SPECIAL GUEST EDITOR SECTION

Phenolic Substances in Foods: Health Effects as Anti-Inflammatory and Antimicrobial Agents

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Background: **The interest in phenolic compounds present in foods of vegetable origin has shown a notable increase in recent decades. This interest is due to the growing number of scientific studies concerning their beneficial role in human health. The interest in polyphenols has been supported by the current and growing awareness, and attention of consumers to food from a food safety viewpoint and also because of the beneficial effects ascribed to polyphenols.** ***Objective:*** **The aim of this article is to highlight antibacterial, antifungal, and anti-inflammatory activities of various phenolic compounds normally found in certain foods.** ***Conclusions:*** **Phenolic compounds exert different biological functions, such as antioxidant activity, modulation of detoxifying enzymes, stimulation of the immune system, reduction of platelet aggregation, modulation of hormonal metabolism, reduction of blood pressure, and anti-inflammatory, antibacterial, antiviral, and antifungal activities.**

In the recent years, consumers have developed a growing interest in the wholesomeness of food. The current trend concerns foods that are not only nutritious but also active in the protection of human health because of enrichment in bioactive secondary metabolites. In this regard, the concept of functional food refers to foods that are provided with one or more compounds useful for the prevention or treatment of certain diseases, often pathologies with a strong social impact. Since the 1990s, particular attention has been paid to phenolic compounds present in plant foods. This phenomenon is due to the growing number of scientific studies that signify the benefits of these compounds for human health. A boost to research has also been given by the food industry through the production of supplements or additives.

This trend has determined a profound change in the study of natural products. The interest of the scientific world has been strongly motivated by the applicability and bioactivity of these substances in different ambits, including the medical and biological, nutraceutical, alimentary, veterinary, and feed sectors. At the same time, an interdisciplinary network was born in recent years, perhaps unique in the scientific world, that developed from the considerable increase in experimental studies on molecules of various origins that have contributed to the knowledge of their versatile and multifaceted properties (1–4).

Polyphenols include a wide variety of compounds, present in foods of plant origin, with evident in vitro and in vivo antioxidant properties. Most of their biological activities have been attributed to the capacity to act as reducing agents. Animals and humans have taken advantage of the availability of antioxidant substances present in vegetable foods, which support the functioning of antioxidant enzymes, as well.

In fact, polyphenols present in foods of vegetable origin, such as fruits, vegetables, oils, and other foods made from tea, cocoa, and grapes, constitute a very large and heterogeneous group

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that can be broadly divided into classes such as hydroxybenzoic acids, hydroxycinnamic acids, stilbenes, lignans, and flavonoids. In turn, flavonoids can be further divided into various subclasses such as anthocyanins, flavonols, flavones, flavanols, flavanones, and isoflavones.

In food products, phenolic compounds are mainly found in the form of glycosides linked to a sugar molecule, especially in leaves, flowers, fruits, and seeds. Aglycones, molecules without sugar, are ubiquitous, especially in woody tissues and seeds. The content of phenolic compounds in plant tissues varies depending on the particular species, variety, organ, physiological stage, and pedoclimatic conditions and from plant to plant within a population.

Phenolic compounds are preferentially accumulated in air organs rather than in the roots and more in the epidermal and subepidermal layers of the plant because of the light-inducing effect on the phenolic metabolism. Lignin, the most abundant organic substance in plants after cellulose, is the exception to the rule, representing the only phenolic compound that accumulates in plant roots (5).

The different biological activities ascribed to polyphenols are linked not only to the heterogeneity of these molecules and to their structural and functional characteristics but also to how these compounds are absorbed and metabolized in the gastrointestinal district. The oral cavity and the gastrointestinal tract play a significant role in the conjugation of polyphenols before they arrive in the circulatory system and in the liver. There, polyphenols undergo different chemical transformations leading to the formation of metabolites with their own biological activity. In saliva, flavonoid glycosides are hydrolyzed to aglycones and turned into compounds that can be absorbed by the oral cavity. In the stomach, there is the reduction of polyphenols to monomeric units. In the small intestine, and subsequently in the liver, the real transformation takes place in two phases: (*1*) deglycosylation and aglycone formation and (*2*) transformation through oxidative metabolism by the enzymes belonging to the cytochrome P450 family or metabolic transformations leading to the formation of methylated, sulfated, and glucuronidated products but also to the opening of the aromatic ring. Further transformation occurs in the colon, where microflora degrade flavonoids to simple phenolic acids, which are then absorbed and metabolized in the liver.

Currently, nutritional epidemiology has made considerable progress, demonstrating that a high consumption of foods of plant origin is inversely related to the incidence of many diseases, such as cardiovascular, metabolic, neurovegetative (e.g., hypersomnia, hyperphagia, weight gain, etc.), and inflammatory diseases.

Essential nutrients present in the plant kingdom alone cannot be responsible for these beneficial effects on humans. They are, in fact, assisted by other substances that perform powerful biological activities as well as essential proteins, fats, carbohydrates, and micronutrients such as vitamins and minerals. These substances are phytochemicals and include thousands of molecules belonging to various chemical classes. This extremely inhomogeneous set includes some common characteristics: they are products of the secondary metabolism, and, in addition, they have complementary and overlapping mechanisms of action. These compounds have different biological functions, such as antioxidant activity, modulation of detoxifying enzymes, stimulation of the immune system, reduction of platelet aggregation, modulation of hormonal metabolism, reduction of blood pressure, and antibacterial, antiviral, and antifungal activities (6).

In this article, we want to highlight antibacterial, antifungal, and anti-inflammatory activities of various known phenolic compounds.

Antimicrobial Properties

Antimicrobial properties of phenolic compounds are widely reported in the literature, with a large number of studies demonstrating the existence of a correlation between phenols and antimicrobial power. This activity, carried out against bacteria, viruses, or fungi, is now, more than ever, an interesting field of study that is potentially able to offer new antibiotic therapies (antiviral, antifungal, and alternative strategies) relevant in cases of antibiotic resistance or antiviral therapies, as well as revolutionary methods for food preservation, replacing artificial preservatives (7), thus representing a valuable innovation for the pharmaceutical and food industries.

Antibacterial Properties

The antibiotic activity of phenolic compounds can be carried out on a wide range of bacterial microorganisms, modifying the structure, the pathogenic capacities, or the metabolism of the germ, thus giving rise to the bactericidal or bacteriostatic action.

Various studies published on the subject represent a wide range of possible mechanisms by which these compounds are able to exert their antibiotic power. However, at the base of these processes, there seems to be a single main activity carried out by the phenols: protein and enzymatic inactivation carried out mainly by tannins and flavonoids (8–10), which are capable of inactivating membrane proteins like adhesins and transport proteins (11). This is possible because of the formation of weak bonds (such as hydrogen or covalent bonds) between the phenolic compound and membrane proteins of the bacterium (12–17).

However, such protein inactivation, responsible for the antibiotic function of the phenolic compounds, can be implemented on various pathogenic bacteria structures, thus giving different outcomes.

The main observed and reported effects are as follows: (*1*) reduction of adhesion capacity to substrates, mainly carried out by phenolic acids and tannins (5, 8), which, by binding to membrane proteins, prevent the bacterium from adhering to the mucous membranes (such as oral cavity and urinary tract) and, therefore, alter the infectious process; (*2*) alteration of the cell membrane and lysis, mainly carried out by phenols and flavonoids that alter the bacterial structure and determine cell death by binding to membrane proteins (9, 18); (*3*) closure of ionic channels, mainly carried out by flavonoids that bind to membrane proteins and alter the metabolism of the bacterium, causing damage and cell death (19); (*4*) complexes of metal ions, mainly carried out by phenols and tannins that, by binding to membrane proteins, alter the metabolism of the bacterium, causing damage and cell death (8, 20); and (*5*) inhibition of energy metabolism, mainly carried out by tannins and flavonoids that bind to intra- or extracellular protein structures, inhibiting oxidative phosphorylation or the production of adenosine triphosphate, resulting in cell death (20, 21).

However, despite these processes involving many species of bacteria, it is important to note that the efficacy of antibiotic action differs between Gram-positive and Gram-negative forms of bacteria. In fact, the latter are more resistant precisely because of their peculiar structure, in which we observe the presence of a lipopolysaccharide external to the bacterial membrane, eliciting a strong protective function (8, 22, 23).

A multitude of species belonging to the plant kingdom have one or more phenolic compounds in their biochemical composition. Among these, some plants clearly show antibacterial power, attributed in some cases to the presence of the phenols, which are reputed to be the creators of this action. This phenomenon is particularly interesting, as it allows humans to easily come into contact with natural antibiotics, e.g., through feeding. For example, it is possible to cite some plants (and derived foods) provided with phenolic compounds to which antibiotic power has been attributed.

First of all, given their peculiarity, are algae, and specifically brown algae, which are edible and widely used in Asian cuisine and rich in phlorotannins. Examples are *Ecklonia cava* and *E. stolonifera* (24, 25). Some species of edible mushrooms, such as *Lactarius deliciosus*, *Sarcodon imbricatus*, and *Tricholoma portentosum* (26), can be also considered.

Plant organisms have also been extensively studied for their antibacterial power, particularly some species of edible medicinal plants used by various populations in the field of traditional medicine for various purposes (from the treatment of enteritis to oral hygiene) as infusions, oils, or seasonings and flavorings. Examples are *Salvia officinalis* and *Thymus vulgaris*, *Sida acuta*, *Ocimum sanctum*, *Hypericum perforatum*, and *Pulicaria odora* (27–31).

With respect to aromatic plants, which are also used in Mediterranean cuisine, the following species can be mentioned: some species of chili (*Capsicum annuum*), garlic (*Allium roseum* var. Odoratissimum), basil (*Ocimum gratissimum*), oregano (*Origanum vulgare*), pepper (*Piper nigrum*), parsley (*Petroselinum crispum*), rosemary (*Rosmarinus officinalis*), and myrtle (*Myrtus communis*; 32–39).

Even some portions of trees, such as bark, leaves, fruits, or roots, show the same properties. Examples are *Ginkgo biloba*, *Bridelia retusa*, and *Magnolia grandiflora* as well as some fruit plants whose products are used in the kitchen, such as chestnut (*Castanea sativa*), date palm (*Phoenix dactylifera*), *Crataegus azarolus*, and moscatina (*Vitis rotundifolia*; 40–46).

Moreover, even some edible tropical species whose leaves, flowers, roots, or fruits are used for infusions, jams, or as food have the aforementioned capacities. This is the case for *Murraya paniculata*, *Grewia asiatica*, *Eugenia jambolana*, *Carissa caranda*, *Spondias mombin*, and *Manihot utilissima* (34, 47–49).

Furthermore, some fruits with antibacterial activity should be mentioned. Examples are berries, which represent an interesting category of plant products, being edible and widely used for food. These include strawberries and berries such as red raspberry, some varieties of blueberry, blackcurrant, raspberry, sorb, empetrum, eleagnus, and blackberry (50–56). Likewise, it is also possible to mention several fruits in common use, including cherries, figs, pomegranates, dates, some varieties of grapes, and apples (such as Golden Delicious), as well as tropical fruits such as persimmon, guava, and sweetsop (57–66). Also, some edible vegetables used in traditional cooking demonstrate the same activity, such as artichoke, kale, tomato, radish, soy, fennel, and Chinese potato (*Plectranthus rotundifolius*; 67–73). Finally, even some edible flowers used in traditional Asian cuisine as spices, vegetables, or preparations for infusions show the same properties, such as *Sesbania grandiflora*, *Rosa damascena*, and pomegranate flowers (*Punica granatum*; 74–76).

In conclusion, having so far treated only plants in possession of phenolic compounds with antibiotic power, the discussion should concern some products deriving from such plants. These substances are widely used in the culinary tradition of some peoples. Among these foods, we remember above all cocoa, honey, oil, tea, and wine as most relevant.

The olive tree (*Olea europaea*) is a fruit tree that boasts antibacterial activities presumably related to the presence of phenolic compounds. Both leaves and fruits contain various phenolic compounds (oleuropein, rutin, vanillin, and caffeic acid) that show antibiotic capacity against some bacteria, such as *Staphylococcus aureus*, *Escherichia coli*, *Salmonella enterica*, and *Bacillus cereus* (77–82). However, it is extremely interesting to observe that some derivatives of the olive tree, especially olive oil, also have a remarkable antibiotic power attributed to the presence of some phenolic compounds (such as oleuropein, leuteolin, ferulic acid, and cinnamic acid), which can explain their useful effects against some bacterial microorganisms, such as *E. coli*, *S. enterica*, *Listeria monocytogenes*, and *Helicobacter pylori* (83–85).

Other foods produced from the vegetable kingdom show the same capacity. For example, there are many varieties of honey in which some phenolic compounds have been found to be present, mainly flavonoids and phenolic acids capable of causing damage to bacteria such as *E. coli*, *Staphylococcus lentus*, and *Klebsiella pneumoniae* (86–89).

Another derivative is wine. This drink, obtained from multiple grape varieties, has phenolic compounds (rutin, quercetin, vanillic acid, gallic acid, and caffeic acid) that, in various studies, seem to be associated with the antibacterial capacity observed against a large slice of microorganisms such as *E. coli*, *Serratia marcescens*, *Proteus mirabilis*, *K. pneumoniae*, *Pseudomonas aeuruginosa*, *Moraxella catarrhalis*, *Enterococcus faecalis*, *S. aureus*, *Streptococcus agalactiae*, and *Streptococcus pneumoniae* (90–93). Finally, cocoa also appears to be a potential helper in the fight against bacterial infections, being able, thanks to its phenolic compounds, to damage some bacteria, such as *E. coli* (94).

Antifungal Properties

In recent decades, there has been a worldwide increase in the incidence of fungal infections, just as an increase in the resistance of some species of fungi to different fungicides used in medical practice has been observed. The significant increase in fungal opportunistic infections has been observed especially in patients treated with immunosuppressive drugs or with chemotherapeutics or in people with acquired immune deficiency syndrome.

Candida albicans is the most frequent cause of opportunistic infections in humans and is responsible for a variety of pathological manifestations ranging from superficial skin lesions to disseminated infections. The discovery of fungicidal drugs has allowed the eradication of many fungal infections, but the prolonged or inadequate use of the therapies has led to the establishment of strains of drug-resistant *C. albicans*. The spread of multiresistant fungal strains and the small number of available drugs have made it necessary to discover new classes of antifungals and compounds that inhibit these resistant mechanisms. The increase in fungal resistance to classic drugs, their toxicity, and high treatment costs justify the search for new strategies. This situation has led to the search for therapeutic alternatives, particularly among medicinal plants and isolated compounds for their empirical antifungal properties. In these natural sources, a series of molecules have been found with antifungal activity against different fungal strains, which are of great importance for humans and plants.

There is a great demand for new antifungal drugs belonging to a wide range of structural classes that act selectively on new targets with fewer side effects. Medicinal plants are important not only for millions of people for whom traditional medicine is the only health care opportunity and for those using plants for various purposes in their daily lives but also as a source of new drugs (95, 96).

The use of medical herbs represents a long history of human interaction with the environment. Plants used in traditional medicine contain a large variety of substances that can be used to treat different infectious diseases. Natural products, both as pure compounds and as standardized plant extracts, provide an unlimited number of opportunities for the creation of new drugs because of the availability of unparalleled chemical diversity. A large number of studies have been carried out on the antifungal activity of natural phenolic compounds, namely simple phenolic compounds, flavones and related flavonoid glycosides, coumarins, and anthraquinone derivatives.

Essential oils represent one of the most important groups of compounds of natural origin because of their high antimicrobial power, recognized since ancient times. Essential oils have a broad spectrum of antimicrobial activity, attributable in most cases to the high content of terpenes. To increase the efficacy of synthetic antifungal drugs, it could represent a winning strategy to combine them with essential oils. Several studies have been directed in this direction; in many cases, a synergistic effect has been demonstrated, as, e.g., with thyme essential oil in association with amphotericin B or fluconazole and nystatin in association with essential oregano oil. In both associations, a synergistic effect was obtained, thus allowing the reduction of drug doses to a minimum amount and also reducing toxic and/or side effects of antifungal drugs. Moreover, this strategy appears to substantially lower the costs of medical treatments (97).

The antifungal efficacy of some foods, such as honey, garlic, tea, and turmeric, and some extracts of essential oils is extremely interesting and widely reported. There are many findings found in nature, from simple foods to medicinal herbs, that express an antifungal power suitable for any fungal infection. Starting from the diet, the first advice is to reduce sugars in the diet because the proliferation of mycosis is stimulated by the high presence of these elements in the blood and in the normal secretions of the body. In addition, it may be useful to introduce foods such as garlic, grapefruit, chamomile, mallow, cloves, and honey into the diet. You can also use the more specifically phytotherapeutic findings, which can be used both by ingestion and by topical application.

The first food treated is honey, the human use of which is traced to about 8000 years ago, as depicted by stone-age paintings. Honey is a natural product widely used for its therapeutic effects. It has been reported that it contains about 200 substances. Honey is mainly composed of fructose and glucose, but it also contains fruit oligosaccharides and many amino acids, vitamins, minerals, and enzymes. The honey composition varies depending on the plants on which the bee feeds. However, almost all natural honey contains flavonoids (such as apigenin, pinocembrin, kaempferol, quercetin, galangine, chrysin, and esperperin), phenolic acids (such as ellagic, caffeic, p-coumaric, and ferulic acids), ascorbic acid, tocopherols, catalase, superoxide dismutase, reduced glutathione, Maillard reaction products, and peptides.

Honey has a very complex chemical composition that depends on the botanical source. It has been used both as food and medicine since ancient times. In addition to the important role of natural honey in traditional medicine, in recent decades it has been studied in laboratory and clinical investigations by different research groups, having found a place in modern medicine. It has been reported that honey has an inhibitory effect on around 60 species of bacteria and some fungi and virus species (98–100).

Pure honey inhibits the growth of fungi, and diluted honey seems able to inhibit the production of toxins (101). An antifungal action has also been observed for some yeasts and species of *Aspergillus* and *Penicillium*, as well as for all common dermatophytes (102). Candidiasis, caused by *C. albicans*, and some superficial skin fungal infections such as ringworm and athlete's foot respond to honey. This reactivity is partly due to the inhibition of the growth of fungi and partly to the inhibition of bacterial infections (103). Furthermore, some studies have reported that topical honey application can be effective in the treatment of seborrheic dermatitis and dandruff (104, 105).

Another important food is garlic, used in folk medicine for its antimicrobial and antifungal properties. Otomycosis due to saprophyte keratolytic fungi represents a small percentage of clinical external otitis. Although some antibacterials and antifungal agents are available, their use should be limited because they are potentially ototoxic, and they cannot be used if the eardrum is perforated. In response to the lack of other preparations, in the study by Pail and coworkers (106), the authors studied the effectiveness of garlic extracts against fungi belonging to the genus *Aspergillus*, which are the most common cause of this infection. Two garlic preparations, aqueous garlic extract (AGE) and concentrated garlic oil (CGO), along with various commercial garlic supplements and pharmaceutical prescriptions, were used in an in vitro study. It has been shown that AGE and especially CGO have antifungal activity. These agents showed similar or better inhibitory effects than pharmaceutical preparations (106).

Antifungal properties are ascribed to tea, belonging to the family *Camellia sinensis*, an evergreen shrub of Chinese origin that can reach a maximum height of 2 m whose leaves are infused to obtain a drink. The first mention of tea in a written text, a treaty of pharmacopeia, dates to 200 BC. Recent studies have shown that black and green tea polyphenols show strong antimicrobial and anticancer properties. Some studies have been conducted to determine the effects of these polyphenols on *C. albicans*. The impairment of proteasome activity by tea polyphenols contributes to the cellular metabolic and structural alterations, accelerating the inhibition of the formation and maintenance of biofilm by *C. albicans* (107). In the study by Ning and colleagues (108), epigallocatechin gallate (EGCG), the main antimicrobial polyphenol in tea, is reported to inhibit the growth of *C. albicans* planktonic cells and potentiate the antifungal activity of antimycotics. EGCG increases the antifungal effects of miconazole, fluconazole and amphotericin B. Combined treatment with EGCG may reduce the dosages of antifungal agents, thus preventing adverse effects and the onset of drug-resistant oral candidiasis (108).

Curcuma longa Linn (Zingiberaceae family) and curcumin, the related polyphenolic compound, have undergone a variety of experiments because of the wide range of traditional uses and its low side effects. The antimicrobial activity of curcumin and of the rhizome extract of *C. longa* has been reported against various bacteria, viruses, fungi, and parasites (109). As with other plant materials, there are differences in the curcumin content of *C. longa* due to the different geographical regions of cultivation and hybridization with other turmeric species. These differences have to be taken into account for the choice of the plants with higher curcumin contents (110). A study of curcumin against 14 *Candida* strains and 10 clinical isolates showed that curcumin is a potent fungicidal compound with minimal inhibitory concentration values between 250 and 2000 μg/mL (111). In another study, the anti-*Candida* activity of curcumin was demonstrated against 38 different strains of *Candida* (*albicans*, *glabrata*, *krusei*, *tropicalis*, *guilliermondii*, etc.), including some strains resistant to fluconazole (112).

Essential oils are rich mixtures of chemical components with complex biochemical and biological properties, particularly terpenes and phenols, which have the peculiarity of interfering with the viability of the bacterial and fungal wall and with the protein replication of bacterial and viral components. Most of these essential oils belong to the Lamiaceae family, i.e., plants with a strong aromatic component and rich phytocomplexity. Spices and aromatic herbs have been used mainly for their aromatic characteristics, and many among those known have been used in the treatment of various diseases, including infections. Studies have shown that, in some cases, these extracts have a remarkable antimicrobial, antifungal, and nematicidal activity. The composition of essential oil from *T. pulegioides* and its antifungal activity on *Candida*, *Aspergillus*, and dermatophytes have been studied.

Essential oils of plant aerial parts were obtained by hydrodistillation and analyzed by GC and GC–MS. The oils showed high content of carvacrol and thymol. Antifungal activity has been evaluated for essential oil and its main components. To clarify its mechanism of action on yeasts and filamentous fungi, studies were performed using cytofluorimetry of cytoplasmic membrane integrity, and the effect on the amount of ergosterol was studied. Obtained results showed that the essential oil of *T. pulegioides* showed significant activity against some mushrooms with clinical significance, mainly because of the formation of lesions in the cytoplasmic membrane and a considerable reduction of the content of ergosterol (113).

The results of the study carried out by Giordani and coworkers (114) indicate that the essential oil of *T. vulgaris* enhances the antifungal action of amphotericin B, suggesting a possible use of this essential oil in addition to antifungal medications for the treatment of mycosis.

Antiviral Properties

In addition to antibiotic and antifungal features, some plants also have a clear antiviral ability due to the presence of some phenolic compounds. The existence of a similar antiviral property in natural products opens the door to the possibility of using them in the pharmacological field as an alternative to drugs or adjuvants to it (115) or as a solution for antiviral therapies against specific pathogens currently not managed by any treatment, if not aspecific.

The antiviral activity of phenolic compounds, expressed mainly by flavonoids (116) and phenolic acids (90, 115), seems to depend on factors such as the number of hydroxyl groups, their position, and the presence of specific phenolic molecules (such as procyanidin) with extracellular action (117–119).

In the literature, the existence of a multiplicity of possible processes by which the phenolic compounds exert their antiviral power has been observed. However, it seems that protein and enzymatic inactivations (carried out by all flavonoids and phenolic acids, as mentioned above) are the main activities. Specific mechanisms of action by which the phenolic compounds perform their antiviral function include the following. (*1*) Inhibition of reverse transcriptase: Among the enzymes inhibited by some phenolic compounds, such as phenols and phenolic acids, there is the polymerase responsible for the transcription of the viral genetic patrimony and, therefore, its replication. In this way, the proliferation and diffusion of the virus within the host organism and the relative onset of the related pathology are prevented. (*2*) Viral alteration: Compounds such as flavonoids are able to bind to viral proteins, denaturing them and irreversibly altering the viral activity itself. (*3*) Prevention of viral adhesion: Some compounds (such as phenolic acids) seem capable of inhibiting the link between cell and virus by binding to membrane proteins to prevent the fusion between the viral envelope and the plasma membrane. (*4*) Prevention of entry into the cell nucleus: Some phenols (such as tannins and flavonoids) are able to avoid the entry of the virus into the cell nucleus, preventing viral replication and diffusion (120–124). The antiviral capacity of phenolic compounds has long been studied, and it has been observed that not all compounds are effective in equal measure against all viruses that can infect humans, e.g., herpex simplex virus (HSV-1 and HSV-2), human immunodeficiency virus (HIV), influenza and parainfluenza virus, poliovirus, cytomegalovirus, rabies virus, hepatitis B virus, and Epstein-Barr virus (EBV; 116, 118, 125–138).

Some examples can be given, including first of all, given their peculiarity, the fungi, represented by *Inonotus hispidus* (active against type A and B viruses responsible for influenza; 139) and some medicinal plants, from which emerges the antiviral capacity attributable to the presence of phenolic compounds (such as tannins), as in the case of *Hamamelis virginiana* and *Shepherdia argentea* against HSV-1 and HIV-1, *Geranium sanguineum* against HSV-1 and HSV-2, *Geum japonicum* and *Syzygium aromaticum* active against HSV (140–145), *Chamaesyce thymifolia* against HSV-1 (130), and *Plantago major* active against HSV (121).

Additionally, aromatic herbs, e.g., cloves (*S. aromaticum*), appear to be effective against HSV (144, 145), whereas oregano (*O. vulgare*) seems effective against HSV-1 and HSV (146).

Some shrubs and plants show this capacity, including a species of hawthorn (*Crataegus sinaica*) effective against HSV-1 (119), *Rubus sanctus* against HIV (147), *Vitex polygama* against HSV-1 (128), and *Mosla scabra* against influenza virus (148). Some trees, such as *Millettia erythrocalyx* and

Artocarpus lakoochaare, are reported to be active against HIV and HSV (149).

Some plants and fruit trees, such as *Spondias mombin* and *Spondias tuberosa*, are effective against the dengue virus. *Ptunus domestica* possesses an action against poliovirus, as do *Morus alba* against HSV-1 and *Artocarpus gomezianus* and *Triphasia trifolia* against HSV and HIV (149–152). In addition, berries also show the same activity, as in the case of raspberries (*Rubus idaeus*; 153). In conclusion, it should be mentioned that some foods that are derived from these plants are commonly used. Among these, it is necessary to remember tea (*C. sinensis*), which seems to possess a strong antiviral power due to the presence of some phenolic compounds involved in the defense system against viruses such as EBV, HSV-1, HIV, and influenza virus (138).

Anti-Inflammatory Properties

The correlation between the presence of phenolic compounds and their anti-inflammatory activity is widely reported in the available literature. This relationship could have particular relevance and arouse great curiosity. The inflammatory process is an innate, nonspecific defense mechanism that constitutes a protective response following the damaging action of physical, chemical, and biological agents, the ultimate goal of which is the elimination of the initial cause of cellular or tissue damage as well as the start of the repair process (154).

To explain a probable association between the flavonoids and the anti-inflammatory processes, we will investigate the anti-inflammatory functions performed by EGCG and quercetin, underlining the existence of a vast number of reactions related to their type. With regard to EGCG, its action has been shown in vitro through the inhibition of inducible nitric oxide and the limitation of action mechanisms of the transcription factors AP-1 and NF-κB. The anti-inflammatory action modality of quercetin, in turn, has been tested in vitro concerning its inhibitory action on the formation of nitric oxide, cyclooxygenase, and lipoxygenase; its influence on inducible nitric oxide synthase has to be considered (155).

Based on these premises, many experimental studies have been conducted that have identified the association between these substances present in some foods and anti-inflammatory activity. Particular attention has been paid to algae, e.g., *Porphyra dentata* (156) and mushrooms such as *Phellinus baumii* (157).

With respect to fruits, some research has been carried out on the anti-inflammatory activity of *A. heterophyllus* (158) and on medicinal plants such as *Moringa oleifera* (159). Berries such as blueberry-blackberry (160) and *Rubus coreanus* Miquel (161) have a probable anti-inflammatory effect. In addition, juices such as grape, orange, and bergamot have antioxidant activity (162–164). As for legumes, García-Lafuente and colleagues demonstrated in vitro the antiphlogistic activity of phenolic compounds extracted from common white and red beans (165).

Conclusions

The potential of the phenolic compounds is limitless, making them not only pillars of proper nutrition but real solutions to emerging health problems, including the preservation of food, the treatment of bacterial or viral infections, and the support of anti-inflammatory therapies.

For these reasons, it is evident that there is a need to intensify the research to deepen and improve the related knowledge, a need that requires ever more appropriate and usable responses, given the whirlwind progress of humanity and related problems. The analytical research concerning polyphenols and other natural substances that may be related to polyphenols, if only in that these compounds are all "natural" principals (e.g., lactones, fructans, natural antibiotics, etc.), has to be taken into account (166–169). On the other hand, certain products, both historical and new, may be found with unknown allergenic substances and, consequently, justify new hygiene and safety worries for official institutions and unaware consumers (170–176).

References

(1) Mondello, F., Marella, A.M., Bellardi, M.G., & Di Vito, M. (2015) *Rapporti ISTISAN 15/6*, Istituto Superiore di Sanità, Rome, Italy

(2) Ferlazzo, N., Visalli, G., Cirmi, S., Lombardo, G.E., Laganà, P., Di Pietro, A., & Navarra, M. (2016) *Environ. Toxicol. Pharmacol*. **43**, 248–256. doi:10.1016/j.etap.2016.03.005

(3) Spanò, A., Laganà, P., Visalli, G., Maugeri, T., & Gugliandolo, C. (2015) *Curr. Microbiol*. **72**, 518–528. doi:10.1007/s00284-015-0981-9

(4) Casella, S., Ielati, S., Piccione, D., Laganà, P., Fazio, F., & Piccione, G. (2012) *Cell Biochem. Funct*. **30**, 406–410. doi:10.1002/cbf.2814

(5) Baiano, A., & Terracone, C. (2010) *I Composti Fenolici Negli Alimenti Classificazione, Distribuzione, Metodi di Estrazione ed Analisi*, Aracne Editrice S.r.l., Rome, Italy

(6) Carratù, B., & Sanzini, E. (2010) in *Rapporti ISTISAN 10/C8*, Istituto Superiore di Sanità, Rome, Italy

(7) Papuc, C., Goran, V.G., Predescu, N.C., Nicorescu, V., & Stefan, G. (2017) *Compr. Rev. Food Sci. Food Saf.* **16**, 1243–1267. doi:10.1111/1541-4337.12298

(8) Cowan, M.M. (1999) *Clin. Microbiol. Rev*. **12**, 564–582. doi:10.1128/CMR.12.4.564

(9) Mendes, L.P.M., Maciel, K.M., Vieira, A.B.R., Mendonça, L.C.V., Silva, R.M.F., Rolim Neto, P.J., Barbosa, W.L.R., & Vieira, J.M.S. (2011) *Revista Ciências Farmacêutica Básica Aplicada* **32**, 121–125

(10) Gatto, M.T., Falcocchio, S., Grippa, E., Mazzanti, G., Battinelli, L., Nicolosi, G., Lambusta, D., & Saso, L. (2002) *Bioorg. Med. Chem*.**10**, 269–272. doi:10.1016/S0968-0896(01)00275-9

(11) Kumar, S., & Pandey, A.K. (2013) *Sci. World J.* **2013**, 162750. doi:10.1155/2013/162750

(12) Huang, X.L., Liu, M.D., Li, J.Y., Zhou, X.D., & ten Cate, J.M. (2012) *Int. J. Oral Sci*. **4**, 146–151. doi:10.1038%2Fijos.2012.44

(13) Haslam, E. (1996) *J. Nat. Prod*. **59**, 205–215. doi:10.1021/np960040

(14) Stern, J.L., Hagerman, A.E., Steinberg, P.D., & Mason, P.K. (1996) *J. Chem. Ecol.* **22**, 1887–1899. doi:10.1007/BF02028510

(15) Ncube, B., & Van Staden, J. (2015) *Molecules* **20**, 12698–12731. doi:10.3390/molecules200712698

(16) Beuchat, L.R., & Golden, D.A. (1989) *Food Technol.* **43**, 134–142

(17) Ceylan, E., & Fung, D.Y.C. (2007) *J. Rapid Methods Autom. Microbiol*. **12**, 1–55. doi:10.1111/j.1745-4581.2004.tb00046.x

(18) Negi, P.S. (2012) *Int. J. Food Microbiol*. **156**, 7–17. doi:10.1016/j.ijfoodmicro.2012.03.006

(19) Guendouze-Bouchefa, N., Madani, K., Chibane, M., Boulekbache-Makhlouf, L., Hauchard, D., Kiendrebeogo, M., Stévigny, C., Okusa, P.N., & Duez, P. (2015) *Ind. Crops Prod.* **70**, 459–466. doi:10.1016/j.indcrop.2015.03.053

(20) Scalbert, A. (1991) *Phytochem.* **30**, 3875–3883. doi:10.1016/0031-9422(91)83426-L
(21) Hendra, R., Ahmad, S., Sukari, A., Shukor, M.Y., & Oskoueian, E. (2011) *Int. J. Mol. Sci.* **12**, 3422–3431. doi:10.3390/ijms12063422
(22) Khan, R., Islam, B., Akram, M., Shakil, S., Ahmad, A., Ali, S.M., Siddiqui, M., & Khan, A.U. (2009) *Molecules* **14**, 586–597. doi:10.3390/molecules14020586
(23) Jang, M., Hong, E., & Kim, G.H. (2010) *J. Food Sci.* **75**, M412–M416. doi:10.1111/j.1750-3841.2010.01725.x
(24) Choi, J.G., Kang, O.H., Brice, O.O., Lee, Y.S., Chae, H.S., Oh, Y.C., Sohn, D.H., Park, H., Choi, H.G., Kim, S.G., Shin, D.W., & Kwon, D.Y. (2010) *Foodborne Pathog. Dis.* **7**, 435–441. doi:10.1089/fpd.2009.0434
(25) Lee, D.S., Kang, M.S., Hwang, H.J., Eom, S.H., Yang, J.Y., Lee, M.S., Lee, W.J., Jeon, Y.J., Choi, J.S., & Kim, Y.M. (2008) *Biotechnol. Bioprocess Eng.* **13**, 758–764. doi:10.1007/s12257-008-0162-9
(26) Barros, L., Calhelha, R., Vaz, J., Ferreira, I.C.F.R., Baptista, P., & Estevinho, L.M. (2007) *Eur. Food Res. Technol.* **225**, 151–156. doi:10.1007/s00217-006-0394-x
(27) El Astal, Z.Y., Ashour, A.E.R.A., & Kerrit, A.A.M. (2005) *Pak. J. Med. Sci.* **21**, 187–193
(28) Karou, D., Dicko, M.H., Simpore, J., & Traore, A.S. (2005) *Afr. J. Biotechnol.* **4**, 823–828
(29) Pattanayak, P., Behera, P., Das, D., & Panda, S.K. (2010) *Pharmacogn Rev.* **4**, 95–105. doi:10.4103/0973-7847.65323
(30) Çelen, G., Özkan, S., & Ayhan, F. (2008) *Hacettepe J. Biol. Chem.* **36**, 339–345
(31) Ezoubeiri, A., Gadhi, C.A., Fdil, N., Benharref, A., Jana, M., & Vanhaelen, M. (2005) *J. Ethnopharmacol.* **99**, 287–292. doi:10.1016/j.jep.2005.02.015
(32) Al-Fartosy, A.J.M., & Zearah, S.A. (2013) *Iraqi Natl. J. Chem.* **49**, 100–112
(33) Dziri, S., Hassen, I., Fatnassi, S., Mrabet, Y., Casabianca, H., Hanchi, B., & Hosni, K. (2012) *J. Funct. Foods* **4**, 423–432. doi:10.1016/j.jff.2012.01.010
(34) Salawu, S.O., Ogundare, A.O., Ola-Salawu, B.B., & Akindahunsi, A.A. (2011) *Afr. J. Pharm. Pharmacol.* **5**, 486–492
(35) Chun, S.S., Vattem, D.A., Lin, Y.T., & Shetty, K. (2005) *Process Biochem.* **40**, 809–816. doi:10.1016/j.procbio.2004.02.018
(36) Pradhan, K.J., Variyar, P.S., & Bandekar, J.R. (1999) *LWT – Food Sci. Technol.* **32**, 121–123. doi:10.1006/fstl.1998.0508
(37) Tadros, L.K., El-Rafey, H.H., Elfadaly, H.A., Taher, M.A., & May, A.E. (2017) *J. Agric. Chem. Biotechnol.* **8**, 183–189
(38) Moreno, S., Scheyer, T., Romano, C.S., & Vojnov, A.A. (2006) *Free Rad. Res.* **40**, 223–231. doi:10.1080/10715760500473834
(39) Addai, Z.R., & Abood, M.S. (2016) *Int. J. Chem. Tech. Res.* **9**, 217–222
(40) Carraturo, A., Raieta, K., Tedesco, I., Kim, J., & Russo, G.L. (2014) *Brit. Microbiol. Res. J.* **4**, 18–27
(41) Tatiya, A.U., Tapadiya, G.G., Kotecha, S., & Surana, S.J. (2010) *Indian J. Nat. Prod. Res.* **2**, 442–447
(42) Clark, A.M., El-Feraly, F.S., & Li, W.S. (1981) *J. Pharm. Sci.* **70**, 951–952. doi:10.1002/jps.2600700833
(43) Živković, J., Mujić, I., Zeković, Z., Vidovic, S., Mujić, A., & Jokić, S. (2009) *J. Central Eur. Agric.* **10**, 175–181
(44) Min, B.R., Pinchak, W.E., Merkel, R., Walker, S., Tomita, G., & Anderson, R.C. (2008) *Sci. Res. Essay* **3**, 66–73
(45) Bahri-Sahloul, R., Fredj, R.B., Boughalleb, N., Shriaa, J., Saguem, S., Hilbert, J.L., Trotin, F., Ammar, S., Bouzid, S., & Harzallah-Skhiri, F. (2014) *J. Bot.* **2014**, 623651. doi:10.1155/2014/623651
(46) Park, Y.J., Biswas, R., Phillips, R.D., & Chen, J. (2011) *J. Food Sci.* **76**, 101–105. doi:10.1111/j.1750-3841.2010.01974.x
(47) Gautam, M.K., Gangwar, M., Nath, G., Rao, C.V., & Goel, R.K. (2012) *Asian Pac. J. Trop. Biomed.* **2**, S1660–S1663. doi:10.1016/S2221-1691(12)60472-9
(48) Siddiqi, R., Naz, S., Ahmad, S., & Sayeed, S.A. (2011) *Int. J. Food Sci. Technol.* **46**, 250–256. doi:10.1111/j.1365-2621.2010.02480.x
(49) Corthout, J., Pieters, L., Claeys, M., Geerts, S., VandenBerghe, D., & Vlietinck, A. (1994) *Planta Med.* **60**, 460–463. doi:10.1055/s-2006-959532
(50) Helnonen, M. (2007) *Mol. Nutr. Food Res.* **51**, 684–691. doi:10.1002/mnfr.200700006
(51) Rauha, J.P., Remes, S., Heinonen, M., Hopia, A., Kähkönen, M., Kujala, T., Vuorela, H., & Vuorela, P. (2000) *Int. J. Food Microbiol.* **56**, 3–12. doi:10.1016/s0168-1605(00)00218-x
(52) Xiaoyong, S., & Cheng, L. (2014) *J. Food Nutr. Res.* **2**, 973–979. doi:10.12691/jfnr-2-12-18
(53) Rodríguez-Pérez, C., Quirantes-Piné, R., Uberos, J., Jiménez-Sánchez, C., Peña, A., & Segura-Carretero, A. (2016) *Food Funct.* **7**, 1564–1573. doi:10.1039/c5fo01441g
(54) Cesoniene, L., Jasutiene, I., & Sarkinas, A. (2009) *Med.* **45**, 992–999. doi:10.3390/medicina45120127
(55) Nohynek, L.J., Alakomi, H.L., Kähkönen, M.P., Heinonen, M., Helander, I.M., Oksman-Caldentey, K.M., & Puupponen-Pimiä, R.H. (2006) *Nutr. Cancer* **54**, 18–32. doi:10.1207/s15327914nc5401_4
(56) Martini, S., D'Addario, C., Colacevich, A., Focardi, S., Borghini, F., Santucci, A., Figura, N., & Rossi, C. (2009) *Int. J. Antimicrob. Ag.* **34**, 50–59. doi:10.1016/j.ijantimicag.2009.01.010.
(57) Häkkinen, S.H., Kärenlampi, S.O., Heinonen, I.M., Mykkänen, H.M., & Törrönen, A.R. (1999) *J. Agric Food Chem.* **47**, 2274–2279. doi:10.1021/jf9811065
(58) Debib, A., Tir-Touil, A., Mothana, R.A., Meddah, B., & Sonnet, P. (2013) *J. Food Biochem.* **38**, 207–215. doi:10.1111/jfbc.12039
(59) Rahnemoon, P., Sarabi Jamab, M., Javanmard Dakheli, M., & Bostan, A. (2016) *Int. J. Agric. Biosyst. Eng.* **10**, 646–651
(60) Qadoos, A.H., Dhafari, H.S., Al Marzooqi, D.A., Yaqoubi, A.Y.I., Kumarappan, A., Nazir, A., & Elsori, D. (2017) *Food Biol.* **6**, 11–15. doi:10.19071/fbiol.2017.v6.3154
(61) Jayaprakasha, G.K., Selvi, T., & Sakariah, K.K. (2003) *Food Res. Int.* **36**, 117–122. doi:10.1016/S0963-9969(02)00116-3
(62) Baydar, N.G., Özkan, G., & Sağdiç, O. (2004) *Food Control* **15**, 335–339. doi:10.1016/S0956-7135(03)00083-5
(63) Singleton, V.L., & Rossi, J.A. (1965) *Am. J. Enol. Vitic.* **16**, 144–158
(64) Alberto, M.R. (2006) *Electron. J. Biotechnol.* **9**, 205–209. doi:10.2225/vol9-issue3-fulltext-1
(65) Zhang, T., Wei, X., Miao, Z., Hassan, H., Song, Y., & Fan, M. (2016) *Chem. Cent. J.* **10**, 47. doi:10.1186/s13065-016-0195-7
(66) Fu, L., Lu, W.Q., & Zhou, X.M. (2016) *BioMed Res. Int.* **2016**, 4287461. doi:10.1155/2016/4287461
(67) Gaafar, A.A., & Salama, Z.A. (2013) *J. Biol. Agric. Healthcare* **3**, 1–6
(68) Ayaz, F.A., Hayırloglu-Ayaz, S., Alpay-Karaoglu, S., Grúz, J., Valentová, K., Ulrichová, J., & Strnad, M. (2008) *Food Chem.* **107**, 19–25. doi:10.1016/j.foodchem.2007.07.003
(69) Silva-Beltrán, N.P., Ruiz-Cruz, S., Cira-Chávez, L.A., Estrada-Alvarado, M.I., Ornelas-Paz, J.J., López-Mata, M.A., Del-Toro-Sánchez, C.L., Ayala-Zavala, J.F., & Márquez-Ríos, E. (2015) *Int. J. Anal. Chem.* **2015**, 284071. doi:10.1155/2015/284071
(70) Khatiwada, B., Kunwar, S., Dhakal, A., Joshi, A., Miya, A.R., & Subedi, P. (2018) *Eur. J. Biotechnol. Biosci.* **6**, 21–25
(71) Hong, H., Landauer, M.R., Foriska, M.A., & Ledney, G.D. (2006) *J. Basic Microbiol.* **46**, 329–335. doi:10.1002/jobm.200510073
(72) Dua, A., Garg, G., & Mahajan, R. (2013) *Eur. J. Exp. Biol.* **3**, 203–208

(73) Murthy, H.N., Herlekar, V.V., Joseph, K.S., Payamalle, S., & Shinde, S. (2018) *J. Herbs Spices Med. Plants* **24**, 213–220. doi:10.1080/10496475.2018.1443188
(74) China, R., Mukherjee, S., Sen, S., Bose, S., Datta, S., Koley, H., Ghosh, S., & Dhar, P. (2012) *Microbiol. Res*. **167**, 500–506. doi:10.1016/j.micres.2012.04.003
(75) Ulusoy, S., Boşgelmez-Tinaz, G., & Seçilmiş-Canbay, H. (2009) *Curr. Microbiol*. **59**, 554–558. doi:10.1007/s00284-009-9475-y
(76) Mahboubi, A., Asgarpanah, J., Sadaghiyani, P.N., & Faizi, M. (2015) *BMC Complementary Altern. Med*. **15**, 366. doi:10.1186/s12906-015-0887-x
(77) Juven, B., & Henis, Y. (1970) *J. Appl. Bacteriol.* **33**, 721–732
(78) Lee, O.H., & Lee, B.Y. (2010) *Biores. Technol.* **101**, 3751–3754. doi:10.1016/j.biortech.2009.12.052
(79) Laaboudi, W., Ghanam, J., Merzouki, M., & Benlemlih, M. (2015) *Eur. J. Sci. Res.* **132**, 255–265
(80) Pereira, J.A., Pereira, A.P., Ferreira, I.C., Valentão, P., Andrade, P.B., Seabra, R., Estevinho, L., & Bento, A. (2006) *J. Agric. Food Chem.* **54**, 8425–8431. doi:10.1021/jf061769j
(81) Nychas, G.J.E., Tassou, S.C., & Board, R.G. (1990) *Lett. Appl. Microbiol*. **10**, 217–220. doi:10.1111/j.1472-765X.1990.tb01337.x
(82) Tunçel, G., & Nergiz, C. (1993) *Lett. Appl. Microbiol*. **17**, 300–302. doi:10.1111/j.1472-765X.1993.tb01472.x
(83) Karaosmanoglu, H., Soyer, F., Ozen, B., & Tokatili, F. (2010) *J. Agric. Food Chem.* **58**, 8238–8245. doi:10.1021/jf1012105
(84) Laincer, F., Laribi, R., Tamendjari, A., Arrar, L., Rovellini, P., & Venturini, S. (2014) *Grasas Aceites* **65**, e001. doi:10.3989/gya.035713
(85) Cicerale, S., Lucas, L.J., & Keast, R.S. (2012) *Curr. Opin. Biotechnol*. **23**, 129–135. doi:10.1016/j.copbio.2011.09.006
(86) Weston, R.J., Mitchell, K.R., & Allen, K.L. (1999) *Food Chem*. **64**, 295–301. doi:10.1016/S0308-8146(98)00100-9
(87) Estevinho, L., Pereira, A.P., Moreira, L., Dias, L.G., & Pereira, E. (2008) *Food Chem. Toxicol.* **46**, 3774–3779. doi:10.1016/j.fct.2008.09.062
(88) Alvarez-Suarez, J.M., Tulipani, S., Díaz, D., Estevez, Y., Romandini, S., Giampieri, F., Damiani, E., Astolfi, P., Bompadre, S., & Battino, M. (2010) *Food Chem. Toxicol.* **48**, 2490–2499. doi:10.1016/j.fct.2010.06.021
(89) Mazol, I., Sroka, Z., Sowa, A., Ostrowska, A., Dryś, A., & Gamian, A. (2016) *Acta Pol. Pharm.* **73**, 379–388
(90) Modi, M., Goel, T., Das, T., Malik, S., Suri, S., Rawat, A.K., Srivastava, S.K., Tuli, R., Malhotra, S., & Gupta, S.K. (2013) *Indian J. Med. Res.* **137**, 540–548
(91) Vaquero, M.J.R., Alberto, M.R., & Manca de Nadra, M.C. (2007) *Food Control* **18**, 93–101. doi:10.1016/j.foodcont.2005.08.010
(92) Cueva, C., Mingo, S., Muñoz-González, I., Bustos, I., Requena, T., del Campo, R., Martín-Álvarez, P.J., Bartolomé, B., & Moreno-Arribas, M.V. (2012) *Lett. Appl. Microbiol*. **54**, 557–563. doi:10.1111/j.1472-765X.2012.03248.x
(93) Laganà, P., Melcarne, L., & Delia, S. (2015) *Int. J. Cardiol*. **187**, 678–679. doi:10.1016/j.ijcard.2015.04.019
(94) Ariza, B.T.S., Mufida, D.C., Fatima, N.N., Hendrayati, T.I., Wahyudi, T., & Misnawi, J. (2014) *Int. Food Res. J.* **21**, 935–940
(95) Montagna, M.T., Lovero, G., Coretti, C., Martinelli, D., De Giglio, O., Iatta, R., Balbino, S., Rosato, A., & Caggiano, G. (2015) *BMC Microbiol*. **20**, 106. doi:10.1186/s12866-015-0442-4
(96) Abad, M.J., Ansuategui, M., & Bermejo, P. (2007) *ARKIVOC* **2007**, 116–145. doi:10.3998/ark.5550190.0008.711
(97) Angiolella, L., Vavala, E., Ragno, R., Colone, M., & Stringaro, A. (2010) *ISTISAN Congressi 10/C8*, Istituto Superiore di Sanità, Rome, Italy
(98) Coniglio, M.A., Laganà, P., Faro, G., & Marranzano, M. (2018) *J. AOAC Int*. **101**, 956–959. doi:10.5740/jaoacint.17-0450
(99) Coniglio, M.A., Faro, G., Giammanco, G., Pignato, S., & Marranzano, M. (2013) *J. Prev. Med. Hyg.* **54**, 223–226
(100) Eteraf-Oskouei, T., & Najafi, M. (2013) *Iran. Basic Med. Sci.* **16**, 731–742
(101) Al-Waili, N.S., & Haq, A. (2004) *J. Med. Food* **7**, 491–494. doi:10.1089/jmf.2004.7.491
(102) Sampath Kumar, K.P., Bhowmik, D., Chiranjib, Biswajit, & Chandira, M.R. (2010) *J. Chem. Pharm. Res*. **2**, 385–395
(103) Obaseiki-Ebor, E.E., & Afonva, T.C.A. (1984) *J. Pharm. Pharmacol*. **36**, 283–284. doi:10.1111/j.2042-7158.1984.tb04373.x
(104) Al-Waili, N.S. (2005) *Arch. Med. Res*. **36**, 10–13. doi:10.1016/j.arcmed.2004.10.002
(105) Dattilo, G., Imbalzano, E., Casale, M., Guarneri, C., Borgia, F., Mondello, S., Laganà, P., Romano, P., Oreto, G., & Cannavò, S. (2018) *Angiology* **69**, 31–37. doi:10.1177/0003319717699329
(106) Pail, S.T., & Platt, M.V. (1995) *Lett. Appl. Microbiol*. **20**, 14–18. doi:org/10.1111/j.1472-765X.1995.tb00397.x
(107) Evensen, N.A., & Braun, P.C. (2009) *Can. J. Microbiol.* **55**, 1033–1039. doi:10.1139/w09-058
(108) Ning, Y., Ling, J., & Wu, C.D. (2015) *Arch. Oral Biol.* **60**, 1565–1570. doi:10.1016/j.archoralbio.2015.07.001
(109) Moghadamtousi, S.Z., Abdul Kadir, H., Hassandarvish, P., Tajik, H., Abubakar, S., & Zandi, K. (2014) *BioMed Res. Int.* **2014**, 186864. doi:10.1155/2014/186864
(110) Hayakawa, H., Minanvia, Y., Ito, K., Yamamoto, Y., & Fukuda, T. (2011) *Am. J. Plant Sci*. **2**, 111–119. doi:10.4236/ajps.2011.22013
(111) Neelofar, K., Shreaz, S., Rimple, B., Muralidhar, S., Nikhat, M., & Khan, L.A. (2011) *Can. J. Microbiol*. **57**, 204–210. doi:10.1139/W10-117
(112) Khan, N., Shreaz, S., Bhatia, R., Ahmad, S.I., Muralidhar, S., Manzoor, N., & Khan, L.A. (2012) *Fitoterapia* **83**, 434–440. doi:10.1016/j.fitote.2011.12.003
(113) Pinto, E., Pina-Vaz, C., Salgueiro, L., Gonçalves, M., Costa-de-Oliveira, S., Cavaleiro, C., Palmeira, A., Rodrigues, A., & Martinez-de-Oliveira, J. (2006) *J. Med. Microbiol.* **55**, 1367–1373. doi:10.1099/jmm.0.46443-0
(114) Giordani, R., Regli, P., Kaloustian, J., Mikaïl, C., Abou, L., & Portugal, H. (2004) *Phytother. Res*. **18**, 990–995. doi:10.1002/ptr.1594
(115) Park, S.W., Kwon, M.J., Yoo, J.Y., Choi, H.J., & Ahn, Y.J. (2014) *BMC Complementary Altern. Med.* **14**, 171. doi:10.1186/1472-6882-14-171
(116) Cotin, S., Calliste, C.A., Mazeron, M.C., Hantz, S., Duroux, J.L., Rawlinson, W.D., Ploy, M.C., & Alain, S. (2012) *Antivir. Res*. **96**, 181–186. doi:10.1016/j.antiviral.2012.09.010
(117) Li, R., Narita, R., Nishimura, H., Marumoto, S., Yamamoto, S.P., Ouda, R., Yatagai, M., Fujita, T., & Watanabe, T. (2018) *ACS Sustainable Chem. Eng*. **6**, 119–126. doi:10.1021/acssuschemeng.7b01265
(118) Fukuchi, K., Sakagami, H., Tanuma, S.I., Kitajima, K., Inoue, Y., Inoue, S., Ichikawa, S., Nonoyama, M., & Konno, K. (1989) *Antivir. Res.* **11**, 285–297. doi:10.1016/0166-3542(89)90038-7
(119) Shahat, A.A., Cos, P., De Bruyne, T., Apers, S., Hammouda, F.M., Ismail, S.I., Azzam, S., Claeys, M., Goovaerts, E., Pieters, L., Vanden Berghe, D., & Vlietinck, A.J. (2002) *Planta Med*. **68**, 539–541. doi:10.1055/s-2002-32547
(120) Jassim, S.A., & Naji, M.A. (2003) *J. Appl. Microbiol*. **95**, 412–427. doi:10.1046/j.1365-2672.2003.02026.x
(121) Chiang, L.C., Chiang, W., Chang, M.Y., Ng, L.T., & Lin, C.C. (2002) *Antivir. Res*. **55**, 53–62. doi:10.1016/S0166-3542(02)00007-4
(122) Formica, J.V., & Regelson, W. (1995) *Food Chem. Toxicol.* **33**, 1061–1080. doi:10.1016/0278-6915(95)00077-1
(123) Cushnie, T.P., & Lamb, A.J. (2005) *Int. J. Antimicrob. Ag*. **26**, 343–356. doi:10.1016/j.ijantimicag.2005.09.002

(124) Hayashi, K., Hayashi, T., Otsuka, H., & Takeda, Y. (1997) *J. Antimicrob. Chemother*. **39**, 821–824. doi:10.1093/jac/39.6.821

(125) Córdoba, M.A., Coto, C.E., & Damonte, E.B. (1991) *Phytother. Res*. **5**, 250–253. doi:10.1002/ptr.2650050604

(126) Cheng, H.Y., Lin, C.C., & Lin, T.C. (2002) *Antivir. Res*. **55**, 447–455. doi:10.1016/S0166-3542(02)00077-3

(127) Ozçelik, B., Kartal, M., & Orhan, I. (2011) *Pharm. Biol.* **49**, 396–402. doi:10.3109/13880209.2010.519390

(128) Gonçalves, J.L., Leitão, S.G., Monache, F.D., Miranda, M.M., Santos, M.G., Romanos, M.T., & Wigg, M.D. (2001) *Phytomedicine* **8**, 477–480. doi:10.1078/S0944-7113(04)70069-0

(129) Wu, J.H., Wang, X.H., Yi, Y.H., & Lee, K.H. (2003) *Bioorg. Med. Chem. Lett.* **13**, 1813–1815. doi:10.1016/S0960-894X(03)00197-5

(130) Amaral, A.C.F., Kuster, R.M., Gonçalves, J.L.S., & Wigg, M.D. (1999) *Fitoterapia* **70**, 293–295. doi:10.1016/S0367-326X(99)00008-8

(131) Buzzini, P., Arapitsas, P., Goretti, M., Branda, E., Turchetti, B., Pinelli, P., Ieri, F., & Romani, A. (2008) *Mini-Rev. Med. Chem.* **8**, 1179–1187. doi:10.2174/138955708786140990

(132) Tripathi, V.D., & Rastogi, R.P. (1981) *Indian J. Sci. Res.* **40**, 116–121

(133) Deca, R.T., Gouzalez, I.J., Mactinez, T.M.V., Moreno, J., & Romo, S.C.A. (1987) *Biochemistry* **19**, 223–231

(134) Bakay, M., Mucsi, I., Beladi, I., & Ganor, M.M. (1968) *Acta Microbiol.* **15**, 223–232

(135) Rajnarayana, K., Reddy, M.S., Chaluvadi, M.R., & Krishna, D.R. (2001) *Indian J. Pharmacol.* **33**, 2–16

(136) Ghazal, S.A., Abuzarqua, M., & Mahansneh, A.M. (1992) *Phytother. Res*. **6**, 265–269. doi:10.1002/ptr.2650060509

(137) Yang, G., & Chen, D. (2008) *Chem. Biodivers.* **5**, 1419–1424. doi:10.1002/cbdv.200890130

(138) Friedman, M. (2007) *Mol. Nutr. Food Res*. **51**, 116–134. doi:10.1002/mnfr.200600173

(139) Awadh Ali, N.A., Mothana, R.A., Lesnau, A., Pilgrim, H., & Lindequist, U. (2003) *Fitoterapia* **74**, 483–485. doi:10.1016/S0367-326X(03)00119-9

(140) Erdelmeier, C.A., Cinatl, J.J., Rabenau, H., Doerr, H.W., Biber, A., & Koch, E. (1996) *Planta Med*. **62**, 241–245. doi:10.1055/s-2006-957868

(141) Yoshida, T., Ito, H., Hatano, T., Kurata, M., Nakanishi, T., Inada, A., Murata, H., Inatomi, Y., Matsuura, N., Ono, K., Nakane, H., Noda, M., Lang, F.A., & Murata, J. (1996) *Chem. Pharm. Bull.* **44**, 1436–1439. doi:10.1248/cpb.44.1436

(142) Serkedjieva, J., & Hay, A.J. (1998) *Antivir. Res*. **37**, 121–130. doi:10.1016/S0166-3542(97)00067-3

(143) Serkedjieva, J., & Ivancheva, S. (1999) *J. Ethnopharmacol*. **64**, 59–68. doi:10.1016/S0378-8741(98)00095-6

(144) Kurokawa, M., Hozumi, T., Basnet, P., Nakano, M., Kadota, S., Namba, T., Kawana, T., & Shiraki, K. (1998) *J. Pharmacol. Exp. Ther.* **284**, 728–735

(145) Takechi, M., & Tanaka, Y. (1981) *Planta Med*. **42**, 69–74. doi:10.1055/s-2007-971548

(146) Zhang, X.L., Guo, Y.S., Wang, C.H., Li, G.Q., Xu, J.J., Chung, H.Y., Ye, W.C., Li, Y.L., & Wang, G.C. (2014) *Food Chem*. **152**, 300–306. doi:10.1016/j.foodchem.2013.11.153

(147) Van Hoof, L., Tottè, J., Corthout, J., Pieters, L.A., Mertens, F., Vanden Berghe, D.A., Vlietinck, A.J., Dommisse, R., & Esmans, E. (1989) *J. Nat. Prod*. **52**, 875–878. doi:10.1021/np50064a038

(148) Wu, Q., Yu, C., Yan, Y., Chen, J., Zhang, C., & Wen, X. (2010) *Fitoterapia* **81**, 429–433. doi:10.1016/j.fitote.2009.12.005

(149) Likhitwitayawuid, K., Sritularak, B., Benchanak, K., Lipipun, V., Mathew, J., & Chinazi, R.F. (2005) *Nat. Prod. Res.* **19**, 177–182. doi:10.1080/14786410410001704813

(150) Silva, A., Morais, S.M., Marques, M.M.M., Lima, D.M., Santos, S.C.C., Almeida, R.R., Vieira, I.G.P., & Guedes, M.I.F. (2011) *J. Venomous Anim. Tosins Incl. Trop. Dis*. **17**, 406–413. doi:10.1590/S1678-91992011000400007

(151) Abonyi, D.O., Adikwu, M.U., Esimone, C.O., & Ibezim, E.C. (2009) *Afr. J. Biotechnol.* **8**, 3989–3994

(152) Du, J., He, Z.D., Jiang, R.W., Ye, W.C., Xu, H.X., & But, P.P.-H. (2003) *Phytochemistry* **62**, 1235–1238. doi:10.1016/S0031-9422(02)00753-7

(153) Cadman, C.H. (1960) in *Phenolics in Plants in Health and Disease: Proceedings of a Plant Phenolics Group Symposium Held at Bristol, April 1959*, J.B. Pridham (Ed.), Pergamon Press, Oxford, United Kingdom, pp 101–105

(154) Hartmann, F., Linzbach, J., Nissen, R., & Schaefer, H. (1959) in *Fischer-Lexicon Medizin I*, Fischer Bücherei, Frankfurt am Main, Germany, pp 1–370

(155) Rathee, P., Chaudhary, H., Rathee, S., Rathee, D., Kumar, V., & Kohli, K. (2009) *Inflammation Allergy: Drug Targets* **8**, 229–235. doi:10.2174/187152809788681029

(156) Kazłowska, K., Hsu, T., Hou, C.C., Yang, W.C., & Tsai, G.J. (2010) *J. Ethnopharmacol*. **128**, 123–130. doi:10.1016 / j.jep.2009.12.037

(157) Lee, S., Lee, D., Jang, T.S., Kang, K.S., Nam, J.W., Lee, H.J, & Kim, K.H. (2017) *Molecules* **22**, 1583. doi:10.3390/molecules22101583

(158) Fang, S.C., Hsu, C.L., & Yen, G.C. (2008) *J. Agric. Food Chem.* **56**, 4463–4468. doi:10.1021/jf800444g

(159) Cheenpracha, S., Park, E.J., Yoshida, W.Y., Barit, C., Wall, M., Pezzuto, J.M., & Chang, L.C. (2010) *Bioorg. Med. Chem.* **18**, 6598–6602. doi:10.1016/j.bmc.2010.03.057

(160) Johnson, M.H., Gonzalez de Mejia, E., Fan, J., Lila, M.A., & Yousef, G.G. (2013) *Mol. Nutr. Food Res.* **57**, 1182–1197. doi:10.1002/mnfr.201200678

(161) Lim, J.W., Hwang, H.J., & Shin, C.S. (2012) *J. Agric. Food Chem.* **60**, 5121–5127. doi:10.1021/jf205350k

(162) Visalli, G., Ferlazzo, N., Cirmi, S., Campiglia, P., Gangemi, S., Di Pietro, A., Calapai, G., & Navarra, M. (2014) *Anti-Cancer Agents Med. Chem.* **14**, 1402–1413. doi:10.2174/1871520614666140829120530

(163) Visalli, G., Ferlazzo, N., Facciolà, A., Picerno, I., Navarra, M., & Di Pietro, A. (2018) *Nat. Prod. Res.* **11**, 1–5. doi:10.1080/14786419.2018.1490906

(164) Ferlazzo, N., Visalli, G., Smeriglio, A., Cirmi, S., Lombardo, G.E., Campiglia, P., Di Pietro, A., & Navarra, M. (2015) *Evidence-Based Complementary Altern. Med.* **2015**, 957031. doi:10.1155/2015/957031

(165) García-Lafuente, A., Moro, C., Manchón, N., Gonzalo-Ruiz, A., Villares, A., Guillamón, E., Rostagno, M., & Mateo-Vivaracho, L. (2014) *Food Chem*. **161**, 216–223. doi:10.1016/j.foodchem.2014.04.004

(166) Austin, S., van Gool, M., Parisi, S., Bhandari, S., Haselberger, P., Jaudzems, G., & Sullivan, D. (2018) *J. AOAC Int.* **101**, 1270–1271. doi:10.5740/jaoacint.SMPR2014.003

(167) Dentali, S.J., Amarillas, C., Blythe, T., Brown, P.N., Bzhelyansky, A., Fields, C., Johnson, H.E., Krepich, S., Kuszak, A., Metcalfe, C., Monagas, M., Mudge, E., Parisi, S., Reif, K., Rimmer, C.A., Sasser, M., Solyom, A.M., Stewart, J., Szpylka, J., Tims, M.C., Van Breemen, R., You, H., Zhao, H., Zielinski, G., & Coates, S.G. (2018) *J. AOAC Int.* **101**, 1256–1260. doi:10.5740/jaoacint.SMPR2018.005

(168) Popping, B., Allred, L., Bourdichon, F., Brunner, K., Diaz-Amigo, C., Galan-Malo, P., Lacorn, M., North, J., Parisi, S., Rogers, A., Sealy-Voyksner, J., Thompson, T., & Yeung, J. (2018) *J. AOAC Int*. **101**, 185–189. doi:10.5740/jaoacint.17-0425

(169) Sharma, R.K., & Parisi, S. (2016) *Toxins and Contaminants in Indian Food Products*, Springer International Publishing, Cham, Switzerland. doi:10.1007/978-3-319-48049-7
(170) Parisi, S. (2018) *J. AOAC Int*. **101**, 914–915. doi:10.5740/jaoacint.17-0444
(171) Mania, I., Barone, C., Pellerito, A., Laganà, P., & Parisi, S. (2017) *Ind. Aliment.* **56**, 18–22
(172) Delgado, A.M., Vaz Almeida, M.D., & Parisi, S. (2016) *Chemistry of the Mediterranean Diet*, Springer International Publishing, Cham, Switzerland. doi:10.1007/978-3-319-29370-7
(173) Zaccheo, A., Palmaccio, E., Venable, M., Locarnini-Sciaroni, I., & Parisi, S. (2016) *Food Hygiene and Applied Food Microbiology in an Anthropological Cross Cultural Perspective*, Springer International Publishing, Cham, Switzerland. doi:10.1007/978-3-319-44975-3
(174) Haddad, M.A. (2017) *J. Food Res*. **6**, 75–81. doi:10.5539/jfr.v6n2p75
(175) Abu-Romman, S.M., Haddad, M.A., & Al-Hadid, K.J. (2015) *Jordan J. Biol. Sci*. **8**, 301–306. doi:10.12816/0027066
(176) Obeidat, M., Abu-Romman, S., Odat, N., Haddad, M., Al-Abbadi, A., & Hawari, A. (2017) *Res. J. Microbiol*. **12**, 218–228. doi:10.3923/jm.2017.218.228