothiocyanate and 2-phenylethyl-isothiocyanate showed the highest antimicrobial activity in comparison with allyl-isothiocyanate. The isothiocyanate 4-(α-L-rhamnosyloxy) benzyl-isothiocyanate extracted from the seeds of *Maringa oleifera* Lam. was able to inhibit the growth of *E. casseliflavus* and *S. aureus* (Galuppo et al., 2013). Allyl-isothiocyanate and benzyl-isothiocyanate have been shown to possess bactericidal effects against *Campylobacter jejuni* (Baysse, 2012); allyl-isothiocyanate was active against *E. coli* O157:H7 (MIC: 51 ppm; MBC: 412 ppm) (Cordeiro et al., 2014) and against *E. coli*, *P. aeruginosa*, *S. aureus* and *Listeria monocytogenes* in the same way as 2-phenylethyl-isothiocyanate (MIC: 100 μg/ml for all bacteria and both compounds; MBC was at least 10 times higher than the MIC) (Borges et al., 2015a,b). Some isothiocyanates showed synergistic interactions with some antibiotics. Dias et al. (2012) conducted a first study on antibacterial activity and synergy between isothiocyanates and antibiotics (gentamicin and vancomycin) against important pathogenic bacteria: *E. coli*, *E. faecalis*, *L. monocytogenes*, *P. aeruginosa* and *S. aureus* using the disc diffusion method. The results showed that benzyl-isothiocyanate was the most effective compound against all bacteria studied. *L. monocytogenes* and *S. aureus* were the bacteria most affected by the isothiocyanate, both alone or in association with antibiotics, whilst *P. aeruginosa* was the least affected. The most relevant registered synergism with antibiotics was between benzyl-isothiocyanate and 2-phenylethyl-isothiocyanate. Synergy with streptomycin was demonstrated by 2-(4-hydroxyphenyl) ethyl-isothiocyanate against *E. coli* and *S. aureus* grown in a glucose-containing medium (Tajima et al., 2001). Unfortunately small changes in the concentrations of both isothiocyanates and streptomycin affect their synergism, suppressing antimicrobial activity (Tajima et al., 2003). Abreu et al. (2013), conducted a study to assess the antibacterial activity of phenyl-isothiocyanate against *E. coli* and *S. aureus*. The MICs was 1000 μg/ml for both strains tested. A synergistic effect was found when phenyl-isothiocyanate was combined with ciprofloxacin and erythromycin against *S. aureus*. Allyl-isothiocyanate was able to reduce the MIC of erythromycin against *S. pyogenes* (Palaniappan and Holley, 2010). Allyl-isothiocyanate and phenylethyl-isothiocyanate showed synergy with streptomycin against gram-negative bacteria such as *E. coli* and *P. aeruginosa* (Saavedra et al., 2010). 2-phenylethyl-isothiocyanate (derived from watercress tissue) was tested against 11 isolates of *E. coli* producing extended spectrum β-lactamases, in combination with aminoglycoside gentamicin and watercress

natural extract. A significant increase in antibacterial activity was observed for most of the isolates when the natural extract was combined with 2-phenylethyl- isothiocyanate (Freitas et al., 2013).

Allicin (diallyl-thiosulfinate) is an organosulfur compound obtained from crushed garlic, in which the enzyme alliinase converts alliin into allicin. This transformation occurs only in crushed plants; in the intact plants aliin and aliinase are kept in different cell compartments only coming into contact when the cloves are broken. Allicin was isolated and identified for the first time in 1944 by Cavallito and Bailey (1944) as the antimicrobial agent present in garlic. The antibacterial and antifungal activities of allicin have been known for a long time. Several studies (Aydin et al., 2000; Cañizares et al., 2004; Jonkers et al., 1999; Kockar et al., 2000) have been conducted to investigate the potential inhibitory effect of allicin on the growth of *H. pylori*. A growth inhibitory effect was observed, with a synergistic effect when allicin was combined with omeprazole but not when combined with antibiotics (no synergistic or antagonistic effect). In contrast, the results of a clinical study conducted by Aydin et al. (2000), showed that eradication did not occur following treatment with allicin on 20 *H. pylori* positive patients. Allicin has also shown antibacterial activity against *S. epidermidis*, *P. aeruginosa*, *S. agalactiae*, *Burkholderia cepacia*, MRSA and oral pathogens causing periodontitis and caries. With regards to *S. epidermidis*, in 2003 Pérez-Giraldo et al. (2003) tested the antibacterial activity of allicin against 38 strains of *S. epidermidis,* 19 of which were methicillin resistant (MRSE) and 19 methicillin susceptible (MSSE), evaluating the inhibitory effect of this compound against biofilm adhesion. The results showed no difference in susceptibility to allicin between MRSE and MSSE with a MIC value ranging from <0.25 to 16 mg/l; 4 mg/ml of allicin was needed to prevent biofilm formation by more than 90%. In 2007, the results of a study conducted by Cai et al. (2007) showed that allicin was unable to inhibit the growth of *S. aureus*, *S. epidermidis* and *P. aeruginosa* (MIC_{90}: >512 μg/ml), but it facilitated the antibacterial effect of oxacillin, cefazolin and cefoperazone tested at subinhibitory concentrations. In 2008 Cai et al. (2008), confirmed that allicin can potentiate the antibacterial effect of some antibiotics, such as cefoperazone, tobramycin and ciprofloxacin, against *P. aeruginosa*. Another study (Zhai et al., 2014) underlined that allicin at a concentration of 4 mg/l, in combination with vancomycin, could inhibit the biofilm formation of *S. epidermidis* on prosthetic joints. There are few data in literature on the activity of allicin on oral pathogens causing periodontitis and caries. On the basis of the results of these studies (Bachrach et al., 2011; Bakri and Douglas, 2005; Velliyagounder et al., 2012) allicin may be used for alleviating dental diseases. Allicin extracted from garlic inhibits the growth of all strains tested. Allicin was found to be bactericidal against *S. agalactiae* (MICs values ranged from 35 to 95 mg/l) (Cutler et al., 2009) and against *B. cepacia* complex (MICs values ranged from 8 to 62 μg/ml) (Wallock-Richards et al., 2014). Regarding *S. aureus*, in 2004 Cutler and Wilson (2004) suggested that allicin could represent an alternative molecule to mupirocin in decreasing the spread of MRSA. In 2011 Leng et al. (2011), suggested that allicin may be also used in the treatment of infections sustained by α-toxin producing *S. aureus*.α-toxin production was reduced in the presence of 2 μg/ml of allicin; allicin at a concentration of 16 μg/ml was able to halt toxin production in all *S. aureus* strains studied. Moreover allicin was active against the tested *S. aureus* with MICs values ranging from 32 to 64 μg/ml. No difference was observed between methicillin susceptible *S. aureus* (MSSA) and MRSA. More recently *in vitro* and *in vivo* studies (Pérez-Köhler et al., 2015a,b) evaluated the possible use of allicin in preventing implant infection of reticular polypropylene mesh used for hernia repair. Mesh fragments were soaked with different antibiotic or antiseptic treatments and were then exposed to an environment contaminated with *S. aureus*. In the *in vitro* study (Pérez-Köhler et al., 2015a) the meshes soaked with vancomycin (40 μg/ml), chlorhexidine digluconate (0.05%) and allicin- chlorhexidine (900 μg/ml of allicin and 0.05% of chlorhexidine digluconate) were not attacked by bacteria, while sole allicin allowed the adhesion of high number of bacteria. An *in vivo* study (Pérez-Köhler et al., 2015a,b) showed that allicin interferes with the inflammatory response and macrophage reaction promoting the survival of bacteria in host tissue. A concentration of 1.1 mg/ml of allicin was needed to reduce biofilm adhesion of *P. aeruginosa* (Ta et al., 2014). In other studies (Lihua et al., 2013) the treatment of 128 μg/ml of allicin resulted in the inhibition of *P. aeruginosa* biofilm adhesion and in a down-regulation of the expression of quorum-sensing (QS) virulence factors. Likewise, ajone from garlic inhibited QS in *P. aeruginosa* and also down-regulated the expression of virulence factors (Jakobsen et al., 2012). Several studies evaluated the efficacy of allicin on fungi and the Authors concluded that this molecule was active, and in addition a synergistic effect was observed in combination with amphotericin B (An et al., 2009; Kim et al., 2012; Ogita et al., 2006).

2.3. Terpenoids

Terpenoids represent a large class of compounds among those produced by plants, characterized by possessing antimicrobial activity (Table 3). Terpenoids are derived from five-carbon isoprene units; most of terpenoids have multi cyclic structures that differ from one another in their functional groups and basic carbon skeletons. Monoterpenes are a class of terpenes that consist of two isoprene units, found in the essential oils extracted from many plants. During the last two decades the antimicrobial activity of these compounds has been studied and several papers show that thymol and carvacrol (phenolic monoterpenoids) are able to inhibit the growth of many bacteria.

Thymol is extracted from the genera *Thymus*, *Oregano*, *Satureja*, *Coridithymus*, *Thymbra* and *Lippia*, while carvacrol is the active compound in oregano, and is present in the essential oil of thyme, pepperwort and wild bergamot. Essential oils such as thymol, carvacrol, eugenol, *trans*-cinnamaldehyde, β-resorcylic acid and vanillin, each at a concentration of 1 mM, showed antimicrobial activity against *E. coli* O157:H7, *Salmonella typhimurium* and *L. monocytogenes* when mixed with soy sauce, while no antibacterial effect was observed for all bacteria tested when these essential oils were used alone (Moon and Rhee, 2016). Another study (Liu et al., 2015) evaluated the antimicrobial activities of essential oils (thymol, berberine, eugenol and cinnamaldehyde) against *S. typhimurium* and *L. monocytogenes*, both alone and in assiociation with streptomycin. The most active compound against *L. monocytogenes* was cinnamaldehyde (MIC: 512 μg/ml) followed by thymol and eugenol (MIC: 1024 μg/ml for both compounds). Moreover thymol and cinnamaldeyde showed synergistic effect with streptomycin. Against *S. typhimurium,* thymol was the most active compound (MIC: 256 μg/ml). Also Chauhan and Kang (2014) showed that thymol was able to inhibit *S. typhimurium* (MIC: 750 mg/l). Essential oils were also found to be active against *Mycobacterium tuberculosis*: carvacrol and thymol were the most active terpenes, with MIC values of 2.02 and 0.78 μg/ml respectively. Cinnamaldehyde and cinnamic acid were the most active phenylpropanes with MIC values of 3.12 and 8.16 μg/ml respectively (Andrade-Ochoa et al., 2015). Recently, the antibacterial activity of essential oils from *Eucalyptus camaldulensis* were evaluated against MDR *Acinetobacter baumannii* wound isolates by Knezevic et al. (2016) *Eucalyptus camaldulensis* leaf extracts have recently been proven to be active against MDR bacteria, including *A. baumannii* (Jazani et al., 2009). It's essential oils were also shown to possess a good antibacterial effects against both gram-positive and gram-negative bacteria (Adeniyi et al., 2006; Akin et al., 2012; Lima et al., 2013; Owlia et al., 2010; Oyedeji et al., 1999; Rasooli et al., 2009). In the study conducted by Knezevic

Table 3
List of terpenoids active against Gram-negative and Gram-positive bacteria.

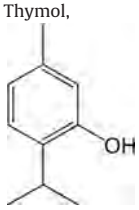
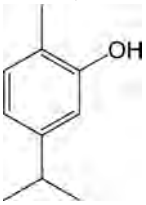
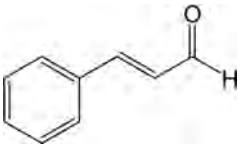
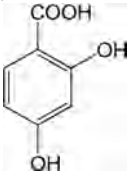
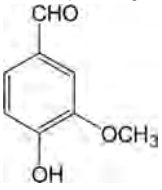
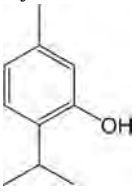
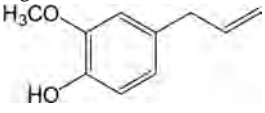
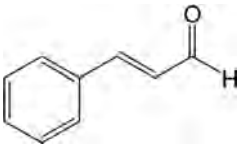
Compound	Bacteria	Ref.
Thymol, 	*E. coli* O157:H7 *S. typhimurium* *L. monocytogenes*	(Moon and Rhee, 2016)
carvacrol, 		
trans-cinnamaldehyde, 		
β-resorcylic acid 		
vanillin (with soy sauce) 		
Thymol 	*S. typhimurium* *L. monocytogenes* *M. tuberculosis*	(Andrade-Ochoa et al., 2015; Chauhan and Kang, 2014; Liu et al., 2015)
Eugenol. 	*S. typhimurium* *L. monocytogenes*	(Liu et al., 2015)
Cinnamaldehyde 	*S. typhimurium* *L. monocytogenes* *M. tuberculosis*	(Andrade-Ochoa et al., 2015; Liu et al., 2015)

Table 3 (*Continued*)

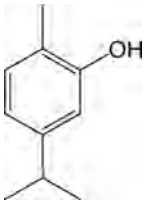
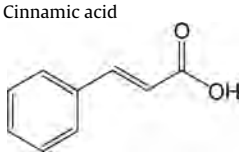
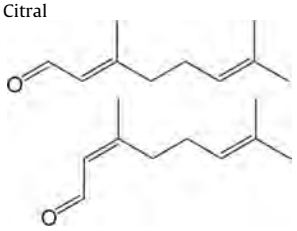
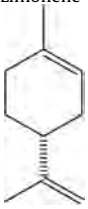
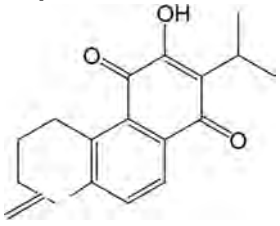
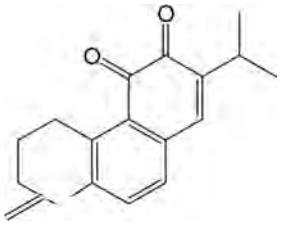
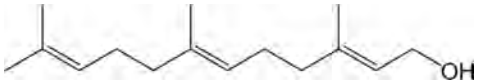
Compound	Bacteria	Ref.
Carvacrol 	*M. tuberculosis* *S. aureus* *L. monocytogenes* *E. coli* *E. faecium* *S. enterica* *P. aeruginosa*	(Ait-Ouazzou et al., 2013; Andrade-Ochoa et al., 2015; Espina et al., 2011, 2015; Fisher and Phillips, 2008; Laird et al., 2012)
Cinnamic acid 	*M. tuberculosis*	(Andrade-Ochoa et al., 2015)
Essential oils from Eucalyptus camaldulensis	MDR *Acinetobacter baumannii* both gram-positive and gram-negative bacteria	(Akin et al., 2012; Knezevic et al., 2016; Owlia et al., 2010; Oyedeji et al., 1999; Rasooli et al., 2009)
Geranium oil from Pelargonium graveolens	enterococcus strains	(Łysakowska et al., 2015)
Essential oils from Laurus nobilis L.	*S. aureus*	(Merghni et al., 2015)
Citral 	*S. aureus* *L. monocytogenes* *E. coli* *E. faecium* *S. enterica* *P. aeruginosa*	(Ait-Ouazzou et al., 2013; Espina et al., 2011, 2015; Fisher and Phillips, 2008; Laird et al., 2012)
Limonene 	*S. aureus,* *L. monocytogenes* *E. coli* *E. faecium* *S. enterica* *P. aeruginosa*	(Ait-Ouazzou et al., 2013; Espina et al., 2011, 2015; Fisher and Phillips, 2008; Laird et al., 2012)
Essential oils containing antiseptic mouthrinse	*S. mutans* *S. mitis*	(Fine et al., 2000; Lobo et al., 2011)
Salvipisone 	*S. aureus,* *S. epidermidis*	(Różalski et al., 2007; Walencka et al., 2007)
and aethiopinone 	*E. faecalis* *S. aureus* *S. epidermidis* MRSA and MRSE strains	
Farnesol, 	*S. aureus* *S. epidermidis.* *B. pseudomallei*	(Castelo-Branco et al., 2015; Gomes et al., 2009; Jabra-Rizk et al., 2006; Masako et al., 2005a,b)

Table 3 (*Continued*)

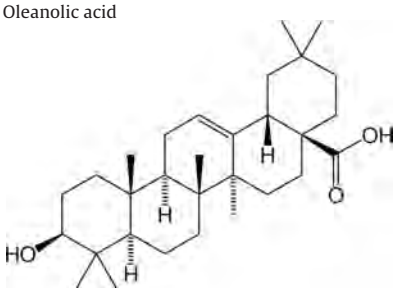
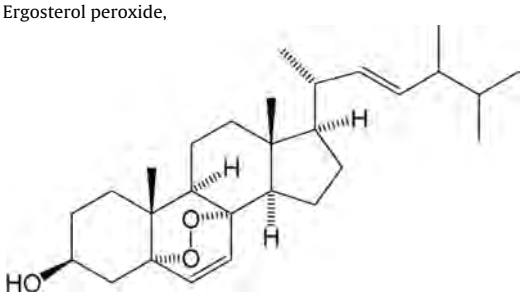
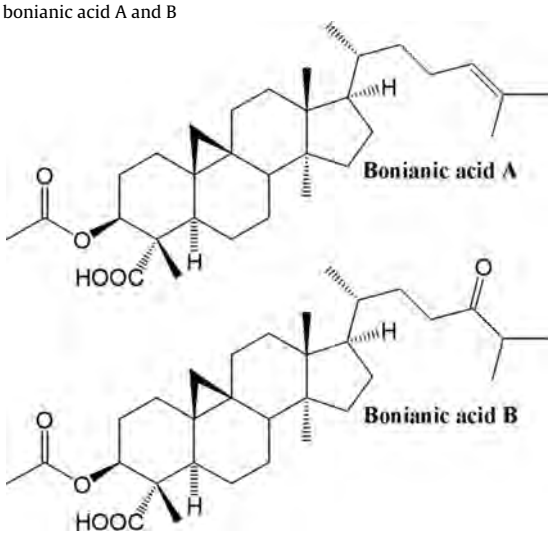
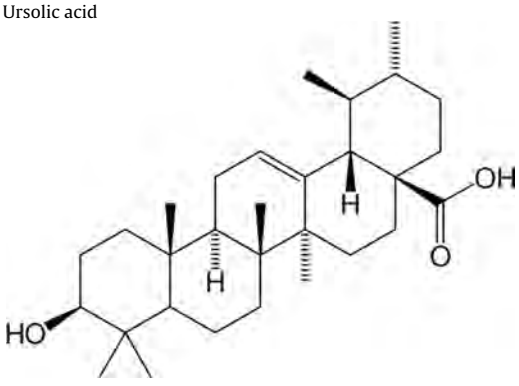
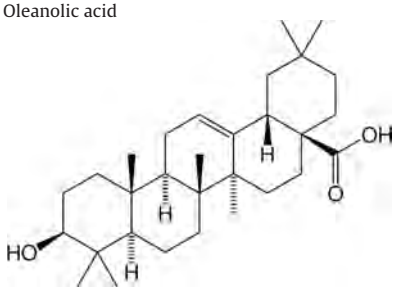
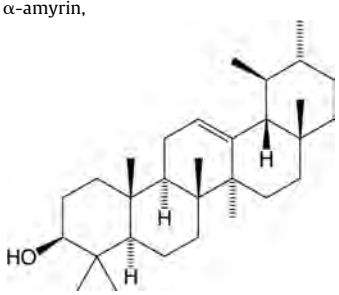
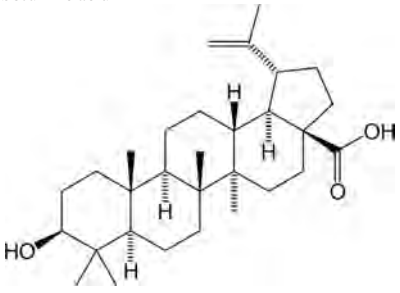
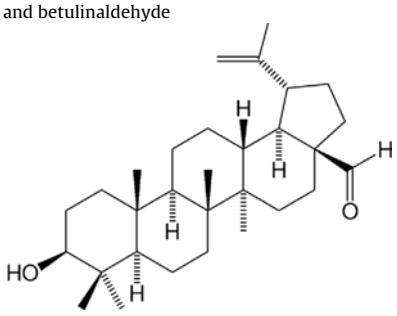
Compound	Bacteria	Ref.
Oleanolic acid 	*M. tuberculosis*	(Ge et al., 2010)
Ergosterol peroxide, 	*M. tuberculosis*	(Duarte et al., 2007)
bonianic acid A and B 		
Ursolic acid 	*M. tuberculosis* *B. cereus* *planktonic cariogenic microorganisms* *S. mutans and* *S. sobrinus* *L. monocytogenes*	(Cunha et al., 2010; Jiménez-Arellanes et al., 2013; Kurek et al., 2010; Zhou et al., 2013; Zou et al., 2014)

Table 3 (*Continued*)

Compound	Bacteria	Ref.
Oleanolic acid 	*M. tuberculosis* *B. cereus and* *S. pneumonia* planktonic cariogenic microorganisms *L. monocytogenes*	(Cunha et al., 2010; Jiménez-Arellanes et al., 2013; Kurek et al., 2010; Zhou et al., 2013)
α-amyrin, 	MRSA and MSSA	(Chung et al., 2014)
betulinic acid 		
and betulinaldehyde 		

et al. (2016), cited above, the interactions of essential oils with certain antibiotics (ciprofloxacin, gentamicin and polymyxin B) has also been evaluated. The results showed that *A. baumannii* is inhibited by essential oils from *Eucalyptus camaldulensis* and MICs values range from 0.5 to 2 μl/ml; the examined essential oils showed synergistic antibacterial effect with antibiotics in most of the cases. Several *in vitro* studies have evaluated and reported that essential oils possess anti-biofilm and anti-QS activities. Geranium oil from *Pelargonium graveolens* A was found to be able to inhibit enteroccocal strains isolated from endodontically treated teeth (MICs values ranging from 1.8 to 4.5 mg/ml) and to eradicate biofilm at a concentrations of 150 mg/ml (Łysakowska et al., 2015), Essential oils from *Laurus nobilis* L. were able to inhibit oral *S. aureus* strains (MICs values ranged from 3.91 to 15.62 mg/ml) and also had a strong biofilm inhibition at a concentration of 0.24 mg/ml (1/16x MIC) (Merghni et al., 2015). The anti-biofilm activity of carvacrol, citral and limonene was evaluated against planktonic cells of many bacterial species, such as *S. aureus*, *L. monocytogenes*, *E. coli*, *E. faecium*, *S. enterica*, or *P. aeruginosa,* by several studies (Ait-Ouazzou et al., 2013; Espina et al., 2015, 2011; Fisher and Phillips, 2008; Laird et al., 2012). The essential oil mouthrinse produced respective reductions of 69.9% and 75.4% in total recoverable streptococci and *S. mutans* in plaque, and corresponding reductions of 50.8% and 39.2% in saliva. The clinical study conducted by Fine et al. (2000), revealed that streptococcal strains from supragingival interproximal plaque and saliva were susceptible to the antibacterial activity of antiseptic mouthrinse containing essential oils. Moreover the results of this study showed that streptococci from the mutans group were more susceptible to the bactericidal activity of these essential oils than streptococci from the mitis group. The antibacterial activity of essential oils against *S. mutans* was confirmed by an *in vivo* study on children conducted by Lobo et al. (2011).

Salvipisone and aethiopinone, two diterpenoids, were isolated from the roots of *Salvia sclarea* and evaluated as antibacterial and anti-biofilm agents against gram-positive and gram-negative bacteria. At a concentration of 37.5 μg/ml, the growth of *S. aureus*, *S. epidermidis* and *E. faecalis* was inhibited by these diterpenoids, and *S. aureus* and *S. epidermidis* pre-formed biofilms were disrupted by at least 85% (Różalski et al., 2007). Another study tested the efficacy of salvipisone and aethiopinone against MRSA and MRSE strains and evaluated the synergy of these terpenoids in combination with oxacillin, vancomycin and linezolid. The results of this study showed that salvipisone and aethiopinone are bactericidal or bacteriostatic against planktonic cultures of tested bacteria. Diterpenoids at the concentrations of 1/2 MIC had synergistic effect with antibiotics tested (Walencka et al., 2007).

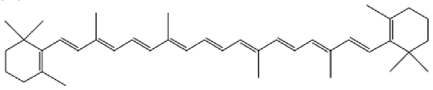
Farnesol, a natural sesquiterpenoid, displayed antibacterial activity against *S. aureus* and *S. epidermidis*. A study conducted in 2009 by Gomes et al. (2009), showed that farnesol at a concentration of 100 μM had a significant effect on *S. epidermidis* planktonic cells, but it was not so efficient on sessile cells. Regarding *S. aureus*, farnesol blocked biofilm formation and was synergic with antibiotics. In 2005 Masako et al. (2005a,b) conducted two studies to assess the effect of a cream with 0.02% of farnesol and 5% of xylitol for treatment of atopic dermatitis. The results of the first study showed that the combination of farnesol and xylitol inhibited the formation of the *S. aureus* biofilm and the second study showed that this combined cream was able to decrease the load of the pathogen *S. aureus* without modifying skin microflora. Jabra-Rizk et al. (2006), investigated the effect of farnesol on *S. aureus* biofilm formation and its interaction with gentamicin. A concentration of 22 μg/ml inhibited growth and biofilm formation for all strains studied. Moreover, the combination of gentamicin at 2.5 times the MIC and 44 μg/ml of farnesol were able to reduce bacterial concentrations by more than 2 log units, showing synergy between the two compounds. Farnesol, both alone and in combination with amoxicillin, doxycycline, ceftazidime and sulfamethoxazole-trimethoprim, was effective against *B. pseudomallei* biofilms (Castelo-Branco et al., 2015). The minimum concentrations for biofilm eradication ranged from 75 to 2400 mmol l^{-1}. Farnesol was able to reduce these values in combination with the antibiotics cited above (reduced by a factor of 256 times for ceftazidime, 16 times for amoxicillin and 4 times for both doxycycline and sulfamethoxazole-trimethoprim). The triterpenes, another group of terpenoids, consist of six isoprene units. Oleanolic acid is a triterpenoid compound endowed with antibacterial activity against many bacteria. It was able to inhibit the growth of *M. tuberculosis,* including drugs-susceptible strains (susceptible to the first-line anti-tuberculosis drugs: rifampicin, isoniazid and ethambutol) with MICs values of 50–100 μg/ml and drug-resistant isolates with MIC values of 100–200 50–100 μg/ml. In addition, the combination of oleanolic acid with rifampicin, isoniazide and ethambutol showed synergistic antibacterial effects against drug-resistant strains. The MIC values of oleanolic acid were significantly decreased in combination with isonizide, rifampicin and ethambutol (MIC value reductions ranging from 4 fold to 32 fold, 16 fold to 128 fold and from 16 fold to 128 fold, respectively). In 2011, three new triterpenoids (bonianic acid A and B and 3-O-acetyluncaric acid) were isolated from *Radermachera boniana* with six known molecules, including ursolic acid, oleanolic acid and ergosterol peroxide, and were tested against *M. tuberculosis* (Truong et al., 2011). Ergosterol peroxide was the most active compound against this pathogen followed by bonianic acids B and A (MIC values of 3.5 μM, 9.9 μM and 34.8 μM, respectively). Other compounds showed less or no activity. The mixture of ursolic and oleanolic acids was also found to have synergistic effects against *M. tuberculosis* (Jiménez-Arellanes et al., 2013). Another study (Cunha et al., 2010) evaluated the antibacterial activity of oleanolic acid and ursolic acid (another triterpenoid compound) extracted from *Miconia ligustroides* against *Bacillus cereus*, *Vibrio cholerae*, *S. choleraesuis*, *K. pneumoniae* and *S. pneumoniae*. Ursolic acid was active against *B. cereus* (MICs value of 20 μg/ml), while oleanolic acid was active against both *B. cereus* and *S. pneumoniae* (MICs values of 80 μg/ml for both strains). The union of the two compounds did not enhance the antibacterial effect. Ursolic acid and oleanolic acid were found to be active against planktonic cariogenic microorganisms and their biofilm (Zhou et al., 2013). In 2014 a research group (Zou et al., 2014) evaluated the synergistic effect of ursolic acid and xylitol against oral biofilms produced by *S. mutans* and *S. sobrinus*. The MICs of ursolic acid ranged from 128 to 256 μg/ml while the MICs of xylitol were 20% for all tested bacteria. The synergistic interaction of the two compounds was observed against all tested microorganisms (Fractional Inhibitory Concentrations: FICs < 1). Oleanolic and ursolic acids were able to affect the virulence factors of *L. monocytogenes*, inhibiting listeriolysin O activity without influencing toxin secretion and reducing the capacity of these bacteria to form biofilms (Kurek et al., 2010). In 2014 Chung et al. (2014), isolated and identified three known triterpenoids (α-amyrin, betulinic acid and betulinaldehyde) from the bark of Calliparca farinosa Roxb.; these molecules showed antimicrobial activity against both MRSA and MSSA (MICs values ranged from 2 to 512 μg/ml) and could represent an alternative to circumvent antibiotic resistance in *S. aureus*.

2.4. Carotenoid

Carotenoids, also known as tetraterpenoids, are formed from 8 isoprenoid units. They play two key roles in plants: they absorb light energy for use in photosynthesis and contribute to photoprotection. Carotenoids are fat-soluble compounds and their release from plants occurs when the plant cells are disrupted such as during food preparation or during mastication (Faulks and Southon, 2005). Carotenoids (approximately 600 identified carotenoids and related compounds) can be divided in two classes, carotenes (such as α-carotene, β-carotene, and lycopene) and xanthophylls (such as β-cryptoxanthin, lutein, and zeaxanthin) and are responsible for the yellow, orange and red colors of vegetables and fruits. Carotenoids are well known for their nutritional properties and health benefits. Several studies have evaluated their antibacterial activity against both gram-positive and gram-negative bacteria (Table 4). In 2005, Molnár et al. (2005), extracted carotenoid fractions from red paprika, Valencia orange peel and the peel of the Golden delicious variety of apple. The extracts were evaluated for their effect against *H. pylori.* Among extract compounds β,β-carotene showed the most anti-*H. pylori* activity with MIC_{50} values of 36 μg/ml, similar to that of metronidazole with MIC_{50} values of 45 μg/ml. Another study conducted by Horváth et al. (2012), compared carotenoids isolated from Rose hips and investigated their anti-*H.pylori* activity. Six main carotenoids were extracted from Rose hips: epimers of neochrome, lutein, zeaxanthin, rubixanthin, lycopene and β,β-carotene. The activity of the extracted carotenoids depended upon the extraction methods. Among the different extracts of Rose hips, only two fractions displayed an anti-*H.pylori* effect (MIC_{50}: 8.2 μg/ml and 11 μg/ml) comparable to metronidazole (MIC_{50}: 7.0 μg/ml).

In 2010, NengGuo et al. (2010), extracted carotenoid compounds from the peel of Shation Pummelo and tested their antibacterial activity against *B. subtilis*, *S. aureus*, *E. coli*, *Aspergillus niger*, *A. flavus*, *Penicillium chrysogenum*, *Rhizopus oryzae* and *Saccaromices cerevisiae*. The results showed that the most susceptible bacteria was *E. coli* (mean inhibition zone (IZ): 19.47 mm and mean MIC value: 18.75 μg/ml) followed by *S. aureus* and *B. subtilis* (mean IZ: 18.63 mm and mean MIC: 35 μg/ml and 18.57 mm and MIC: 70 μg/ml, respectively). High antifungal activity was found against *S. cerevisiae* (mean IZ: 13.17 mm and MIC value 140 μg/ml); while

Table 4
List of Carotenoids and related compounds against Gram-negative and Gram-positive bacteria.

Compound	Bacteria	Ref.
β,β-carotene 	*H. pylori*	(Molnár et al., 2005)
Carotenoids from Shation Pummelo	*E. coli* *S. aureus* *B. subtilis* *S. cerevisiae*	(NengGuo et al., 2010)
Lycopene. 6E,8E,10E,12E,14E,16E,18E,20E,22E,24E,26E)-2,6,10,14,19,23,27,31-Octamethyldotriaconta-2,6,8,10,12,14,16,18,20,22,24,26,30-tridecaene	*B. subtilis* *E. coli* *S. aureus*	(Dos Santos et al., 2015)
Carotenoids from Bixa Orellana L., Daucus carota L., Zea mays L. and Solanum Lycopersicum L. extracts	*S. aureus*	(Natividad and Rafael, 2014)
carotenoids extracted from Thuja Occidentalis	*B. subtilis* *B. cereus* *B. amyloliquifaciens* *B. magaterium* *Proteus vulgaris* *S. typhy*	(Pooja et al., 2015)
carotenoids pigments extracted from Peltophorum Petrocarpum	*S. aureus,* *Enterobacter* spp. *Streptococcus* spp. *E. coli*	(Amalya and Sumathy, 2015)
crude compounds extracted from Peltophorum Petrocarpum leaf and flowers	*S. aureus* *Enterobacter* spp. *Streptococcus* spp. *S. paratyphi* *E. coli*	(Amalya and Sumathy, 2015)

the carotenoid extracts showed no activity against *A. niger*, *A. flavus* and *P. chrysogenum*. Lycopene, the red pigment found in tomatoes, showed effective inhibition against *B. subtilis* (IZ: 25 mm) (Dhanawade and Sakhare, 2012). Recently, the effects of lycopene and other phytochemicals were investigated in combination with certain antimicrobials (gentamicin, amoxicillin, cephalexin and ciprofloxacin) against *E. coli* and *S. aureus* (Dos Santos et al., 2015). No synergistic activity was found against *S. aureus* strains for any of the tested combinations; a strong decrease in antibacterial activity was observed for all drugs tested. For *E. coli*, the combinations of cephalexin and amoxicillin with the natural compounds markely diminished the antibacterial activity of drugs. In 2014, Natividad and Rafel analysed (Natividad and Rafael, 2014) the carotenoids found in annatto (*Bixa Orellana* L.), carrot (*Daucus carota* L.) corn (*Zea mays* L.) and tomato (*Solanum Lycopersicum* L.) extracts. Their study quantified the amount of total carotenoids in these plants and compared their antimicrobial activity against *E. coli* and *S. aureus*. All extracts were unable to inhibit *E. coli*; while extracts of annatto, tomato and carrot displayed antibacterial activity against *S. aureus*. Annatto extract has the greatest content (931.30 μg/g) of total carotenoids among the extracts studied and showed the highest mean IZ against *S. aureus* (9.17 mm). Another study (Pooja et al., 2015) showed that carotenoids extracted from *Thuja Occidentalis* possessed good antibacterial activity against *B. subtilis*, *B. cereus*, *B. amyloliquifaciens*, *B. magaterium*, *Proteus vulgaris* and *S. typhy*. A recent study (Amalya and Sumathy, 2015) showed that the carotenoid pigments extracted from *Peltophorum Petrocarpum* by column chromatografy exhibited antibacterial activity against *S. aureus*, *Enterobacter* spp. *Streptococcus* spp. and *E. coli,* while the crude compounds extracted from leaves and flowers were active on *S. aureus*, *Enterobacter* spp., *Streptococcus* spp., *S. paratyphi* and *E. coli.*

2.5. Polyphenols

Polyphenols constitute a great portion of the phytochemicals found abundantly in fruits, vegetables, nuts, seeds, stems, flowers and beverages such as coffee, tea and red wine. In recent years dietary polyphenols have been successfully evaluated as chemopreventive and therapeutic agents thanks to their direct antimicrobial action and antibiotic modulation activity (Gibbons, 2005; Stermitz et al., 2000). To date more than 8000 phenolic structures have been studied and can be divided into many sub-groups according to their chemical structure, source of origin and biological functions. Regarding their chemical structure, polyphenols can be classified as flavonoids and non-flavonoids.

Flavonoids are a large group of compounds found in many fruits, vegetables and legumes. Many natural flavonoids have been reported as possessing various pharmacological properties, with potential utility in the chemoprevention of various diseases associated with oxidative stress, such as cancer, cardiovascular and neurodegenerative disease (Ferrazzano et al., 2011; Heim et al., 2002; Kuroda and Hara, 1999; Ramassamy, 2006). In addition to their antioxidant activity, flavonoids also show good antibacterial activity against both gram-positive and gram-negative isolates (Table 5) (Coppo and Marchese, 2014; Daglia, 2012) likely due to their ability to inhibit DNA gyrase, cell membrane function and bacterial energy metabolism (Cushnie and Lamb, 2005; Njume et al., 2009). DNA replication is one of the most basic biological functions and should be a prime target in antibiotic development. In recent years, flavonoids have been studied for their ability to interact with DNA helicases, proteins essential for DNA replication, repair, and recombination (Lohman et al., 2008), and to prevent dNTPs binding. In particular Chen and Huang (2011), studied 4 flavonoids (galangin, kaempferol, quercetin and myrecetin at 10 μM) capa-

Table 5
List of polyphenols active against Gram-negative and Gram-positive bacteria.

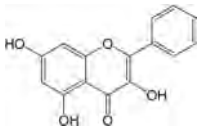
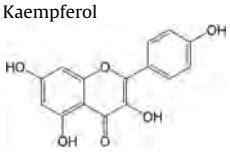
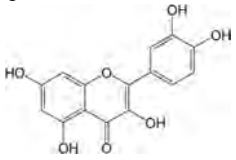
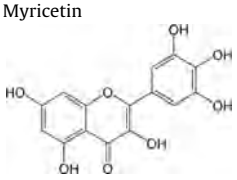
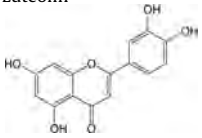
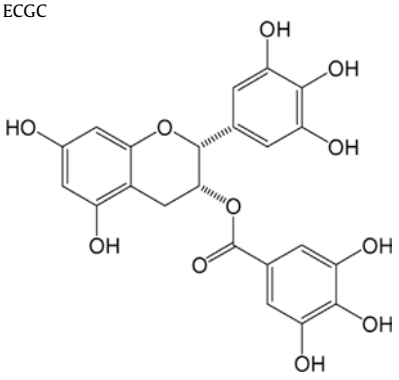
Compound	Bacteria	Ref.
Galangin 	*K. pneumoniae*	(Chen and Huang, 2011)
Kaempferol 	*K. pneumonia* *S. aureus*	(Chen and Huang, 2011; Huang et al., 2015)
Quercetin. 	*K. pneumonia* *S. aureus* *S. haemolyticus* *E. coli* O157:H7 *S. pyogenes*	(Chen and Huang, 2011; Lee et al., 2010; Liu et al., 2010; Siriwong et al., 2015)
Myricetin 	*K. pneumonia* *S. aureus*	(Chen and Huang, 2011; Huang et al., 2015)
Luteolin 	*S. pyogenes* *S. aureus* *E. coli* *vesicatoria* *A. tumefaciens* *P. lachrymans* *B. sublitis* *S. haemolyticus*	(Liu et al., 2010; Siriwong et al., 2015)
Chrysin 	*S. aureus* *E. coli* *vesicatoria* *A. tumefaciens* *P. lachrymans* *B. sublitis* *S. haemolyticus*	(Liu et al., 2010)
Camellia sinensis polyphenols	*S. aureus* *S. marcescens* *P. aeruginosa* *H. pylori* *E. coli*	(Ankolekar et al., 2011; Cho et al., 2008; Jazani et al., 2007; Lee et al., 2009b; Mabe et al., 1999; Radji et al., 2013; Thakur et al., 2016; Yi et al., 2010, 2014)
ECGC 	*S. aureus* *S. mutans* *S. pyogenes* *E. faecalis* *E. coli* *S. pyogenes* *S. thypi* *P. gingivalis* *P. aeruginosa* *K. pneumoniae*	(Asahi et al., 2014; Betts et al., 2015; Cho et al., 2011; Cui et al., 2012; Jeon et al., 2014; Lee et al., 2009a; Lee and Tan, 2015; Xu et al., 2011; Yoda et al., 2004)

Table 5 (*Continued*)

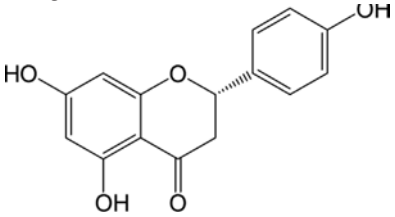
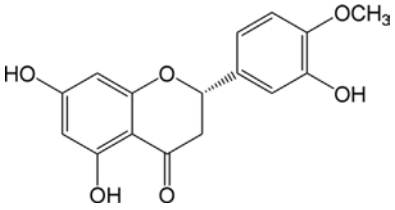
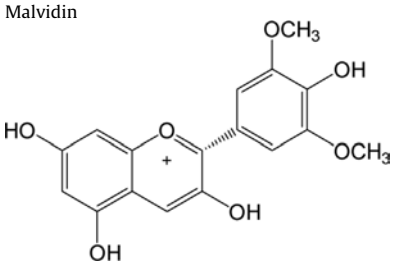
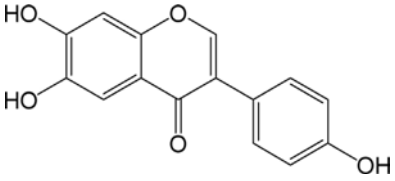
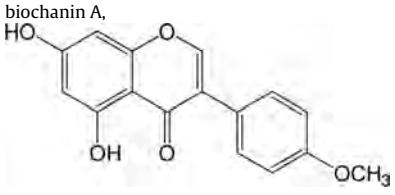
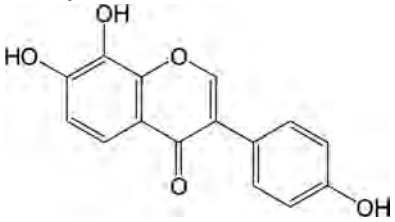
Compound	Bacteria	Ref.
Naringenin 	*S. typhimurium* *P. aeruginosa*	(Vandeputte et al., 2011; Vikram et al., 2011)
Hesperetin 	*S. aureus* *A. hydrophylia*	(Abuelsaad et al., 2013; Bakar et al., 2012)
Malvidin 	*K. pneumoniae*	(Gopu et al., 2015)
Demethyltexasin, 	staphylococci	(Hummelova et al., 2015)
hydroxyldaidzein, 		
biochanin A, 		
demethylretusin 		
and genistein 		

Table 5 (*Continued*)

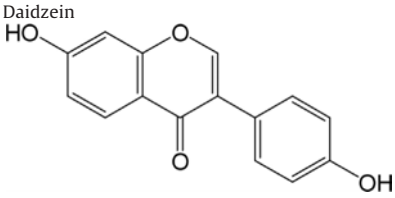
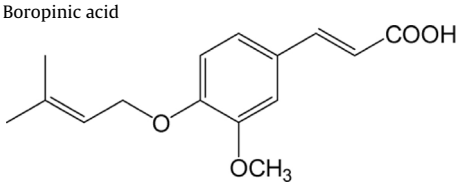
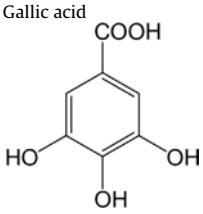
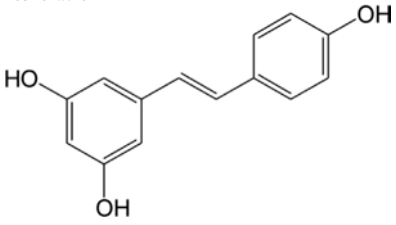
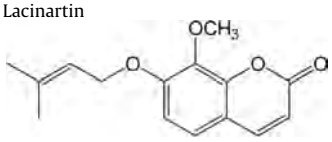
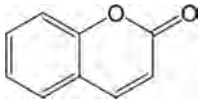
Compound	Bacteria	Ref.
Daidzein 	Vancomycin-Resistant *E. faecalis*	(Chin et al., 2012)
Soy bean fermentation broth	*H. pylori*	(Chin et al., 2012)
Sugarcane Saccharum officinarum L. bogasse extract	*S. aureus*	(Zhao et al., 2015)
Boropinic acid 	*H. pylori*	(Epifano et al., 2006)
Gallic acid 	*E. coli* *S. mutans*	(Dwivedi et al., 2016; Shao et al., 2015)
Resveratrol 	*V. cholerae* *P. mirabilis*	(Augustine et al., 2014; Morinaga et al., 2010; Wang et al., 2006)
Lacinartin 	*P. gingivalis*	(Marquis et al., 2012)
Coumarins 	*H. pylori*	(Basile et al., 2009; Kawase et al., 2003; Takeda et al., 2007)

Table 5 (*Continued*)

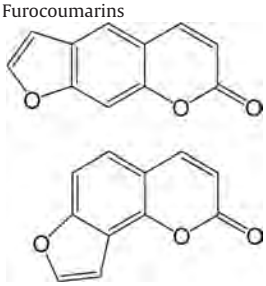
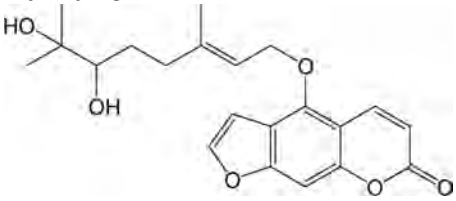
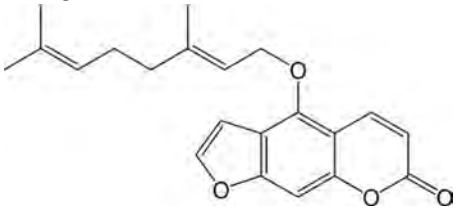
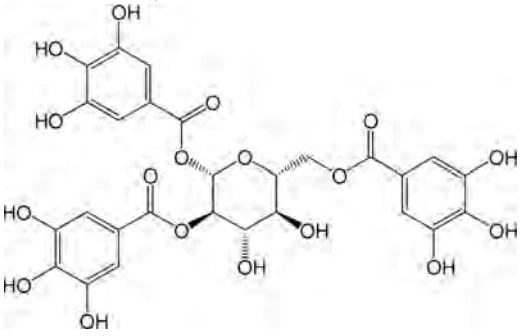
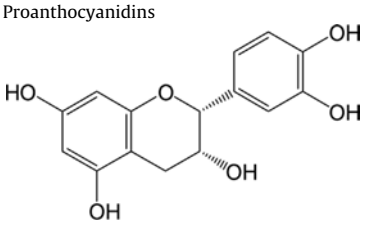
Compound	Bacteria	Ref.
Furocoumarins 	*E. coli* O157:H7 *S. typhimurium*	(Girennavar et al., 2008)
Dihydroxybergamotin 		
and bergamottin 		
Extracts of Anadenanthera colubrina, Commiphora leptophloeos and Myracrodruon urundeuva,	*P. aeruginosa*	(Trentin et al., 2013)
1,2,6-tri-*O*-galloyl-β-D-glucopyranose 	*E. coli* *K. pneumoniae* *P. aeruginosa* *S. aureus*	(Bag et al., 2013)
Sanguiin H-6	*Corynebacterium diphtheriae* *S. epidermidis* *Streptococcus group A* *S. pneumoniae* *C. sporogenes* *S. aureus* *B. subtilis* *Moraxella catarrhalis* *Streptococcus group B and G* *E. faecalis* *Neisseria meningitidis* *Haemophylus influenzae* *H. pylori and* *K. pneumoniae*	(Funatogawa et al., 2004; Krauze-Baranowska et al., 2014)

Table 5 (*Continued*)

Compound	Bacteria	Ref.
Blueberry proanthocyanidins	*L. monocytogenes* *H. pylori* *S. typhimurium* *E. coli* *C. sakazakii*	(Chatterjee et al., 2004; Joshi et al., 2014; Lacombe et al., 2012; Park et al., 2011)
Dalea purpurea Vent proanthocyanidins	*E. coli* O157:H7	(Liu et al., 2013b; Wang et al., 2013)
Proanthocyanidins 	*E. coli* *P. aerugionosa* *S. epidermidis* oral pathogens	(Koo et al., 2010; Leshem et al., 2011; Polak et al., 2013; Tapiainen et al., 2012; Ulrey et al., 2014; Yamanaka et al., 2007)

ble of inhibiting the interaction of *K. pneumoniae* DnaB helicase with dNTPs, while Huang et al. (2015), demonstrated that some flavonoids (kaempferol and myrecetin, at 35 μM) inhibit the PriA helicase activity of *S. aureus*. Flavonoids can be further divided into six subfamilies on the basis of differences in their molecular backbone structure: flavonols, flavones, flavanols, flavanones, anthocyanidins and isoflavonoids.

Among flavonols, some compounds such as quercetin (Al-Saif et al., 2014; Hossion et al., 2011; Lee et al., 2010; Liu et al., 2010; Hossion and Sasaki, 2013), galangin (Cushnie and Lamb, 2006; Eumkeb et al., 2010; Pepeljnjak and Kosalec, 2004), kaempferol, and myrecetin (Ansari et al., 2015) have shown antimicrobial activity against gram-negative and gram-positive bacteria. Quercetin is the main flavonol present in our diet (Scalbert and Williamson, 2000). It is mostly found in onions and propolis and is the most studied flavonol due to its biological properties, including anticancer, anti-inflammatory and antibacterial activities (Harborne and Williams, 2000; Middleton et al., 2000). Liu et al. (2010), studied the antimicrobial activity of flavonoids from *Halostachys caspica*, a Chinese plant used in desert areas as high yield forage with good nutritional properties. In this research, quercetin aglicones showed strong antimicrobial activity against *S. aureus* (MIC: 6.25 μg/ml) and *S. haemolyticus* (MIC: 50 μg/ml). In another study quercetin showed antimicrobial effects against *E. coli* O157:H7 cell growth and lipopolysaccharide production (Lee et al., 2010). Recently, Siriwong et al. (2015), evaluated the activity of quercetin and luteolin against ceftazidime-susceptible *S. pyogenes*. The two tested flavonols slightly increased the cytoplasmic membrane permeability of *S. pyogenes* resulting in a small inhibitory effect against this gram-positive bacterium (MIC: 128 μg/ml). In the same study, both quercetin and luteolin showed a synergistic effect with ceftazidime (FIC index: 0.37 and 0.27 respectively) in agreement with other studies that demonstrated the synergistic effects of flavonols with several antibiotics (Eumkeb et al., 2012).

Flavones are only found in citrus varieties as un-conjugated polymethyl-flavone (Hollman and Arts, 2000). The antimicrobial activity of these compounds, against both bacteria and fungi, is well known. In particular, many studies have reported the antimicrobial activity of apigenin (Liu et al., 2013a), luteolin (Benmalek et al., 2013; Eumkeb et al., 2012; Lv et al., 2009) and chrysin (Kummee and Intaraksa, 2008; Liu et al., 2010) against both gram-positive and gram-negative bacteria. In a study conducted by Liu et al. (2010), the strongest activity shown by chrysin was against *S. aureus*, *E. coli*, and *Xanthomonas vesicatoria* (MIC: 6.25 μg/ml) followed by *Agrobacterium tumefaciens*, *P. lachrymans*, *B. sublitis* and *S. haemolyticus* (MIC: 12.5 μg/ml). Indeed, the corresponding glicosides (chrysin 7-*O*-β-D-glucopyranoside), showed a lower antimicrobial activity against the studied pathogens (MIC range: 150–400 μg/ml). In the same study luteolin showed less antimicrobial activity than chrysin (MIC range: 50–200 μg/ml).

Flavanols are a large group of flavonoids which include catechin, epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG) and epigallocatechin gallate (EGCG). These polyphenols are the most important constituents of tea leaves and appear to have great health benefits in humans (Daglia et al., 2014). The antimicrobial activity of tea polyphenols has been well known since the 1900s (McNaught, 1906) and this has been linked to their chemical structure and their ability to form complexes with bacterial membranes and proteins (Yi et al., 2014). Several studies have shown the antibacterial activity of tea polyphenols against *S. aureus* (Cho et al., 2008; Radji et al., 2013), *Serratia marcescens* (Yi et al., 2014), *P. aeruginosa* (Jazani et al., 2007; Lee et al., 2009a; Radji et al., 2013; Yi et al., 2010), *H. pylori* (Ankolekar et al., 2011; Mabe et al., 1999). *Camellia sinensis* (*Theaceae*) is a promising medicinal herb with several health benefits. Thakur et al. (2016), studied the interaction of *C. sinensis* aqueous extract, at a concentation of ~500 μg/ml, in combination with some antibiotics (colistin, tigecycline, meropenem, ertapenem and amoxicillin-clavulanate) against New Delhi metallo-beta-lactamase-1 (NDM-1) harbouring *E. coli* using the checkerboard method. The combination of *C. sinensis* extract with antibiotics showed a synergistic effect, in particular *C. sinensis* extract plus tigecycline (FIC index: 0.275) and plus ertapenem (FIC index: 0.3) showed strong synergism. ECGC is the most abundant tea catechin and exhibits the strongest bactericidal and biological activities. Many Authors describe its remarkable antimicrobial activity against many gram-positive bacteria such as *S. aureus*, coagulase negative staphylococci (Betts et al., 2015; Yoda et al., 2004), *S. mutans* (Cui et al., 2012; Xu et al., 2011) and *S. pyogenes* (Vance et al., 2011). Recently, Lee and Tan (2015), studied the activity of ECGC against *E. faecalis*. The MIC and MCB values of EGCG were 5 μg/ml and 20 μg/ml respectively. The exposure to EGCG also significantly reduced *E. faecalis* biofilm, completely eradicating it at an EGCG concentration of 500 μg/ml. At 0.5xMIC (2.5 μg/ml) EGCG also significantly reduced the expression of certain *E. faecalis* virulence factors such as gelatinase, collagen-binding antigen and cytolysins and suppressed the expression and activities of virulence factors associated with acidogenity and acidurity of *S. mutans*. These results suggest that EGCG could be a potential anti-caries agent (Xu et al., 2011). ECGC exerts its antimicrobial activity against gram-positive bacteria by different kinds of mechanisms including damage of the lipid layer of the membrane (Cui

et al., 2012), biofilm inhibition (Roccaro et al., 2004) and binding enterotoxin B (Hisano et al., 2003).

It has been reported that EGCG shows stronger effects against gram-positive bacteria than against gram-negative due to the presence of a lipopolysaccharide layer in gram-negative strains. Some Authors describe weak-moderate activity of ECGC against gram-negative strains such as *E. coli* (Cui et al., 2012; Jeon et al., 2014; Lee et al., 2009a), *S. thypi* (Yoda et al., 2004), *Porphyromonas gingivalis* (Asahi et al., 2014), *P. aeruginosa* (Cui et al., 2012; Jeon et al., 2014) and carbapenem resistant *K. pneumonia* (Cho et al., 2011), an emerging MDR nosocomial pathogen. Cho et al. (2011), demonstrated that EGCG inhibits the growth of imipenem-resistant *K. pneumoniae* at 300–650 μg/ml. Bacterial cell exposure to these tea catechins results in proteomic changes: some proteins important in stress response and survival (DnaK, GroEL, AhpC and SodB) are upregolated, while levels of energy metabolism proteins, biosynthesis proteins, cell envelope proteins and DNA metabolism proteins dramatically decrease in imipenem-resistant *K. pneumoniae* after exposition to EGCG. In addition, the Authors studied the possible synergistic effect of EGCG (0.25xMIC and 0.5xMIC) plus imipenem, showing that the imipenem MIC decreased to 64 fold for all 12 imipenem-resistant tested strains. ECGC was also able to reduce transcription of some gram-negative virulence genes, such as QS regulated virulence genes, and inhibited biofilm formation at concentrations below its MIC in many pathogenic bacteria (Blanco et al., 2005; Huber et al., 2003; Lee et al., 2009b). Asahi et al. (2014), conducted the first study on the effects of EGCG on biofilms formed by *Porphyromonas gingivalis,* a gram-negative oral anaerobe that is involved in the pathogenesis of periodontitis, by quantifying total adenosine triphosphate (ATP) levels. In the presence of EGCG at 500 mg/l or 5 g/l (concentrations higher than the MIC), ATP levels were significantly lower compared to controls, moreover biofilm formation was significantly reduced to 10% of control when in the presence of 100 mg/l EGCG. The results of this study demonstrated that EGCG destroys established *P. gingivalis* biofilms and inhibits biofilm formation.

Flavanones are mostly found in citrus fruits such as oranges, grapefruit and lemons. Within this group, the antimicrobial activity of naringenin, eriodictyol and hesperetin is well known (Burger et al., 2002; Fukai et al., 2002; Mandalari et al., 2007; Rauha et al., 2000; Tombola et al., 2003). Naringenin, a flavanone abundant in citrus fruits and tomatoes, was found to be active against *S. typhimurium.* This compound could repress many pathogenicity genes and down-regulate other genes involved in flagella and motility (Vikram et al., 2011). Naringenin also dramatically reduced the production of as acyl-homoserine lactones: *N*-(3-oxododecanoyl)-Lhomoserine lactone and *N*-butanoyl-Lhomoserine lactone in *P. aeruginosa* (Vandeputte et al., 2011). More recently, the antimicrobial activity of hesperetin derived from citrus fruits against vancomycin-intermediate *S. aureus* (Bakar et al., 2012), and *Aeromonas hydrophylia* (Abuelsaad et al., 2013) has been described.

Anthocyanins are a large group of compounds that are responsible for the colors of many flowers, vegetables, fruits and berries (Pazmiño-Durán et al., 2001). In recent years, anthocyanins have received increasing attention thanks to their anticancer, anti-inflammatory and vasoprotective effects (Prior and Wu, 2009; Tsai et al., 2002) and their use as natural colourants in food (Longo and Vasapollo, 2006). The most studied anthocyanidins are cyanidin, pelargonidin, peodinin and malvidin. Recently, Gopu et al. (2015), investigated *Syzygium cumini*, an Indian blackberry belonging to the family of *Myrtaceae* used in traditional medicine for the treatment of diabetes, asthma, bronchitis and dysentery. They described the inhibition of biofilm formation, the QS inhibitory activity and the synergistic effects with antibiotics against *K. pneumoniae*. *S. cumini* is rich in anthocyanidins, such as petunidin, malvidin and cyanidin. In this study the Authors demonstrated that anthocyanidins of *S. cumini*, especially malvidin, have a pronounced inhibitory effect against QS regulated violacein production (81.16%), biofilm formation (72.70%) and exopolysaccharid production (81.16%) in *K. pneumoniae*.

Isoflavones are mainly found in leguminous plants, the soybean in particular. The predominant soy isoflavones present in soy foods are genistein (50% of the total soy bean isoflavones), daidzein (40%) and glycitein (10%) (Murphy et al., 1999). Hummelova et al. (Hummelova et al., 2015), tested 15 naturally occurring isoflavones against nine gram-positive and gram-negative bacteria using the broth microdilution method. Demethyltexasin, hydroxyldaidzein, biochanin A, demethylretusin and genistein showed significant antibacterial activity. Demethyltexasin was the most effective compound and it also exhibited a significant anti-staphylococcal effect (MIC ranging from 16 to 128 μg/ml). In a study conducted by Chin et al. (2012), three isoflavones: daidzin, genistein and daidzein extracted from a soy bean fermentation broth, were studied against *S. typhimurium*, *B. subtilis*, *E. coli*, *P. aeruginosa*, *P. vulgaris*, *S. aureus*, Vancomycin-Resistant *E. faecalis* (VRE) and MRSA. The most active compound *in vitro* was daidzein (MIC range: 16–128 μg/ml) and the most susceptible strain was VRE (MIC: 16 μg/ml). Authors reported that this soy bean fermentation broth could inhibit the growth of *H. pylori* (MIC value: ≤1.25%–≤5%) and may also exert eradication effects.

The non-flavonid polyphenol groups include: phenolic acids, stilbenes, coumarins and tannins.

Phenolic acids are plant metabolites widely spread throughout the plant kingdom. They are mainly contained in chokeberry and blueberry, in dark plum and cherry among fruits while among beverages the best sources of phenolic acids are coffee as well as green and black teas. Recently, Zhao et al. (2015), studied the antimicrobial activity of phenolic compounds of sugarcane *Saccharum officinarum* L. bogasse extract. Gallic acid was the most predominant phenolic acid in the extract (4.36 mg/g of extract) followed by ferulic acid (1.87 mg/ml), coumaric acid (1.66 mg/ml) and chlorogenic acid (1.63 mg/ml). The sugarcane bogasse extract showed antibacterial activity at 20 mg/ml, against selected food borne pathogens. Overall, the highest activity was observed against *S. aureus* (MIC: 0.625 mg/ml) with less in gram-negative strains (MIC range 1.25–2.50 mg/ml). The extract also induced morphological changes in bacterial cells (leading to an irregular shape with a wrinkled surface and induced leakage of cytoplasmic components) when incubated at the MIC for 6 h. Boropinic acid is a prenyloxycinnamic acid isolated from the Australian shrub *Boronia pinnata* Sm., recently reported to inhibit the growth of *H. pylori in vitro* (MIC: 6.17 μM) (Epifano et al., 2006) and *in vivo* (5–100 μM) (Touati et al., 2009) suggesting a potential use as a novel class of *H. pylori* inhibitory agents. Gallic acid is found in almost every plant part: bark, wood, leaf, fruit, root and seed, and in many common foodstuffs such as blueberry, blackberry, strawberry, plums, grapes, wine and tea among others (Daglia et al., 2014). Recently, other Authors described the inhibitory activity of gallic acid on the growth and biofilm formation of *E. coli* and *S. mutans*: with the same effective concentration of gallic acid (8 and 16 mg/ml) the diameters of IZ were significantly higher for *E. coli* than for *S. mutans,* indicating higher antibacterial activity of gallic acid *vs* gram-negative species (Shao et al., 2015). Dwivedi et al. (Dwivedi et al., 2016), studied the drug resistance reversal potential of gallic acid and derived compounds in combination with conventional antibiotics (tetracycline and oxy-tetracycline, ofloxacin, amikacin, tobramycin, ampicillin, cefoxitin, cefotaxime) against MDR *E. coli*. The MIC of gallic acid and derived compounds varied from 500 to 2000 mg/l (weak-moderate activity) but in combination, they were able to reduce the MIC of clinically used antibiotics (norfloxacin,

ofloxacin, amikacin, tobramycin, ampicillin, cefoxitin, cefotaxime, tetracycline, and oxy-tetracycline) by 2–8-fold.

Stilbenes are naturally occurring non-flavonoid polyphenols produced in the leaves and sapwood of a number of plant families, including *Vitaceae*. These compounds are produced in plants during the invasion of pathogens, with the most studied stilbene being resveratrol, a constitutive compound found in some foods and drinks such as red wine, of which it is a major component. In recent years much research has been directed towards establishing the role of resveratrol in human health, with some studies on the antimicrobial activity of this compound. In particular, resveratrol inhibits cholera toxin activity both by binding directly to the toxin and indirectly inhibiting the endocytosis into Vero cells (Morinaga et al., 2010). In research conducted by Wang et al. (2006), resveratrol, at a concentration of 30–60 μg/ml, inhibited swarming and virulence factor expression in wild type strains of *P. mirabilis*. Augustine et al. (2014), showed that resveratrol had antimicrobial activity against *V. cholerae* and inhibited biofilm formation. In this study, the MIC of resveratrol was 60 μg/ml and sub-inhibitory concentrations significantly reduced the formation of biofilm. Nnotably, resveratrol at 1/2 MIC decreased biofilm formation by 85%.

Coumarins are phenolic compounds responsible for the characteristic odour of hay (Cowan, 1999). They are classified by their chemical structure, going from simple coumarins to many other categories of polycyclic coumarins (furocoumarins, pyranocoumarins) (Skalicka-Woźniak et al., 2016). Auraptene was first isolated in 1930 by Komatsu et al. (1930), and is the most abundant prenyloxycoumarin found in citrus fruits (Ogawa et al., 2000). Marquis et al. (2012), studied the effect of auraptene and lacinartin (coumarins with similar structure) on oral health: they demonstrated that lacinartin at a concentration of 50–100 μg/ml, inhibited the growth of *P. gingivalis* almost completely in iron limited conditions, and at the same concentration it also inhibited biofilm formation by approximately 75% and caused the destruction of a pre-formed *P. gingivalis* biofilm. Auraptene, at 100 μg/ml, inhibited the growth of *P. gingivalis* less than lacinartin and increased the formation of biofilm. Both these coumarins at 100 μg/ml, moreover, reduced the adhesion of *P. gingivalis* to epithelial cells, suggesting possible uses as anti-periodontitis agents. The activity of coumarins against *H. pylori* is also known (Basile et al., 2009; Kawase et al., 2003; Takeda et al., 2007). Regarding the polycyclic coumarins, the furocoumarins dihydroxybergamottin (DHB) and bergamottin are known to interfere with cell–cell signalling, inhibiting *E. coli* O157:H7 and *S. typhimurium* biofilm formation, while *P. aeruginosa* was less affected (Girennavar et al., 2008). In the same study the Authors investigated the effect of Rio red juice, a beverage rich in furocoumarins, in comparison with purified coumarins. Juice inhibited the cell signalling less than DHB and bergamottin alone, but it showed a strong inhibitory effect on biofilm formation in *E. coli* O157:H7 (60%) and in *S. typhimurium* (32%).

Tannins are found in many parts of plants: bark, wood, leaves, fruits and roots (Hoste et al., 2006). Many tannin-rich plants are commonly used in traditional medicine as external anti-inflammatory, antioxidant and antimicrobial agents (Lipińska et al., 2014; Piwowarski et al., 2014). The antimicrobial activity of tannins is well-known and is likely due to several mechanisms, such as inhibition of extracellular microbial enzymes, complexation of metal ions, and/or deprivation of substrates (Buzzini et al., 2008; Njume et al., 2009; Scalbert, 1991). Trentin et al. (2013), demonstrated that extracts of *Anadenanthera colubrina*, *Commiphora leptophloeos* and *Myracrodruon urundeuva,* plants used in Brazilian traditional medicine, rich in proanthocyanidins and hydrolysable tannins, induced morphological changes (stalked nubs) in *P. aeruginosa*, providing bacteriostatic effects. At MIC, the extracts were also able to inhibit bacterial adhesion and prevent biofilm formation on a polystyrene surface for 6 and 24 h after incubation. Tannins are divided into two categories based on their chemical nature: hydrolysable and condensed tannins (proanthocyanidins).

Hydrolysable tannins can be divided in gallotannins and ellagitannins depending on the acid component of the compound. Bag et al. (2013), described the inhibitory activity of gallotannin (1,2,6-tri-*O*-galloyl-β-D-glucopyranose) isolated from *Terminalia chebula* fruit against MDR uropathogenic bacteria (*E. coli*, *K. pneumoniae*, *P. aeruginosa* and *S. aureus*). This tannin compound exhibited strong antibacterial activity against studied bacteria with MIC_{50} ranging from 12.10 μg/ml (*S. aureus*) to 67 μg/ml (*P. aeruginosa*). Besides raw antibacterial activity, the Authors described synergy or additivity effects of the gallotannin with some conventional antibiotics (gentamicin, trimethoprim, ciprofloxacin, amoxicillin and ceftazidime). The best synergistic combination was gallotannin plus trimethoprim (FIC index range: 0.18–0.50) followed by gallotannin plus gentamicin (FIC index range: 0.18–1), while the combination of gallotannin and ciprofloxacin, ceftazidime and amoxicillin showed synergistic effects of 9.5%, 4.8% and 0% respectively. Ellagitannins are a heterogeneous class of plant polyphenols with a complex chemical structure and high molecular weight. Ellagic acid conjugates are the major components of raspberry fruits, with other phenols, such as flavonoids and phenolic acids, occurring in significantly lower concentrations (Mazur et al., 2014). The predominant ellagitannin in *Rubus* berries is a dimeric hexahydroxydiphenic form called sanguiin H-6. This compound displayed bactericidal activity against *Corynebacterium diphtheriae* (MIC and MBC: 0.03 mg/ml), *S. epidermidis* (MIC and MBC: 0.125 mg/ml), *Streptococcus* group A and *S. pneumoniae* (MIC and MBC: 0.5 mg/ml) and inhibitory activity against *C. sporogenes* (MIC: 0.06 mg/ml, MBC: >1 mg/ml), *S. aureus* (MIC: 0.25 mg/ml, MBC: >1 mg/ml), *B. subtilis* and *Moraxella catarrhalis* (MIC: 0.5 mg/ml, MBC: >1 mg/ml). For other tested bacteria (*Streptococcus* group B and G, *E. faecalis*, *Neisseria meningitidis*, *Haemophylus influenzae*, *H. pylori* and *K. pneumoniae*) Ellagitannin sanguiin H-6 showed MIC and MBC >1 mg/ml (Krauze-Baranowska et al., 2014). Hydrolysable tannins are also good anti-*H. pylori* agents (Funatogawa et al., 2004) and could be used as alternative treatments for *H. pylori* infections with minimal effect on the host.

Condensed tannins or proanthocyanidins (PACs) are polymers of flavan-3-ol with several antimicrobial activities. The most studied PACs are those derived from berries, and the A-type proanthocyanidins found in cranberries and blueberry in particular displayed significant antimicrobial effects. Blueberry PACs exert antimicrobial activity against *L. monocytogenes*, *H. pylori*, *S. typhimurium*, *E. coli,* and *Cronobacter sakazakii* (Chatterjee et al., 2004; Joshi et al., 2014; Lacombe et al., 2012; Park et al., 2011). Purple prairie clover (PPC) (*Dalea purpurea* Vent.) is a legume forage that contains high concentrations of condensed tannins. PACs isolated from PPC possess stronger anti-*E. coli* O157:H7 activity *in vitro* due to its capacity to increase the outer membrane permeability of *E. coli,* involving an alteration in the fatty acid composition and disruption of the outer membrane of the cell (Liu et al., 2013b; Wang et al., 2013). In particular Liu et al. (2013b), studied the anti-*E. coli* activity of condensed tannins from PPC and sainfoin. PPC condensed tannins completely inhibited *E. coli* and *E. coli* O157:H7 growth (MIC range: 20–40 μg/ml and 20–50 μg/ml, respectively). In contrast, the MIC for sainfoin condensed tannins was higher, ranging between 100 and 150 μg/ml. PACs act primarily as anti-*E. coli* compounds causing disruption in the bacterial outer membrane. PACs have also been shown to prevent adhesion and reduce biofilm production by a variety of pathogens including uropathogenic *E. coli* (Tapiainen et al., 2012), *P. aerugionosa* (Ulrey et al., 2014), *S. epidermidis* (Leshem et al., 2011) and oral pathogens (Koo et al., 2010; Polak et al., 2013; Yamanaka et al., 2007).

3. Conclusion

In the era of antibiotic-resistant "superbugs" the development of new antibacterial agents is very important and plant extracts are an attractive source for new drugs. Plant derived phytochemicals are often produced by plants as defensive molecules against pathogens. To date, more than 1000 different phytochemicals extracted from various plants, foods and beverages have shown interesting antibacterial, antifungal and antiviral activity against several human pathogens. The antibacterial activity of phytochemicals is a well-known phenomenon and in recent years, knowledge regarding these bioactive compounds has widely increased. Many mechanisms of antimicrobial action have been suggested. Generally phytochemicals cause damage to the bacterial membrane, suppression of some virulence factors, including enzymes and toxins, and inhibition of bacterial biofilm formation.

Some phytochemicals, besides having direct antimicrobial activity, have been reported to have antibiotic resistance modifying activities *in vitro* when used at low MIC levels and the synergistic effect of these compounds with conventional antibiotics could provide effective therapies against resistant bacteria.Currently available screening methods for the detection of the antimicrobial activity of natural products include qualitative techniques such as disk diffusion assays, and semi-quantitative or quantitative assay as dilution methods (broth micro and macro dilution). However, standardized methods for *in vitro* testing and established breakpoints to facilitate proper interpretation of results are missing. In conclusion, from this review it is clear that plant-derived phytochemicals represent a possible source of effective, cheap and safe antimicrobial agents. However, much work must still be conducted both *in vitro* and *in vivo* to ensure the selection of active and non toxic antimicrobial phytochemicals.

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