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Plant Origin Phenolics as Prospective Antioxidants: State-of-Art for Application

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***Abstract*— In the recent years there is a growing demand for plant origin antioxidants, due to their potential therapeutic value and low level of side effects. Among the plant origin substances, the metabolites with antioxidant activity are the widely used which are mainly belong to the phenolic group of compounds as well as carotenoids and vitamins. These natural antioxidants act via different mechanisms: they can decrease the level of oxidative damage in cells directly reacting with free radicals or indirectly - by inhibition the activity and expression of free radical generating enzymes or enhancing the activity or expression of intracellular antioxidant defense enzymes. The manuscript is focused on the main group of phenolics which can be used in pharmacological, food and other areas.**

Keywords—antioxidants, plant born metabolites, phenolics, flavonoids

I. Introduction

Plants possess various antioxidant mechanisms to quench the deleterious effects of the oxidative stress. They are able to produce both enzymatic and non-enzymatic antioxidants. Catalases, superoxide dismutases (SOD), peroxidases (PX), and some others (ascorbate peroxidase, monodehydroascorbate reductase (MDHAR or MDAR), dehydroascorbate reductase (DHAR or DAR), glutathione reductase (GR) belong to the enzymatic plant antioxidants group [1]. The main non-enzymatic plant antioxidants are ascorbate, glutathione (GSH), carotenoids, tocopherols and phenolic compounds [2]. Among the plant-born antioxidants poliphenolics are the most abundant and broadly used substances. A wide number of investigations are made to reveal the possible mechanisms of their action [3]. The bioavailability of these substances is under the focus of a number of studies since a long period of time [4].

Poliphenolics are characterized by the presence of the phenolic rings and exist as monomers, dimers and polymers of the base units and can be esterized or non-esterized. There are several classes of poliphenols such as flavonoids, aromatic acids and quinines, stilbenes, lignans and tannins [4]. Poliphenolics are characterized by the broad spectrum of biological activity.

II. Flavonoids and Their Biological Activity

Flavonoids are the broadest group of poliphenols, which belong to the plant secondary metabolites and can be found in large number of fruits and vegetables. They are widely used in pharmaceutical, food, cosmetics industry due to their antioxidant, neuroprotective, anti-inflammatory, anticancer, anti-mutagenic and antibacterial effects [5]. The possible mechanisms of their action are considered to be the ability to inhibit several enzymes, such as xanthine oxidase (XO), cyclo-oxygenase (COX), lipoxygenase and phosphoinositide 3-kinase [6-8]. A vast part of flavonoids possesses antioxidative and free radical scavenging capacity, coronary heart disease prevention ability, immunomodulatory, hepatoprotective, anti-inflammatory, and anticancer activities, while some flavonoids exhibit potential antiviral activities. In plant organism flavonoids help in combating oxidative stress and act as growth regulators as well as serve as responsible for color and aroma [1, 9]. More than 5000 different flavonoids have been described, having a polyphenolic structure (Fig. 1) [10].

Depending on the structural features and carbon of the C ring on which the B ring is attached and the degree of unsaturation and oxidation of the C ring, flavonoids can be subdivided into different sub-groups: flavones, flavonols,

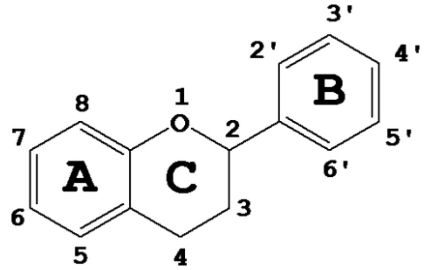


Fig. 1. Basic structure of flavonoids.

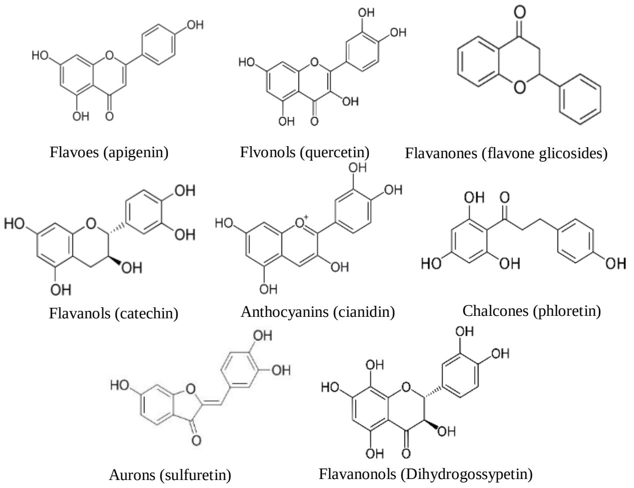


Fig. 2. The structures of various sub-groups of flavonoids.

flavanones, flavanonols, flavanols (catechins), anthocyanins, aurones and chalcones (Fig. 1, 2).

It has been reported that flavones and catechins are the most powerful flavonoids for protecting the body againstreactive oxygen species (ROS) [4]. Flavonoids may have an additive effect to the other ROS scavenging compounds such as enzymatic (SODs, catalases, peroxidases etc.) and non-enzymatic (glutathione, ascorbic acid and α-tocopherol) ones [9].

The main sources of dietary flavonoids are fruits, some beverages, vegetables, spices and others [11, 12]. Our studies have shown that the total flavonoid amount in ethanol extract (EE) of oregano, growing in Armenia, was 3.9±0.7 mg g^{-1} catechin equivalent [12]. According to the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay the antiradical activity of oregano EE, expressed with IC_{50} value, was 19.97 µg mL^{-1} [12]. This extract showed also an expressed Fe^{2+} chelating capability, ability to inhibit tyrosinase and prevent the lipid peroxidation [12].

III. Gallic acid as plant-born biologically active compound

Phenolic acids are an important and abundant sub-group of phenolic compounds with the basic chemical structure of C_6-C_1 (hydroxybenzoic acids) or C_6-C_3 (hydroxycinnamic acids), consisting of a phenolic ring and a carboxyl substituent. The shikimic acid pathway of plant metabolism usually brings to the biosynthesis of phenolic acids. In some cases, phenolic acids are the precursors of other important phytochemicals, such as tannins, coumarins, benzoquinones, and naphthoquinones.

Caffeic acid, ferulic acid, *p*-hydroxybenzoic acid, protocatechuic acid, vanillic acid, salicylic acid, and gallic acid are the most common members of phenolic acids (Fig.3).

Gallic acid and its derivatives are among the most useful antioxidant agents (Fig. 4), belonging to the aromatic acids group of phenolic substances [13]. It is reported to have several health-promoting effects.

Gallic acid is one of the most abundant phenolic acids. It has been isolated from different plant species such, but also is produced through the hydrolytic breakdown of tannic acid using a glycoprotein esterase [14].

Gallic acid and its derivatives such as lauryl gallate, propyl gallate, octyl gallate, tetradecyl gallate, and hexadecyl gallate, can inhibit the oxidation of oils and fats due to their free radical scavenging and antioxidant activity [15]. A huge number of literature data stating the high biological and pharmacological activities of these

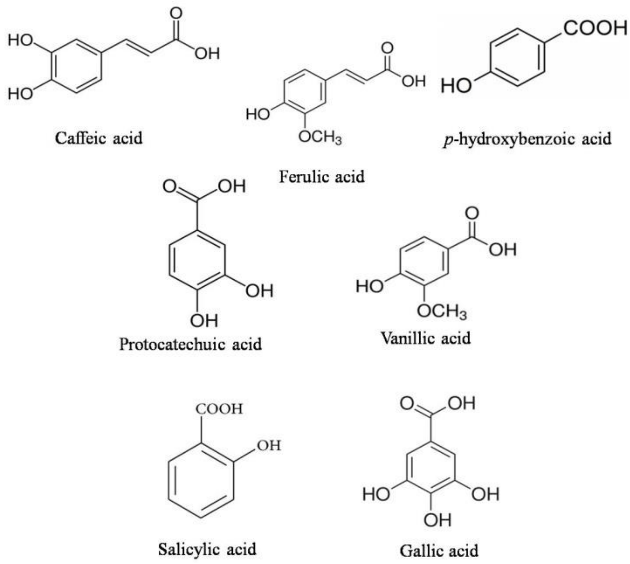
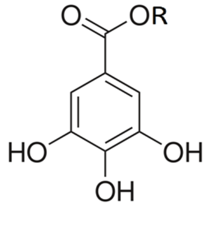


Fig. 3. Structures of the most common phenolic acids.



	R
Gallic acid	H
Methyl gallate	CH_3
Ethyl gallate	CH_2CH_3
Propyl gallate	$(CH_2)_2CH_3$
Isopropyl gallate	$CH(CH_3)_2$
Butyl gallate	$(CH_2)_3CH_3$
Pentyl gallate	$(CH_2)_4CH_3$
Isobutyl gallate	$CH_2CH(CH_3)_2$
Hexyl gallate	$(CH_2)_5CH_3$
Heptyl gallate	$(CH_2)_6CH_3$
Octyl gallate	$(CH_2)_7CH_3$
Decyl gallate	$(CH_2)_9CH_3$
Undecyl gallate	$(CH_2)_{10}CH_3$
Dodecyl gallate	$(CH_2)_{11}CH_3$
Tetradecyl gallate	$(CH_2)_{13}CH$

Fig. 4. Gallic acid and its derivatives.

phytochemicals, with emphasis on antioxidant, antimicrobial, anti-inflammatory, anticancer, cardioprotective, gastroprotective, and neuroprotective effects [13, 15-18]. Some authors stating that such range of activity is related to the antioxidant mechanisms *in vitro* [17]. Our investigations are stating that plants of the genus Artemisia, represented in Armenian flora, possess excellent antioxidant potential due to containing of high amount of phenolic substances. Around 300 species of this genus have been reported and 16 are described as part of the Armenian flora [18]. Thus, Babayan et al. [19] were able to demonstrate that *Artemisia vulgaris* L., *A. fragrans* Willd., *A. absinthium* L., and *A. splendens* Willd. collected from the Aragatsotn region (1500 – 1600 m above see's level) during the flowering period displayed high antioxidant potential.

IV. Resveratrol: the most famous poliphenolic of stilbenoid group

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a stilbenoid, possessing two phenol rings linked to each other by an ethylene bridge (Fig 5) [20].

Resveratrol is a well-known biologically active phenolic substance, synthesized by more than 70 plant species. It's high concentration was observed in grapes [20, 21]. In plant organism, it acts as a phytoalexin and synthesize when undergoing the ionizing radiation and microbial invasions [22]. Now around 90 new resveratrol compounds are known (monomers, dimmers, trimers, tetramers, hexamers, pentamers and octamer), which were identified in a number of plant families, such as *Dipterocarpaceae*, *Paeoniaceae*, *Vitaceae*, *Leguminosae*, *Gnetaceae*, *Cyperaceae*, *Polygonaceae* *Gramineae* and *Poaceae* families [20, 23]. Modification of resveratrol structure is of interest, as many resveratrol derivatives have been synthesized (methoxylated, hydroxylated and halogenated forms) with favorable therapeutic potential [24-26]. Resveratrol is present in food products, as glycosylated forms. Though, plants and pathogens, and even human digestive tract possess enzymes able to triggers polyphenols oxidation (and subsequent inactivation), the glycosylation prevents enzymatic oxidation of resveratrol, thereby preserving its biological effects and increasing its overall stability and bioavailability. Moreover, intestinal cells can absorb only resveratrol aglycone form. So, absorption process requires glycosidases [20, 27].

Resveratrol possesses a wide range of biological properties, such as antioxidant, cardioprotective, neuroprotective, anti-inflammatory and anticancer activities [20, 28]. Among them the best described resveratrol property is their capacity to act as a potent antioxidant [20, 29].

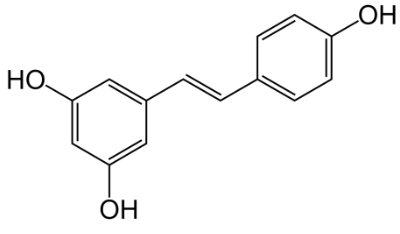


Fig. 5. The chemical structure of resveratrol.

Resveratrol antioxidant activity depends upon the arrangement of functional groups on nuclear structure. Therefore, configuration, substitution, and a number of total hydroxyl groups influence mechanisms of antioxidant activity, such as radical scavenging and metal ion chelation properties. Resveratrol can also be used in minimizing or preventing lipid oxidation in pharmaceutical products, delaying toxic oxidation products formation, and maintaining both nutritional quality and prolonging pharmaceuticals shelf-life [20, 30-33].

V. Conclusions

Current manuscript confirms the fact that plants can serve as excellent sources for the valuable substances with antioxidant properties, which are useful in pharmacological and therapeutic interventions in multiple health problems; however, available data mostly limited to just *in vitro* and animal studies. Future investigations are needed to further define the safety and therapeutic efficacy of plant-born poliphenolic and other antioxidants in humans.

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