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Review

# Antimicrobial Activity of Natural Polyphenols

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**Abstract**

This paper deals with the antimicrobial activity of different polyphenols in fruits, vegetables, herbs, spices, and honey. Polyphenols are secondary metabolites which protect plants from different pathogens, such as viruses, bacteria, fungi, insects, and herbivores. They are divided into two main groups: simple phenols and phenolic acids. Flavonoids represent one of the most abundant groups of polyphenols. Polyphenols are usually metabolized in the human liver but can also remain unaffected as they pass through the gastrointestinal tract. They undergo certain biochemical transformations in the colon under the action of specific lactobacilli and bifidobacteria. Polyphenols are detected in numerous plants - olives, tomatoes, peppers, parsley, onion, garlic as well as in honey. Their amount differs significantly across different species and varieties. This landscape analysis of scientific literature summarizes the antibacterial, antiviral and antifungal activity of polyphenols. Polyphenolic extracts obtained at 80ºC show higher antibacterial activity compared to those extracted at 100ºC, while methanolic extracts possess greater activity than ethanolic ones. Selected herbs, fruits and vegetables rich in antimicrobial polyphenols are a source of highly effective novel antimicrobial substances.

**Резюме**

Тази статия разглежда антимикробната активност на различни полифеноли в плодове, зеленчуци, билки, подправки и мед. Полифенолите са вторични метаболити, които предпазват растенията от различни патогени, като вируси, бактерии, гъбички, насекоми и тревопасни животни. Те са разделени на две основни групи: прости феноли и фенолни киселини. Флавоноидите представляват една от най-разпространените групи полифеноли. Полифенолите обикновено се метаболизират в човешкия черен дроб, но също така могат да останат незасегнати, докато преминават през стомашно-чревния тракт. Те претърпяват определени биохимични трансформации в дебелото черво под действието на специфични лактобацили и бифидобактерии. Полифенолите се откриват в множество растения - маслини, домати, чушки, магданоз, лук, чесън, както и в меда. Количеството им се различава значително при различните видове и сортове. Този детайлен анализ на научната литература обобщава антибактериалната, антивирусната и противогъбичната активност на полифенолите. Полифенолните екстракти, получени при 80°C, показват по-висока антибактериална активност в сравнение с тези, екстрахирани при 100°C, докато метанолните екстракти притежават по-голяма активност от етанолните. Избрани билки, плодове и зеленчуци, богати на антимикробни полифеноли, са източник на високоефективни нови антимикробни вещества.

## Introduction

The widespread antibiotic resistance has become a severe global problem. This has directed scientists' attention to the search of new antimicrobials from powerful natural sources. Plants and their metabolites are a promising source of novel antimicrobial molecules. One group of plant metabolites - polyphenols exert strong antimicrobial and antioxidant effect at very low concentrations. Phenol is known as an aromatic compound which contains a phenyl ring with one hydroxyl group. Polyphenols consist of one or more aromatic rings and several hydroxyl groups. They play an important role in the defense of plants against bacteria, viruses, fungi, insects and herbivores. Polyphenol synthesis derives from two aromatic amino acids - tyrosine and phenylalanine. As secondary plant me-

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tabolites, their amount is estimated around only 10 % of the plant metabolites (Othman, 2019).

Among the 300 000 plant species that exist in the world only 15% have been investigated for their pharmacological potential, the rest of them are a potential source of new natural antimicrobial products (de Luca *et al*., 2012). According to the WHO, the global market of plant products is estimated at the huge amount of US $83 billion and currently continues to grow (WHO).

the beneficial intestinal bacteria. In this way, they significantly improve human health (Abbas, 2017). According to their chemical structure, polyphenols are divided into simple phenols and phenolic acids, shown in Fig. 1. Currently, more than 9 000 flavonoids have been identified.

*Salicylic acid* (2), an ortho-hydroxylated benzoic acid, is a beta hydroxy acid that occurs as a natural compound in plants. It is highly active as an anti-inflammatory agent and is a proven antibacte-

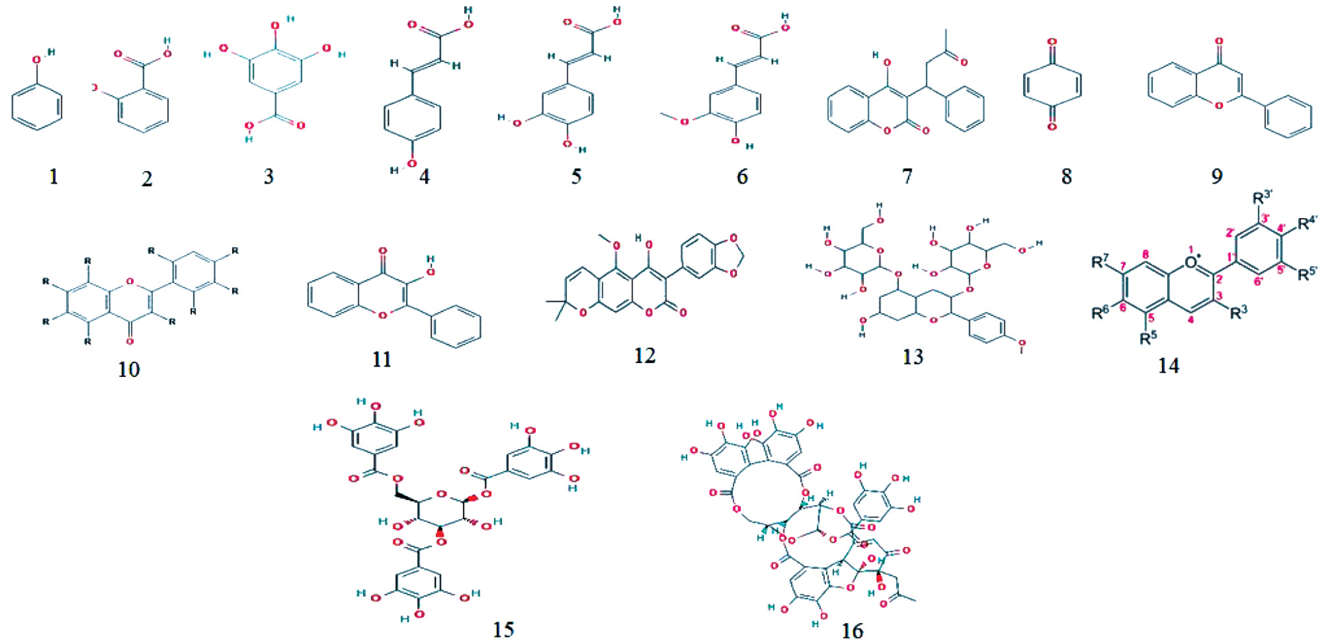


**Fig. 1.** Chemical structure of polyphenols: 1 - Phenol ($C_6H_5OH$); 2 - 2-Hydroxybenzoic acid (Salicylic acid) ($HOC_6H_4COOH$); 3 - 3,4,5-Trihydroxybenzoic acid (Gallic acid) ($C_6H_2(OH)_3COOH$); 4 - 4-Hydroxycinnamic (p-Coumaric acid) ($C_9H_8O_3$); 5 - 3,4-Dihydroxycinnamic acid (Caffeic acid) ($C_9H_8O_4$); 6 - 4-Hydroxy-3-methoxycinnamic acid (Ferulic acid) $(C_{10}H_{10}O)_4$; 7 - 4-hydroxy-3-(3-oxo-1-phenylbutyl)chromen-2-one, Warfarine (Coumarins) ($C_{19}H_{16}O_4$); 8 - 1,4- Benzoquinone (p-Benzoquinone) (Quinone)($C_6H_4O_2$); 9 - 2,3-Dihydroflavone (Flavanone) ($C_{15}H_{12}O_2$); 10 - 2-Phenyl-4H-chromen-4-one (Flavone) ($C_{15}H_{10}O_2$); 11 - 3-Hydroxy-2-phenyl-4H-chromen-4-one (Flavonol) ($C_{15}H_{10}O_3$); 12 - 7-(1,3-benzodioxol-5-yl)-6-hydroxy-5-methoxy-2,2-dimethylpyrano[3,2-g]chromen-8-one (Robustin) (Isoflavonoid) ($C_{22}H_{18}O_7$); 13 - 2-(4-Hydroxyphenyl)chromenylium-3,5,7-triol (Pelargonidine) (Anthocianidine) ($C_{15}H_{11}O_5^+$); 14 – Anthocianins; 15- 1,3,6-tri-O-galloyl-beta-D-glucose (Gallotanin) (Tanins) ($C_{27}H_{24}O_{18}$); 16 - Galloyl 3-O,6-O-[(4,4',5,5',6,6'-hexahydroxy-1,1'-biphenyl)-2,2'-diylbiscarbonyl]-2-O,4-O-[[[(4aS)-3,4,4a,9balpha-tetrahydro-3-oxo-4-(2-oxopropyl)-4beta,4aalpha,6,7-tetrahydroxydibenzofuran]-1,9-diyl]dicarbonyl]beta-D-glucopyranoside (Elagitannin) (Tannins) ($C_{44}H_{32}O_{27}$) (Source of figures and short description of substances below - Pubchem)

A wide spectrum of plant secondary metabolites can be obtained *via* aqueous or alcoholic extracts. Both extracts contain high concentrations of flavonoids and polyphenols. Once inside the body, phenol is retained in the human body bound to other molecules, most often to proteins. Absorbed or unabsorbed, while passing through the gastrointestinal tract, polyphenols strongly influence human microbiota. As described earlier, polyphenols inhibit gastrointestinal pathogenic bacteria and enrich

rial agent due to its ability to promote exfoliation. Salicylic acid has been found in human liver and skin tissues, and has also been primarily detected in saliva, feces, urine, and blood. Salicylic acid exists in all eukaryotes, ranging from yeast to humans. Salicylic acid tastes like phenol and is found in different foods such as cereals and cardamom.

*Gallic acid* (3), also known as gallate, belongs to the class of organic compounds known as gallic acids. It is an organic compound that contains 3, 4, 5-trihydroxybenzoic acid. Gallic acid is detected in feces, urine, and blood. Gallic acid also exists in all eukaryotes, ranging from yeast to humans. In addition to the human body, gallic acid can be found in a number of foods, such as apple, ginger, and yellow pepper. Gallic acid is known as a strong antioxidant.

*Hydroxycinnamic acids* (4) contain cinnamic acid, where the benzene ring is hydroxylated at C-4. Similarly, to gallic acid, they can be detected in human feces, urine, and blood. Inside the cell, hydroxycinnamic acids are compounds of the cytoplasm and mitochondria. Trans-4-coumaric acid, which is present in all eukaryotes, is widespread. The following plants are a source of this acid: green pepper, apricot, and blueberry.

*Caffeic acid* (5) is a polyphenol, a hydroxycinnamic acid derivative. It exhibits antioxidant, anti-inflammatory, and antineoplastic activities. It prevents oxidative stress leading to prevention of DNA damage caused by free radicals. Caffeic acid inhibits the histone demethylase (HDM) oncoprotein gene, which is amplified in squamous cell carcinoma 1 and inhibits cancer proliferation. In the human body, it was extracted from human epidermis and prostate tissues. It is also found in the blood, feces and urine. Along with its beneficial effect, caffeic acid is classified as a possible carcinogen (IARC classification of cancerogenic xenobiotics - Group 2B) and toxic compound.

*Ferulic acid* (6), known also as ferulate, consists of trans-cinnamic acid bearing methoxy and hydroxy substituents at positions 3 and 4, respectively, on the phenyl ring. The name is derived from the genus *Ferula*, referring to the giant fennel (*Ferula communis*) but the ferrulic acid is ubiquitous in the plant kingdom. Root vegetables, barley, flaxseeds, cooked sweetcorn andmolluscs are rich in ferulic acid. Ferulic acid is a component of lignocellulose, cross-linking lignin. It plays the role of an antioxidant, anti-inflammatory agent, and an apoptosis inhibitor. Ferulic acid is known as a cardioprotective, skin anti-aging substance, and food preservative. Ferulate can be found in the human epidermis tissue, in the blood and urine.

*Warfarin* (7) belongs to the class of 4-hydroxycoumarins and is a synthetic oral anticoagulant. Warfarin inhibits the synthesis of vitamin K dependent clotting factors, which include Factors II, VII, IX and X, and the anticoagulant proteins C and S. Vitamin K is an essential cofactor for the post ribosomal synthesis of the vitamin K dependent clotting factors. The vitamin promotes the biosynthesis of gamma-carboxyglutamic acid residues in these proteins, which are essential for biological activity. Warfarin is a drug which is used for the treatment of pulmonary embolism, cerebral embolism, cerebral ischaemia, arterial embolism and thrombosis. Warfarin is considered to be insoluble in water. It is detected in the human blood and urine. In the cell, it is located in the membrane.

1,4-*Benzoquinone* (8) is the simplest member of the class of 1,4-benzoquinones, a metabolite of benzene. Quinone, also known as benzoquinone or 1, 4-benzoquinon, belongs to the class of organic compounds known as p-benzoquinones. These are benzoquinones, where the two C=O groups are attached at the 1- and 4-positions, respectively. Soluble in water, it has been found in most human tissues and is primarily detected in the urine. Mitochondria and the cytoplasm are the cell structures harboring quinone. Quinone takes part in many enzymatic reactions. In particular, quinone and L-dihydroorotic acid can be converted into orotic acid. A buildup of orotic acid can lead to orotic aciduria due to metabolic disorders leading to higher release of ammonia. Moreover, quinone and dihydroxyacetone phosphate can be converted into glycerol 3-phosphate and hydroquinone-metabolites of glycolysis. Quinone is also responsible for the metabolism of many carbohydrates which is catalyzed by the mitochondrial enzyme glycerol-3-phosphate dehydrogenase. In humans, quinone is involved in riboflavin (Vit. B12) metabolism. Anise, barley, and olive are sources of quinone.

*Flavanone* (9) is the simplest member of the class of flavanones that consists of flavan bearing an oxo substituent at position 4. Flavone is a flavonoid lipid molecule and is practically insoluble in water. This compound has been found in human prostate, spleen, and placenta tissues. In the cell, flavone is generally located in the membrane. Flavone is a bitter-tasting compound that can be found in pomegranate, rosemary, and dill.

3-*Hydroxyflavone* (10), also known as flavon-3-ol, belongs to the class of organic compounds known as flavonols. It is insoluble in water and located in the cell membrane within the cell. 3-hydroxyflavone is a precursor of tambulin – an anti-aging and anti-Parkinsonian compound. Foods rich in this substance are brassicas, tea, fenugreek and papaya.

Another derivative of flavone is *Flavonol* (11), a monohydroxyflavone or 3-hydroxy derivative of flavone.

*Pelargonidin* (13) can be found in almost all berries - blueberries, blackberries, cranberries, raspberries, strawberries, and aronia. Large amounts of pelargonidin aretypically found in plums and pomegranates, and it is also responsible for the color of radishes.

*Gallotannins* (15) is a class of tannins obtained by condensation of the carboxy group of gallic acid and the hydroxy group of glucose.

**Antimicrobial activity of selected herbal polyphenols**

As it is known, the Mediterranean diet is rich in polyphenols. In the last decade, a few Mediterranean herbs containing polyphenols have been reported to demonstrate antibacterial activity against *B. subtilis.* Shehadi *et al.* (2014), described the plants rosemary (*Rosemary officinalis*), cloves (*Eugenia caryofillata*), mint (*Menta piperita*), and wild cherry (*Prunus avium*) according to their antibacterial activity. The strongest effect among them was shown by the extracts of cloves (1,6 mg/ml) and wild cherry (4 mg/ml). An interesting finding of the authors is that the effectiveness of the extracts depends on the temperature they are obtained at. Extracts obtained at 100$^{o}$C showed lower inhibitory effect (0.6 and for cloves and 2.4 mg/ml for wild cherry, respectively)

Other authors (Alamni and Mustafa, 2012) reported the antibacterial activity of the castor oil plant (*Ricinnus communis* L.), and leek (*Allium ampeloprasum* var. *porrum* L.) against nine types of bacteria – *P. aeruginosa, Staphylococcus aureus*, *S. epidermidis*, *E. coli*, *Acinetobacter* sp.*, Klebsiella pneumonniae*, *Proteus* sp., *Micrococcus* sp., and *Bacillus* sp. of the two plants, *R. communis* exhibited higher antibacterial activity. At a concentration of 20 mg/ml, its ethanolic leaf extract margined a wider inhibition zone of 27 mm while the extract of *A. ampeloprasum* reached 23 mm inhibition zone. Among the tested bacteria, the highest activity was demonstrated against the Gram (-) *P. aeruginosa* (Gamma-Proteobacteria) and against the Gram (+) *Micrococcus* sp. (*Actinobacteria*). As described by the authors, HPLS analysis confirmed the presence of five phenolic compounds in these plants: phenolic acid, cinnamic acid, p-coumaric acid, ferulic acid as well as sinapic acid and catechin, all representatives of polyphenols.

Interesting data on the treatment of resistant bacteria MRSA strains using ethanolic exract of *Syrium propolis* were reported by Harfouch *et al.* (2016). The ethanolic extract, abundant in phenolic acids, phenolic aldehydes, flavonoids and quinones, was also able to inhibit the growth of the causative agent of nosocomial infections *Acinetobacter baumanii*.

Another polyphenol-containing plant – the golden chamomile *Martricaria aurea* L., a typical Saudi Arabian herb, was reported to exhibit activity of its methanolic extract against *Bacillus subtilis* (25 mm) followed by *Streptococcus pyogenes* (23 mm), *S. aureus* and *K. pneumoniae* (both, 21 mm). Comparing the activity of both methanolic and ethanolic extracts of the herb, the authors (Rizwana *et al*., 2016) found that the methanolic extract possesses greater activity than the ethanolic one. Using scanning electron microscopy, cell damage and destruction of bacteria was observed after implementation of polyphenolic extracts. GS-MS analysis has proven the presence of phenols and phenolic acids, as described by the authors.

Many Bulgarian medicinal plants have also been reported to contain high polyphenol contents (Ivanova *et al*., 2005). In this paper, the authors have proved that Bulgarian plants contain significantly higher amounts of polyphenols than foreign plants. In this study, seven local plant species were investigated: *Hypericum perforatum* L. (Hypericaceae), *Agrimonia eupatoria* L. (*Rosaceae*), *Origanum vulgare* L. (*Lamiaceae*), *Melissa officinalis* L. (*Lamiaceae*), *Rubus* sp. *diversa* (*Rosaceae*), *Cotinus coggygria* Scop. (*Anacardiaceae*). In their investigation, the authors found a link between the high-phenolic content and the high antioxidant activity.

Another Bulgarian research group, Ivancheva *et al*. (1992), reported the anti-infectious activity of Bulgarian medicinal plants. The examined extracts were effective against both Gram-negative bacteria (*K. pneumoniae*, *P. vulgaris*, *E. coli*, *P. aeruginosa*) and the Gram-positive bacterium (*S. aureus*), and against the fungus *Candida albicans*.

Due to its polyphenol content, parsley also demonstrates antibacterial properties. Papuc K. *et al.* (2016) announced the presence of several classes of polyphenols in parsley, especially flavonoids. The major flavonoids are flavonnols (kaempferol and quercetin) and glycosylated flovones (apigenin and luteolin). The reason for the sanogenous effect is due to the high flovonoid content (100 mg/100 g fresh weight). This herb is known for its high antioxidant ability; it is a proven scavenger of free radicals and blood-improver. Tomov *et al.* (2015) examined the antibacterial activity of fresh chopped parsley but it showed weak antibacterial activity.

The antimicrobial activity of phytochemicals against *S. epidermidis* was described in detail by Zou *et al.* (2019). The antimicrobial activity of lavandula phenolic extract was found by a Moroccan research team (Es Zoubi *et al*. 20). The authors reported that lavandula inhibits the growth of a clinical isolate from a Moroccan hospital. Georgiev *et al.* (2009) reported on the antoxidant activity of *Lavandula vera* as well. Mihajlova *et al.* (2014) describes the phenolic profile and the antibacterial activity of mallow (*Malvia silvestris*).

**Antimicrobial activity of selected fruit and vegetable polyphenols**

In addition to herbs, phenol-containing fruits have also been estimated and proven to be active against many bacterial pathogens. Such data were supplied for pomegranate (*Pommes granatum* L.). Pomegranate juice is known for its rich polyphenol content, including caffeic acid, gallic acid and epigallocatechin, which is also the main component of green tea. Divyarhree and Kunniah (2014) examined the hydrochloric extract on the microorganisms inhabiting the dental plaque. The authors found that the extract was active against *Porphyromonas gingvinalis*, the Gram (-) putative anaerobe *Prevotella intermedia,* and the facultative anaerobe *Aggregatibacter actinomycetemcomitans*, a small fastidious Gram (-) coccobacillus, all causing aggressive periodontitis.

Remarkable Mediterranean fruits rich in polyphenols are olives (*Olea europea*). The main phenolic component in olives responsible for their health beneficial effect is hydroxytyrosol (Gorzinik-Debicka *et al.*, 2018). Hydroxytyrosol is a superior antioxidant and radical scavenger, which induces apoptosis and arrests the cell cycle in cancer cells. Hydroxytyrosol demonstrated antimicrobial activity (Tuck *et al*., 2002) and is renally excreted *via* many metabolites as glucuronide conjugate, sulfate conjugate, homovalliic acid, and 3,4 – dihydrophenylacetaldehide. Along with hydroxytyrosol, other phenolic compounds in olives are tyrosol, the bitter olive glycoside oleuropein, oleocanthal and oleacein.

The antimicrobial activity of the polyphenols containing *Sida alba* was also proven by phytochemical and pharmacological studies Konate *et al*. (2012). The antimicrobial activity of fruit extracts was reported by Marinova *et al.* (2005), who examined more than 20 fruits for their polyphenolic content. Their results showed a high number of phenols in the studied fruits. Vilhelminova-Ilieva and Galabov (2017) presented an overview on tannins and their biological role, reporting data on the antibacterial effect of tannins as polyphenols. Some ambivalent results were published by Docheva *et al.* (2018) discussing the tobacco plant as rich in polyphenols and its antioxidant activity.

Interestingly, polyphenols act synergistically in combinations with antibiotics against resistant pathogenic bacteria as described in the review on polyphenols published by Daglia (2012), Mojzer *et al.* (2016). In the same paper, the authors discussed the role of polyphenols as active agents against human pathogens, acting directly on the pathogenic microorganisms, inhibiting the virulence factors.

Green tea is also rich in polyphenols and possesses a strong antimicrobial effect (Gopal *et al.*, 2016). Some authors report the AB activity of tomatoes. Tomatoes rank second in world consumption among all vegetables (Marti *et al*., 2016). Our previous research (Tomov *et al*., 2015) showed no significant difference between raw and cooked tomato products against bacteria. The antibacterial effect (up to 7 mm zone) was not a strong one compared to the antibacterial effect of garlic and onion. Interestingly, the tomato seeds of two out of six tomato varieties slightly inhibited the growth of *B. subtilis* but showed no antibacterial activity against *E. coli*. The inhibition zones were 4 mm to 7 mm diameter. These results coincided with the results obtained by Unnisa *et al.* (2012), who reported low antibacterial activity of tomato fruit against *E. coli*.

Onions are a vegetable with strong antimicrobial activity. The antibacterial activity of garlic (*Allium sativa*) was studied by Chen *et al.* (2013), Tomov *et al*. (2015) and Obied *et al*., (2018). It possesses pronounced antibacterial activity and reaches a 30 mm zone against *B. subtilis* (7 mm) and *E. coli* (30 mm) as described by Tomov *et al.* (2015). *A. cepa,* however, also rich in polyphenols like garlic, showed lower antibacterial activity in comparison to garlic (Tomov *et al.,* 2015) against the tested strains. *A. ursinum* and its polyphenols were studied by Myhaylova *et al.* (2012). Santas *et al*. (2010) described *Allium* extracts to be more effective against Gram-positive microorganisms, while Gram-negative bacteria were reported to be less susceptible. Ramos (2006) discussed the water extracts from yellow onion skin and found that even onion skin is active against Gram (-) bacteria. An interesting finding summarized from the literature is that the synthesis of antibacterial substances in onions occurs intensively in the mature onion and garlic, not in the green ones, and continues at room temperature (22$^{o}$C), ending at refrigerator temperature.

As a matter of fact, two flavonoid classes are mainly found in onion – anthocyanins and flavonols. Anthocyanins impart the red color of some varieties. Flavonols as quercetin and its derivatives deliver yellow and brown onion skin. It has been reported that 25 different flavonols were phythochemically determined in the onion. Among these flavonols, quercetin was the single one found in all onion varieties. Two flavonol molecules - quercetin 4'-glucoside and quercetin 3,4'-glucoside account for about 80% of total flavonols in the onion.

Cayenne pepper is known for its high phenol content (Hamed *et al.*, 2019). Chili peppers lead the ranking of antimicrobial activity, as shown by (Omolo *et al.*, 2014). Our investigations (Tomov *et al*., 2015) on Cayenne pepper fruits and seeds showed inhibition of the growth of both *E. coli* and *B. subtilis*. Pepper tissues displayed no antibacterial activity but cayenne pepper discs showed antibacterial activity against both *E. coli* (25 mm zone) and *B. subtilis* (24 mm zone). Interestingly, similarly to tomatoes seeds, pepper seeds exhibited inhibition zones of 11 mm against *E. coli* and 7 mm against *B. subtilis*. The results of Mariângela *et al.* (2011), Koffi-Nevri *et al.,* (2012), and Nascimento *et al.* (2014) describe similar activity of the capsicum fruit against both Gram (+) and Gram (-) bacteria.

A widely used substance of animal origin, propolis, has been described to possess broad-spectrum antimicrobial activity against many bacterial strains and microscopic fungi. Its phenolic content was examined by Cianciosi *et al.* (2012).

## Conclusions

Selected herbs, fruits and vegetables contain high polyphenol concentrations. They show pronounced antimicrobial activity acting against a plethora of pathogenic bacteria, viruses and fungi, especially against resistant ones described in this paper. Plant polyphenolic extracts obtained at 80 ºC possess higher antibacterial activity compared to those extracted at 100ºC, while the methanolic extracts possess a greater activity than the ethanolic ones. Due to their antimicrobial activity, selected herbs, fruits and vegetables rich in antimicrobial polyphenols are sources of highly effective novel antimicrobial substances.

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