Review Article

Evaluating the Potential of Phytochemicals as Natural Substitute for Synthetic Antioxidant: A review

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ABSTRACT

This study aimed at investigating the antioxidant potential of flavonoids as a subgroup of polyphenols and ultimately entirely and partially substitute the synthetic antioxidant with natural them. All relevant databases were searched for the terms including 'phytochemical', polyphenol', 'flavonoid', 'natural additive', as well as 'antioxidant activity' combined with *in vivo* and *in vitro* phrases. Free radicals are among the damaging factors to macromolecules. The oxidative reaction caused by these radicals is one of the reasons for food spoilage, which causes unpleasant odor, loss of taste, damaged tissue and appearance, and loss of nutritional value of exposed material. The common antioxidants employed in foods include Butylated hydroxytoluene (BHT), Butylated hydroxyanisole (BHA), Tert-butyl hydroquinone (TBHQ), and Propyl gallate (P.G.). Synthetic antioxidants have adverse effects such as causing mutation and carcinogenicity in the human body despite their high performance; hence, many studies have been carried out on replacing them with natural antioxidants. Phytochemicals and a widespread group of them known as polyphenols possess a high antioxidant activity. A major subset of polyphenols, Flavonoids, are secondary metabolites in plants with many applications. These compounds are potential antioxidants because of their capabilities, such as scavenging the free radicals donating hydrogen atoms, electrons, and chelate metal cations. The antioxidant mechanism of action of flavonoids is transferring hydrogen toward free radicals. Accordingly, the more the flavonoid structure makes the hydrogen transfer faster and easier, the more the flavonoid's antioxidant power will be. Therefore, the antioxidant activity of the flavonoids with hydroxy groups in their structure is higher among the different flavonoids. Besides health promotion and some disease prevention effects, various in vitro studies have shown that flavonoids possess a high antioxidant activity that is competitive with synthetic antioxidants. However, to make it commercially available, cheaper and high-performance extraction methods of flavonoids will have to be developed.

Keywords: antioxidant, flavonoids, food preservation, phytochemical, polyphenol,

1. INTRODUCTION

Most food products are made up of various chemical components that are easily oxidized. Lipids (fats, oils, and waxes) in general have significant potential to lose electrons. Their auto-oxidation in food products initiated by metal ions exposure, metallo-protein catalysts, light, heat, or ionizing radiation can deteriorate the color, flavor, texture, quality, and safety of food. Food fats are chemically made of triglycerides, and oxidation occurs at the unsaturated sites of the triglycerides, resulting in rancidity [1,2]. Free radicals are the most frequent oxidants in biological systems. These are atoms, molecules, or ions with one or more unpaired electrons, turning theme to highly reactive and unstable. In order to stabilize themselves, unpaired electrons in these free radicals seek out and acquire electrons from other substances. However, the first assault pairs the odd electron, another free radical is produced in the process, resulting in a chain reaction. The free radicals cause considerable damages to the macromolecules in organisms (of bodies), including DNA, proteins, lipids, and carbohydrates. The damages caused by free radicals are also referred to as oxidative damages [3-6]. Free radicals are frequently derived from oxygen, nitrogen, and sulfur molecules in biological systems. These free radicals are constituents of the reactive oxygen species (ROS), reactive nitrogen species (RNS), and reactive sulfur species (RSS) molecular families. Free radicals such as superoxide anion (O2-•), per hydroxyl radical (HO2•), hydroxyl radical (O.H.), nitric oxide, and other species like hydrogen peroxide (H2O2), singlet oxygen (O2), hypochlorous acid (HOCl), and peroxynitrite (ONOO-) are forms of ROS. Nitric oxide is converted to RNS by reacting with O2-• to generate ONOO-. By reacting thiols with ROS, RSS is quickly produced. The production of ROS occurs as a result of cellular metabolism and functional activities [1,7].

Antioxidants are one of the factors which prevent oxidative damages. The structure of antioxidants is such that although they release hydrogen atoms, the reactivity of these atoms is extremely low [8]. In general, antioxidants are divided into two groups - synthetic and natural. Because synthetic antioxidants are cheaper, more accessible, having high efficiency and stability, they were gradually considered as alternatives to their natural type after World War II [9]. Phenolic compounds among the phytochemical are known to be the most important natural antioxidants, and they are recognized as excellent antioxidants due to their capacity of scavenging free radicals, donating hydrogen atoms, electrons, and chelate metal cations [10,11]. The natural antioxidant can be considered as health-promoting compounds as well as food preservatives. These antioxidants can help to limit or prevent the production of chemical toxins, improving the nutritional value and health benefits of the food products and also extending their shelf life. While called natural, overdose usage of these antioxidants can cause poisoning in consumers; hence legislation for their utilization on the industrial scale should be considered [12]. Nowadays, synthetic antioxidants are commonly used in industries, the most common of which include Butylated hydroxytoluene (BHT), Butylated hydroxyanisole (BHA), Tert-butyl hydroquinone (TBHQ), and Propyl gallate (P.G.). Many other suggested compounds have antioxidant activity, of which only a few can be used in foods. Ethoxyquin (EMQ) is a synthetic antioxidant with a non-phenolic structure, the use of which is not permitted for human consumption compared to other antioxidants mentioned earlier; however, it is used for food preservation in animal feeds [13]. Synthetic antioxidants are available for the industries with an economically profitable price which consequently leads to lower price of the product for costumers; they possess the effective potential to preserve the product and extend the shelf life, the common type of them are applicable for a wide range of the products and have a specified dosage for utilization in each product as well as known changes associate with their addition. Nevertheless, synthetic antioxidants can also initiate or development of numerous diseases such as cancer, cardiovascular diseases, type 2 diabetes mellitus, cataract, rheumatoid arthritis, or different neurodegenerative diseases. They can damage DNA and induce mutations, resulting in the onset of neoplasia. Furthermore, these antioxidants may cause lipid and blood cholesterol levels to surge in the body lead to the development of enzymes for its metabolization in the liver, posing a risk of destroying vital chemicals like vitamin D, acting as inducers of urticaria and eczematous dermatitis [14, 15].

The use of antioxidants in foods has been limited by the regulatory laws of one country or international standards [16], so the consumption of synthetic antioxidants is limited due to their toxic effects and carcinogenicity. Since the carcinogenicity of synthetic antioxidants has been observed, the necessity of using alternatives without adverse effects is becoming increasingly important [17]. Therefore, in recent years, the demand for natural antioxidants, especially of plant origins, has increased because of growing concern on consumption health due to their toxicological effects [18-20]. Hence, this review has been conducted to investigate the antioxidant activity of phytochemicals, emphasizing *in vitro* studies to shed light on the potential of flavonoids to be utilized as natural antioxidants in food and examine their capability to substitute the synthetic antioxidants.

2. METHODOLOGY

This review was conducted to investigate the antioxidant activity of flavonoids and their potential to entirely or partially substitute synthetic antioxidants in food products. All relevant databases were searched for the terms including 'phytochemical', polyphenol', 'flavonoid', 'natural additive', as well as 'antioxidant activity' combined with *in vivo* and *in vitro* phrases. It should also be mentioned that in the process of selecting relevant papers, priority was given to the research providing *in vitro* information regarding the antioxidant activity of phytochemicals. Data was collected through search using Scopus, Pubmed, Web of Science, Science Direct, Google Scholar databases, and related books and reliable websites, as well as prominent conferences and congresses with various publication dates ranging from 1981 to 2021.

3. DISCUSSION

Phytochemicals are chemical compounds and bioactive substances of plants that are naturally found in plants associated with biological activities beneficial for human health. These compounds are categorized by their chemical structures and include polyphenols (flavonoids and non-flavonoid polyphenols), carotenoids, phytosterols, betalains, and organosulfur. Phytochemical compounds cause the color, odor, and taste of plants to be changeless and play an important role in the plant defense system. More than 5000 pigments in plants are considered phytochemicals. These compounds can reveal their biological activity through various mechanisms such as antiviral, antibacterial properties, antioxidant, anti-inflammatory, anticancer, modulation of enzyme activities, stimulation of the immune system, gene expression, regulation of cholesterol synthesis, and blood pressure. They can also improve health and prevent diseases [21, 22]. Studies have shown that the presence of these compounds in the fruits and vegetables-rich diets help in delaying aging, reducing inflammation and oxidative stress risk and also decreasing the risk of chronic diseases such as cardiovascular diseases, arteriosclerosis, cancer, diabetes, cataract, neurological diseases, and disorders of the cognitive function [23-25]. Fruits, vegetables, legumes, and whole grains are the primary sources of phytochemicals in the diet [26]. There are different methods for extracting phytochemical compounds. These compounds can be extracted from plants through physical and chemical methods such as ultrasonication, super-critical fluid extraction, solvent extraction, and cold pressing [21, 27]. It should be pointed out that many phytochemicals are insoluble in aqueous solutions and do not have acceptable oil solubility. These compounds are chemically unstable and will decompose rapidly if being exposed to the external environment and adjacent to oxygen, temperature, light, pH, and some other reactive substances.

Phenolic compounds or polyphenols are important groups of phytochemical compounds in plants [28, 29]. Phenolic compounds have excellent antioxidant characteristics and are often found in fruits and vegetables [30]. These compounds include flavonoids, flavanols, anthocyanins, anthraquinones, benzoyl acetyl, and their derivatives. Polyphenols have two general classes, one is flavonoids, and the other is phenolic acids. Different parts of the plant produce compounds that are mainly phenolic and are known as natural antioxidants. Compounds such as flavonoids, coumarins, tocopherols, carotenoids, organic acids, and derivatives of cinnamic acid are phenolic antioxidants from the plant source. In this category of compounds, the hydroxyl group is directly bonded to an aromatic hydrocarbon [31]. There are at least 8000 known structures of phenolic compounds, the simplest of which is Phenol shown in Figure 1 [28]. Phenolic compounds are known for their antioxidant activity that depends on the structure, especially the number and location of hydroxyl groups and the nature of substituents in aromatic rings [32].

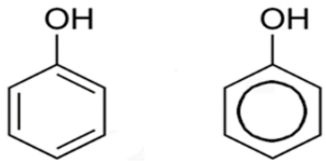
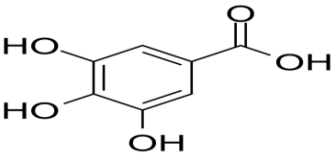
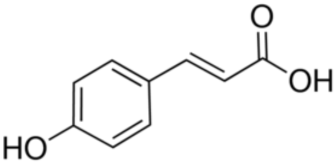
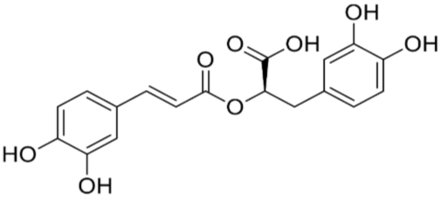


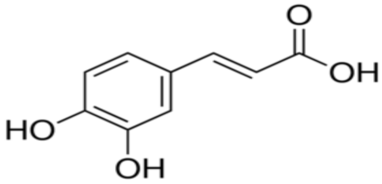
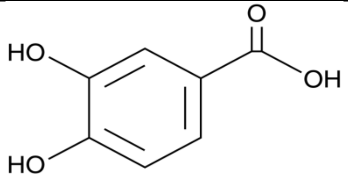
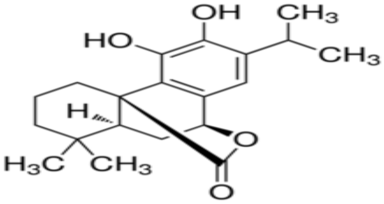
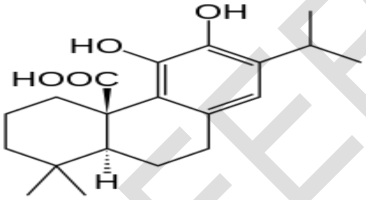
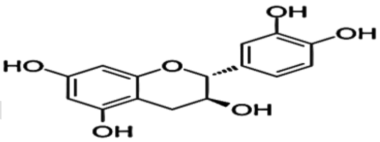
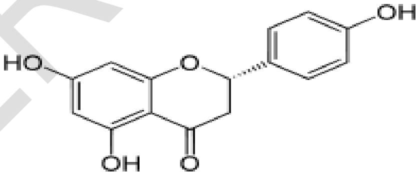
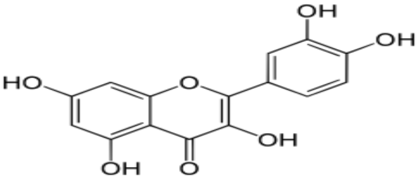
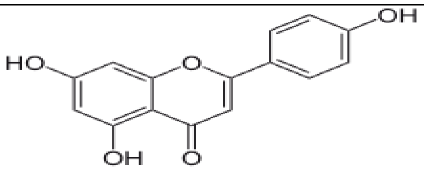
Fig. 1. Phenol, the most straightforward component of phenolic compounds

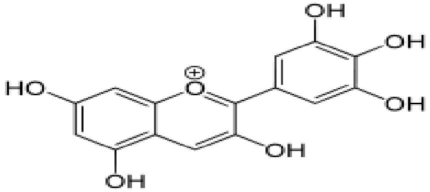
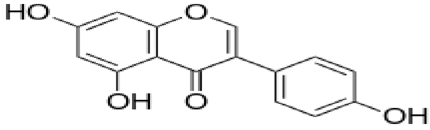
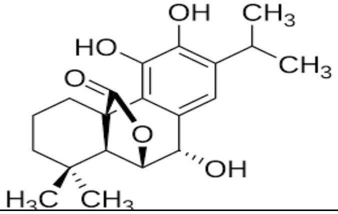
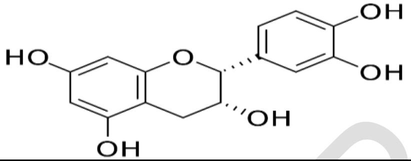
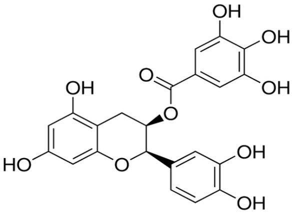
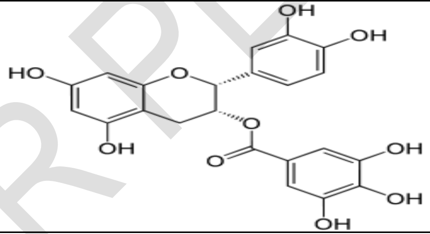
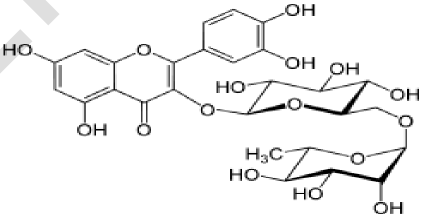
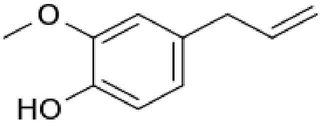
Phenolic compounds are referred to as health promotion compounds and have the capability of preventing chronic heart disease [33, 34]. The antioxidant characteristics of phenolic compounds depend on their capability of giving electrons to trap free radicals by the formation of stable phenoxyl compounds [35].

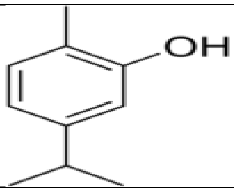
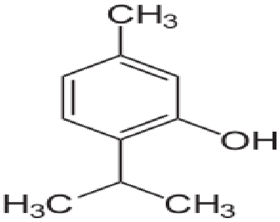
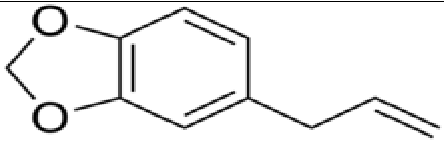
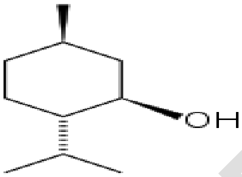
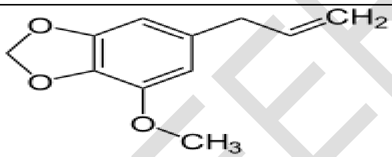
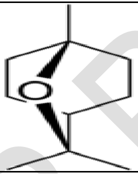
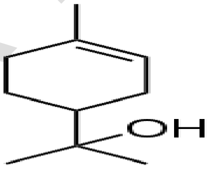
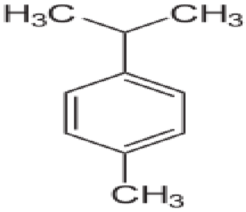
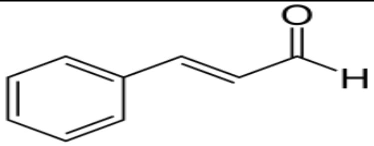
Plants have always been excellent food sources for the consumption of valuable bioactive compounds [36]. These natural antioxidants have been extracted from plants in the form of essential oils and extract from various sources such as fruits (grapes, pomegranates, dates, kinnow), vegetables (broccoli, potatoes, drumstick, pumpkin, Indian turmeric, nettle), medicinal plants, and spices (tea, rosemary, oregano, cinnamon, common sage, thyme, peppermint, ginger, clove) and have been investigated for reducing fat oxidation [37-42]. Phenolic compounds are discovered in combination with saccharides (monosaccharides and polysaccharides) bonded to one or more phenolic groups. Although some phenolic compounds are ubiquitous, others are specific to particular plant families and are found in particular plant organs or at specific stages of plant growth [43]. Important phenolic compounds in plants that have been reported to possess antioxidant activity in *in vitro* and *in vivo* studies are listed in Table 1.

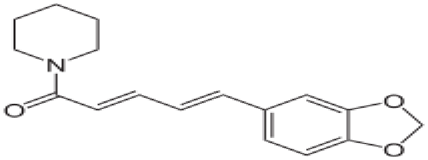
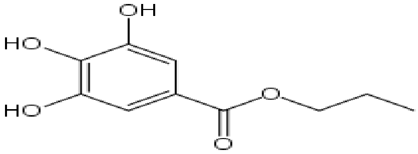
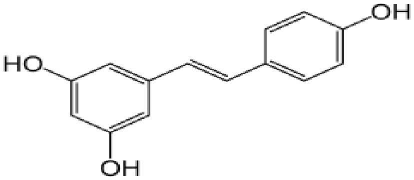
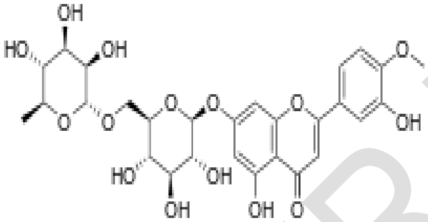
Table 1. The phenolic compounds with high antioxidant activity

Name	Chemical formula	Structure	Reference(s)
Gallic acid	$C_7H_6O_5$		Gallic acid prevents the melanogenesis, rancidity, and spoilage of fats and oils due to its antioxidant nature, facilitating its application as food additives in various eatable materials like baked goods, candy, chewing gums, and cosmetics [44,45].
p-Coumaric acid	$C_9H_8O_3$		p-coumaric acid occurs widely in the cell walls of graminaceous plants. It decreases low-density lipoprotein peroxidation, shows antioxidant and antimicrobial activities, and plays a vital role in human health. It is a good antioxidant and a good antimicrobial; therefore, it is a natural alternative instead of synthetic additives [46].
Rosmarinic acid	$C_{18}H_{16}O_8$		A significant number of herbal preparations and food supplements containing rosmarinic acid are marketed with claims for beneficial health effects. Due to lipid peroxidation and bacterial growth inhibition, Rosmarinic acid is approved for use as a natural antioxidant and/or preservative in the food industry [47].

Caffeic acid	$C_9H_8O_4$		Natural phenolic antioxidants, including caffeic and ferulic acids, gained attention as photoprotective agents. Caffeic acid is a α-tocopherol protective in low-density lipoprotein. Furthermore, their combination with other products, such as chlorogenic and caftaric acids, showed more potent antioxidant activity in various systems [48].
Protocatechuic acid	$C_7H_6O_4$		Protocatechuic acid is a type of widely distributed naturally occurring phenolic acid. Protocatechuic acid has structural similarities with gallic acid, caffeic acid, vanillic acid, and syringic acid, which are well-known antioxidant compounds. Hence, it could therefore be used in the pharmacological or food industry as a natural antioxidant [49].
Carnosol	$C_{20}H_{26}O_4$		Several *in vitro* studies were reviewed regarding the antioxidant activity of the carnosol and carnosic acid. Using the 2,2-diphenyl-1-picrylhydrazyl method, these bioactive compounds were validated for their antioxidant activity. Also, using the thiobarbituric acid, superoxide anion, and lipid-free radicals scavenging activity assays and Rancimat methods (determination of oxidative stability of fat), carnosol has been reported to inhibit lipid peroxidation through the lipid-free radical scavenging mechanism. These studies have shown the antioxidant potential of carnosol and carnosic acid, whose properties are closely related to other biological activities, such as cytoprotective and anticancer, primarily due to their ability to neutralize reactive oxygen species [50].
Carnosic acid	$C_{20}H_{28}O_4$		
Flavanol (catechin)	$C_{15}H_{14}O_6$		It has been revealed that catechin is antioxidant at all concentrations and attributed the antioxidant behavior to iron chelation. Consequently, catechin has been a widely used antioxidant in combination with other biopolymers for the development of active food packaging [51,52].
Flavanone (naringenin)	$C_{15}H_{12}O_5$		Naringenin has exhibited higher antioxidant capacity and hydroxyl and superoxide radical scavenger efficiency than naringin. Additionally, naringenin has shown greater effectiveness in the protection against oxidative damage to lipids in a dose-dependent manner [53].
Flavonol (quercetin)	$C_{15}H_{10}O_7$		Due to the capacity of quercetin to scavenge free radicals and bind transition metal ions, quercetin is considered a powerful antioxidant. Because of these qualities, quercetin can prevent lipid peroxidation [54].
Flavone (Apigenin)	$C_{15}H_{10}O_5$		Apigenin is a widely distributed flavonoid responsible for antioxidant potential and chelating redox-active metals. The antioxidant mechanism of apigenin includes oxidant enzymes inhibition, modulation of redox signaling pathways, reinforcing enzymatic and nonenzymatic antioxidants, metal chelation, and free radical scavenging [55].

Anthocyanin (delphinidin)	$C_{15}H_{11}O_7^+$		Anthocyanins are polyphenols with the known antioxidant activity which can be responsible for various biological activities. The antioxidant capacity of plant-derived anthocyanins has been demonstrated with various assay methods, including ORAC, FRAP, TEAC, and DPPH. [56].
Isoflavone (genistein)	$C_{15}H_{10}O_5$		Genistein has been widely studied as an antioxidant, with some research claiming that it may have the ability to scavenge reactive oxygen and nitrogen species (ROS and RNS) effectively [57].
Rosmanol	$C_{20}H_{26}O_5$		Comparison between rosmanol and synthetic antioxidants has shown that rosmanol possesses an antioxidant capacity four times higher than synthetic antioxidants of BRT and BRA [58].
Epicatechin	$C_{15}H_{14}O_6$		Catechin and epicatechin are two flavan-3-ol stereoisomers that, according to their structure, have comparable radical scavenging and antioxidant activity. Both have the ability to bind the iron ion and scavenge hydroxyl, peroxyl, and 2,2-diphenyl-1picrylhydrazyl (DPPH) radicals [59].
Epicatechin gallate(ECG)	$C_{22}H_{18}O_{10}$		Evaluation of radical scavenging activity of some catechins *in vitro* revealed that in each of the assays, including DPPH, ABTS, and FRAP after epigallocatechin gallate, epicatechin gallate had the highest potential [60].
Epigallocatechin gallate (EGCG)	$C_{22}H_{18}O_{11}$		Epigallocatechin gallate effectively protected against supercoiled DNA nicking caused by peroxyl and hydroxyl radicals. In scavenging the 1,1-diphenyl-2-picylhydrazyl (DPPH) radical, epigallocatechin gallate had a synergistic impact with -tocopherol, demonstrating a direct free radical scavenging potential [61].
Rutin	$C_{27}H_{30}O_{16}$		Rutin has exhibited strong DPPH radical scavenging activity. In addition, rutin possesses effective inhibition property of lipid peroxidation. The antioxidant activity of rutin is competitive with various antioxidants such as BHT and Vc (ascorbic acid) [62].
Eugenol	$C_{10}H_{12}O_2$		Antioxidant activity of eugenol has been evaluated with different assays such as DPPH, ABTS, and DMPD are competitive with inhibiting potential for lipid peroxidation of standard antioxidants including BHA, BHT, α-tocopherol, and Trolox [63].

Carvacrol	$C_{10}H_{14}O$		The antioxidant activity of carvacrol has been shown through a series of *in vitro* assays, including hydroxyl radical, superoxide, nitric oxide, DPPH, and ABTS radical scavenging assays [64].
Thymol	$C_{10}H_{14}O$		Different reports regarding antioxidant properties of thymol are due to its ability to donate H-atoms from phenol hydroxyl groups, which could react with peroxyl radicals to produce stabilized phenoxyl radicals and, consequently, terminate lipid peroxidation chain reactions [65].
Safrole	$C_{10}H_{10}O_2$		The antioxidant activity of safrole oil has been reported to be comparatively lower than the Trolox reference standard, which is known to have high antioxidant activity. However, free radicals scavenging activity of safrole is still considered eminent [66]
Menthol	$C_{10}H_{20}O$		Different studies have reported that the antioxidant activity of some of the plant-derived essential oils is related to menthol; for instance, the radical scavenging activity of peppermint essential oil is associated with the presence of menthol and menthone, which contains the hydroxyl radical ($^{-}$O.H.) [67, 68].
Myristicin	$C_{11}H_{12}O_3$		While evaluating the myristicin with DPPH and ABS methods revealed its antioxidant activity inadequacy compared to BHA, the synergetic effect of myristin with other antioxidants can be considered [69].
Eucalyptol	$C_{10}H_{18}O$	 	Previous researches have shown that there might be a direct relationship between the high scavenging activity of essential oil over BHTand the high content of Eucalyptol in the essential oil [70, 71].
Terpineol	$C_{10}H_{18}O$		Due to various biological activities, terpineol is a proper compound to be improved the shelf life of food products, as it has been shown to be effective for enhancing the antioxidant activity of chitosan biopolymer to inhibit free radicals mediated deterioration [72].
p-Cymene	$C_{10}H_{14}$		Previous investigations on DPPH free radical scavenging by some plant-derived essential oils have revealed that *p*-Cymene, as one of the main constituents, plays a prominent role in the antioxidant activity of the essential oils [73].
Cinnamaldehyde	C_9H_8O		Cinnamaldehyde enhances the antioxidant defense against reactive oxygen species and reduces the levels of lipid peroxidation products, and increases the activities of antioxidant enzymes [74].

Piperine	$C_{17}H_{19}NO_3$		Piperine interacts readily with highly oxidizing radicals and binds redox-active metal ions, indicating that it could potentially function as an effective antioxidant [75].
Propyl gallate	$C_{10}H_{12}O_5$		As it has become determined by free radical scavenging assays, the propyl gallate compound has the potential to inhibit lipid oxidation which is competitive with TBHQ [76].
Resveratrol	$C_{14}H_{12}O_3$		In different studies, resveratrol has exhibited a robust reducing power, chelating activity on Fe^{2+}, free radical-scavenging, hydrogen peroxide scavenging, and hydroxyl radical scavenging activities [77].
Diosmin	$C_{28}H_{32}O_{15}$		The *in vitro* studies on diosmin showed its free radical scavenging activity. The hydroxyl free radical scavenging and superoxide free radical scavenging activities of diosmin have been evidenced by the *in vitro* studies [78].

3.1 The Structure of Flavonoids and Their Antioxidant Activity

Flavonoids are the largest group of phytochemicals and are also considered as the most widespread group of polyphenols found in fruits and vegetables. Flavonoids have excellent antioxidant properties and can exhibit their antioxidant activity by scavenging free radicals and reactive oxygen species, chelating the metals, and preventing the oxidation of low-density lipoproteins (LDLs) [30, 79]. Flavones are the most basic structures of flavonoids. From the structural point of view, all flavonoids possess a C6-C3-C6 carbon skeleton in which the carbon atoms are arranged in three phenolic rings A, B, and C, and the C ring normally contains oxygen [80, 81]. Figure 2 indicates a Phenylbenzopyrane as the basic structure of flavonoids.

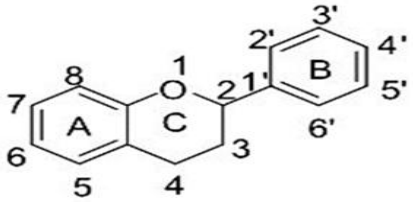


Fig. 2 basic structure of flavonoids (Phenylbenzopyrane)

Flavonoids have different families, each of which has different members. The flavonoid families include Flavones, Isoflavones, Flavonols, Flavanones, Dihydroflavonols, Flavan-3-ols (monomers), Proanthocyanidins (oligomeric flavan-3-ols), and Anthocyanidins. These families, along with their members, are shown in Table 2 [82].

Each of these flavonoids can possess completely distinct antioxidant activity due to their specific structure. Many in vitro and in vivo studies utilizing natural flavonoids have been conducted to confirm the relationships between flavonoid structure and antioxidant activity. The hydroxyl groups (C in figure 3), ortho-dihydroxy arrangement in the B ring (A in figure 3), C2-C3 unsaturated bond combined with C-4 carbonyl group in the C skeleton (B in figure 3), and O-methylation have all been identified as distinct chemical structures related to flavonoids antioxidant activities [83, 84].

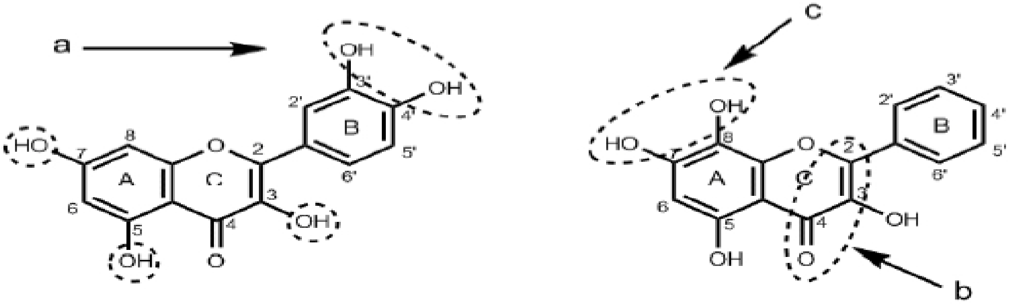


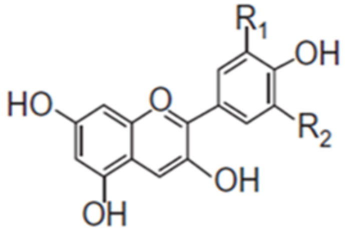
Fig. 3 The flavonoid structure-antioxidant activity relationships

The free hydroxyl group will donate its hydrogen atom to a radical molecule, stabilizing it and generating a flavonoid phenoxyl radical that is relatively stable. This stable molecule can then react with a second radical (Alkoxyl) to form a stable quinone structure. Furthermore, the location of the hydroxyl groups, rather than the overall quantity of hydroxyl groups, has a significant impact on antioxidative action. Scavenging of both oxygen and nitrogen-centered free radicals is dominated by the B-ring hydroxyl structure. Hydroxyl groups on this nucleus provide hydroxyl, peroxyl, and peroxynitrite radicals hydrogen and an electron, stabilizing them and forming a fairly stable flavonoid radical. Moreover, the twisting angle of the B-ring in relation to the remainder of the molecule has a significant impact on its capacity to scavenge free radicals [85-88].

Table 2. Flavonoids family

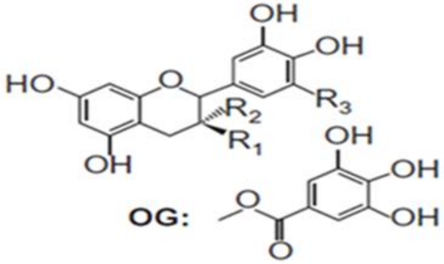
Primary structure	R groups alterations	Primary structure	R groups alterations

Anthocyanidins



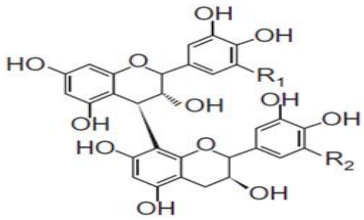
	R1	R2
Pelargonidin	H	H
Cyanidin	OH	H
Delphinidin	OH	OH
Peonidin	OCH_3	H
Petunidin	OCH_3	OH
Malvidin	OCH_3	OCH_3

Flavan-3-ols (monomers)



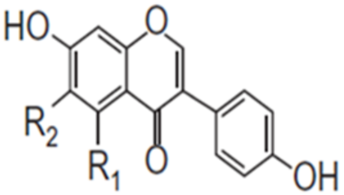
	R1	R2	R3
(+)Catchin	OH	H	H
(-)Epicatechin	H	OH	H
(+)Gallocatechol	OH	H	OH
(-)Epigallocatechin	H	OH	OH
(+)Catechin gallate	OG	H	H
(-)Epigallocatechin gallate	H	OG	H
(+)Gallocatechin gallate	OG	H	OH
(-)Epigallocatechin gallate	H	OG	OH

Proanthocyanidins (oligomeric flavan-3-ols)



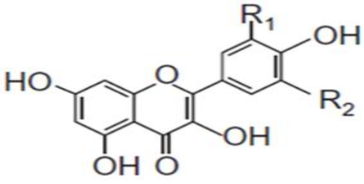
	R1	R2
Procyanidin B1 EC (4b-8)-C	H	H
Prodelphinidin B1 EGC-(4b-8)-GC	OH	OH

Isoflavones



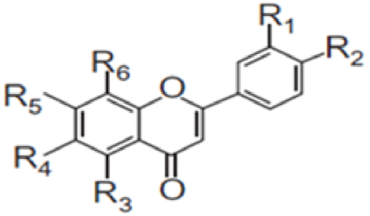
	R1	R2
Daidzein	H	H
Genistein	OH	H
Glycitein	H	OCH_3

Flavonols



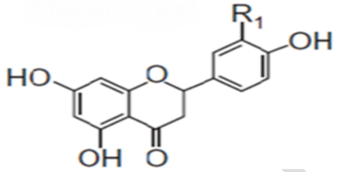
	R1	R2
Kaempferol	H	H
Quercetin	OH	H
Myricetin	OH	OH

Flavones



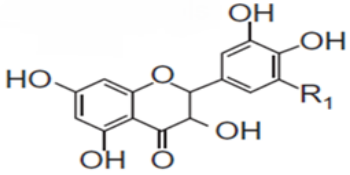
	R1	R2	R3	R4	R5	R6
Apigenin	H	OH	OH	H	OH	H
Luteolin	OH	OH	OH	H	OH	H
Tangeretin	H	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3
Nobiletin	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3

Flavanones



	R1
Naringin	H
Eriodictyol	OH
Hesperetin	OCH_3

Dihydroflavonols



	R1
Taxifolin	H
Ampelopsin	OH

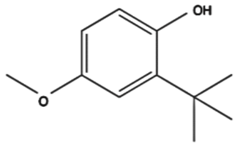
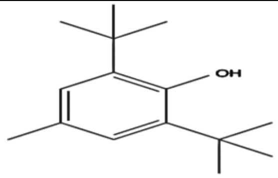
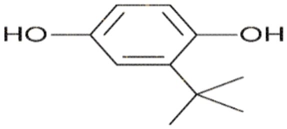
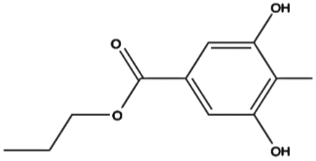
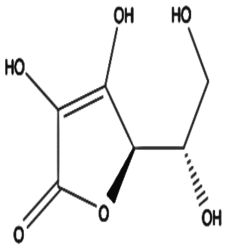
3. 2 Regulations Regarding Synthetic and Natural Antioxidants

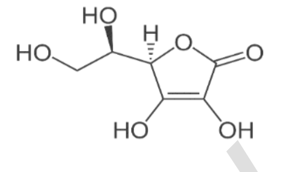
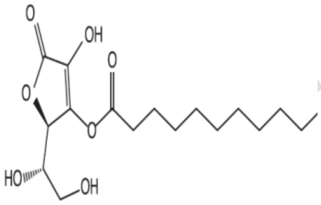
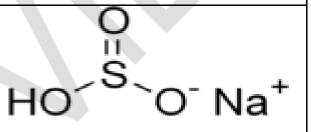
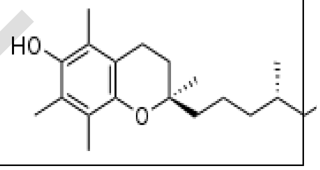
Many scientists claim that there should be a shift away from synthetic antioxidants due to the growing interest in natural food antioxidants; however, it has not yet been achieved, and thus the natural or synthetic origin of the various antioxidants currently used in the food industry is not specified in the official tables showing the amounts and permissions for the use of each additive in each type of food [89]. The Codex Alimentarius Commission is the worldwide standard-setting authority in charge of regulating and establishing the framework of food regulations that guide the use of antioxidants in foods. Since food regulatory systems and legal frameworks in respect to the use of antioxidants as food additives differ by country, these criteria are neither required nor immediately applicable [90]. The European Food Safety Authority (EFSA) of the European Union and the Food and Drug Administration (FDA) of the United States of America are the two primary guiding authorities in charge of regulating the licensing of food additives across the world [91]. Under the E.U., regulation E.C. No 1129/2011 specifies a list of antioxidants, categorized according to their E-numbers, that are regulated in the section of "other food additives." The natural antioxidants recognized as food additives by the E.U. include rosemary extracts (E392), ascorbic acid (E300), and tocopherols (E306–E309), according to this regulation [92]. Food products and ingredients are monitored by various authorities in the United States of America, the most relevant of which is the U.S. Food and Drug Administration (FDA). The FDA's regulations for food items are listed in Title 21 of the Code of Federal Regulations of the United States. There is no distinct category for natural antioxidants in the Code of Federal Regulations (21 CFR 182; 21 CFR 172), as there is in European regulations [93-95]. Although natural antioxidants such as ascorbic acid and tocopherols are specifically designated for use in food, the U.S. regulation is far more comprehensive than the European one and includes additional substances that fall into other categories but yet have demonstrated antioxidant activity. Several of the compounds allowed for use as coloring adjuncts, spices, or natural flavorings, such as phloretin glycoside (flavonoids), carotene, and astaxanthin (carotenoids), or extracts of rosemary or sage, have recognizable antioxidant potential. These antioxidants - phloretin, astaxanthin, and sage extract are not listed as food additives in any category in E.U. regulations, although they are classified for technical applications in U.S. standards [96, 97]. Considering the mentioned regulations, it is evident that regardless of utilization of natural or synthetic antioxidants, the optimal choice of antioxidant for each food matrix should be determined on a case-by-case basis, as *in vitro* antioxidant activities are not always reproduced in the food, and there are frequent changes due to food processing or interactions with other food matrix components that have antioxidant or prooxidant activities [98].

3. 3 Antioxidants in Food Preservation

Once lipid oxidation in a food matrix is analyzed over time, there is frequently a lag phase during which the deposition of lipid oxidation by-products is moderated. This lag phase is associated with the presence of antioxidants in the food matrix, which limit the synthesis of free radicals that target fatty acids, as well as the low free radical generation that precedes the concentration of hydroperoxides and ß-scission reactions [89]. The objective of the food industry is to extend the lag period during which the concentrations of the components that cause rancidity taste are below human detection limits. When the food matrix lacks natural antioxidants and/or includes significant endogenous prooxidants, the most typical technique employed by food manufacturers to limit oxidation is to add antioxidants directly to the food matrix [98]. In the context of food science, the phrase "antioxidant" refers to substances that prevent lipid peroxidation and other oxidative reactions, hence preserving the freshness and shelf-life extension of foods. The method of action is the same whether the antioxidant is natural or synthetic, and it comprises free radical scavenging, metal chelating, and singlet oxygen quenching [99, 100]. Due to their stability, low cost, and wide availability, synthetic antioxidants are frequently employed. Phenolic antioxidants are the most extensively used synthetic antioxidants in the food industry, with Butylated hydroxyanisole (BHA) (E320), Butylated hydroxytoluene (BHT) (E321), Propyl gallate (P.G.) (E310), and Tert-butyl hydroquinone (TBHQ) (E319) being the most common. In table 3, some critical information regarding the chemical structure as well as health-related concerns about the consumption of these antioxidants has been revealed [89, 101-110]. Despite the fact that these synthetic antioxidants are widely used and tightly regulated, there are concerns about their safety owing to overdose usage and/or misuse; for instance, combining various antioxidants may exacerbate their toxic effects. High concentrations of chemical synthetic antioxidants may induce DNA damage or *in vitro* toxicity in some tissues [111-1114]. The food industry is attempting to reduce the use of synthetic compounds by substituting natural alternatives in response to consumer concerns that they are being exposed to potentially toxic chemical synthetic compounds through their regular diet. Though, just because plant antioxidants are natural, it does not mean they are safe by default; toxicity tests are always required for each case [111].

Table 3. Chemical structures of food industry antioxidants

Antioxidants	Molecular formula	Carcinogenic potential	Allergenic potential	Chemical structures
Butylated hydroxyanisole (BHA)	$C_{11}H_{16}O_2$	Category 1 (use within limit on body = 5.2 % w/w; face >100% w/w; hands >100 % w/w)	Moderate sensitizer (max dose = 0.0729 µg/cm^2 /hr)	
		Acceptable daily intake (ADI)*: below 1.0 mg/kg body weight		
Butylated Hydroxytoluene (BHT)	$C_{15}H_{24}O$	–	Weak sensitizer (max dose = 14.6 µg/cm^2 /hr)	
		Acceptable daily intake (ADI): 0.25 mg/kg body weight		
tert-Butylhydroquinone (TBHQ)	$C_{10}H_{14}O_2$	–	–	
		Acceptable daily intake (ADI): 0.7 mg/kg body weight		
Propyl Gallate (P.G.)	$C_{10}H_{12}O_5$	–	Moderate sensitizer (max dose = 0.0255 µg/cm^2 /hr)	
		Acceptable daily intake (ADI): 0.5 mg/kg body weight		
Ascorbic Acid (Vitamin C)	$C_6H_8O_6$	Category 3 (use with precaution)	–	
		Acceptable daily intake (ADI): there is no safety concern for the use of ascorbic acid (E300), sodium ascorbate (E301), and calcium ascorbate (E302) as food additives at the reported uses and use levels, and there is no need for a numerical ADI for ascorbic acid and its salts.		

<table>
<tr><td rowspan="2">Erythorbic acid</td><td rowspan="2">$C_6H_8O_6$</td><td>–</td><td>–</td><td rowspan="2"></td></tr>
<tr><td colspan="2">Acceptable daily intake (ADI): 6 mg/kg body weight</td></tr>
<tr><td rowspan="2">Ascorbyl Palmitate</td><td rowspan="2">$C_{22}H_{38}O_7$</td><td>–</td><td>Weak sensitizer (max dose = 7.29 µg/cm^2 /hr)</td><td rowspan="2"></td></tr>
<tr><td colspan="2">Acceptable daily intake (ADI): considering the available data, the Panel concluded that there is no safety concern for the use of ascorbyl palmitate (E304(i)) and ascorbyl stearate (E304(ii)) as food additives at the reported uses and use levels</td></tr>
<tr><td rowspan="2">Sodium bisulfite</td><td rowspan="2">$NaHSO_3$</td><td>–</td><td>–</td><td rowspan="2"></td></tr>
<tr><td colspan="2">Acceptable daily intake (ADI): 0.7 mg SO_2 equivalent/kg body weight</td></tr>
<tr><td rowspan="2">alpha-tocopherol</td><td rowspan="2">$C_{29}H_{50}O_2$</td><td>–</td><td>–</td><td rowspan="2"></td></tr>
<tr><td colspan="2">Acceptable daily intake (ADI): 11-13 mg/kg body weight</td></tr>
</table>

*Mentioned quantities are specified for adults. For more details or quantity for a specific age group, please refer to the released document at European Food Safety Authority.

3. 4 The Structure of Flavonoids and Their Antioxidant Properties

Flavonoids are active polyphenol compounds that are found in almost all fruits and vegetables. Aglycones, glycosides, and methylated derivatives are different forms of flavonoids. Aglycones are produced when the glycosyl group in a glycoside is replaced by a hydrogen atom. Glycosides are composed of two parts — sugars (glycons) and non-sugars (aglycones) — and play different roles in plants [6]. Various species of flavonoids differ in terms of oxidation rate and C-ring substituent; in other words, the presence of one double bond, one carbonyl group, and one hydroxy group in the pyranyl C ring is used to classify them into species and subspecies. The substituents of A and B rings with hydroxy groups are used to identify the available members in a species. Flavonoids in plants are often derived from glycosylate and play a role in the production of shining blue, reddish-yellow, and reddish-orange shades in leaves, flowers, and fruits. Regardless of the variety of fruits and vegetables, flavonoids are found in seeds, nuts, buds, spices, herbal medications, and some drinks such as wine, especially red and tea wines, and in smaller quantities in beer. The antioxidant properties are among the most important properties of flavonoids. Flavonoids are highly effective antioxidants in general, and it has been observed that they protect the body against cardiovascular diseases by reducing the oxidation of low-density lipoproteins (LDLs). In many studies, flavonoid-rich plant extracts have been used to prevent food oxidation [7]. Despite the many benefits of synthetic antioxidants compared to natural ones, such as their low prices, the use of antioxidants in food has been limited by regulatory laws of one country or international standards [13]. Hence, the use of synthetic antioxidants is limited due to their toxic effects and carcinogenicity. Synthetic antioxidants have a limit of using 0.02% fat of food [6]. Since the carcinogenic properties of synthetic antioxidants have been observed, the necessity of the use of alternatives without adverse effects has become increasingly important [14]. Therefore, in recent years, the demand for natural antioxidants, especially of plant origin, has increased due to the increasing concern among consumers about these synthetic antioxidants considering potential toxicological effects [20]. As a whole, flavonoids are highly effective antioxidants, and there are pieces of evidence that they protect the body against cardiovascular diseases by reducing the oxidation of low-density lipoproteins (LDLs). Flavonoids both prevent lipid peroxidation and act as scavengers of radicals such as superoxides, lipid peroxyls, and hydroxyls, and also lead to inactivation of single oxygen molecules and prevention of the activity of lipoxygenases. The high potency of flavonoids in inhibiting free radicals relates to their ability to transfer a hydrogen atom from a hydroxy group to the free radical and ultimately stabilize it:

FLOH + R° → FLO° + R.H.

Flavones and catechins are the most powerful flavonoids with antioxidant properties that can protect the body against reactive oxygen species (ROS). According to many studies, the free radical scavenging activity for flavonoids has been reported as follow [6, 115]:

Myricetin > quercetin > rhamnetin > morin > diosmetin > naringenin > apigenin > catechin > 5,7-Dihydroxy-3,3',4'-trimethoxyflavone > robinin > kaempferol > flavone

Many flavonoids have significantly higher antioxidant capacity than vitamins C and E. On an in vitro scale, flavonoids can prevent free radical harm through the mechanisms including direct scavenging of ROS, activation of antioxidant enzymes, metal chelating activity, reduction of α-tocopheryl radicals, inhibition of oxidases, mitigation of oxidative stress caused by nitric oxide, increase in uric acid levels, and increase in antioxidant properties of low molecular antioxidants [116].
Based on the direct scavenging of ROS mechanism, flavonoids may directly scavenge free radicals by donating hydrogen atoms. The following equation is used to render radicals inactive; $R^{\cdot}$ is a free radical, and $Fl\text{-}O^{\cdot}$ is a flavonoid phenoxyl radical [117].

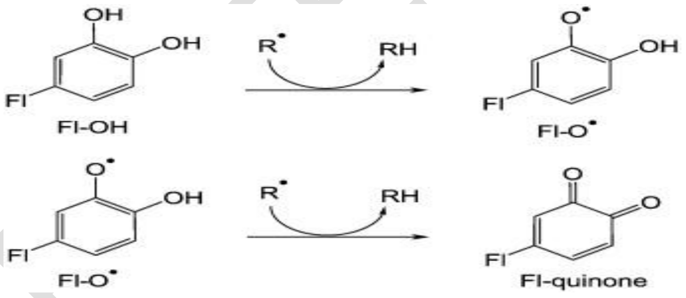


Fig. 4 Scavenging of reactive oxygen species ($R^{\cdot}$) by flavonoid. The free radical $Fl\text{-}O^{\cdot}$ may react with a second radical, acquiring a stable quinone structure [117]

By activation of antioxidant enzymes approach, flavonoids can induce phase II detoxifying enzymes such NAD(P)H-quinone oxidoreductase, glutathione S-transferase, and UDP-glucuronosyl transferase, all of which are important defense enzymes against electrophilic toxicants and oxidative stress. Furthermore, some effects might be a resetting of a combination of radical scavenging and enzyme activity [116, 118]. Specific flavonoids possess the metal chelating activity and have been shown to chelate iron and copper, eliminating a potential source of free radicals. The catechol moiety in ring B, the 3-hydroxyl and 4-oxo groups in the heterocyclic ring C, and the 4-oxo and 5-hydroxyl groups in the C and A rings are all trace metal-binding sites in flavonoids [117].

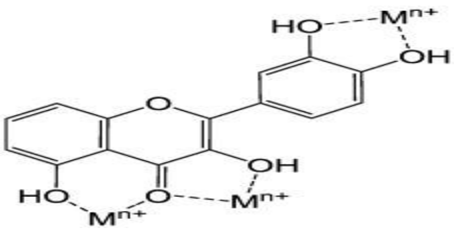


Fig. 5 Binding sites for trace metals [117]

In cell membranes and human low-density lipoproteins (LDL), α-tocopherol is a crucial antioxidant that protects lipoprotein molecules from oxidative damage. Based on the reduction of α-tocopheryl radicals mechanism, the flavonoids can assist the α-tocopheryl radical, which is a potential prooxidant, by acting as hydrogen donors. They also have the ability to delay the oxidation of LDL by interacting with the α-tocopheryl radical [119]. Flavonoids can cause inhibition of oxidases, so that inhibiting the enzymes responsible for superoxide ($O_2^{\bullet -}$) production, such as protein kinase C. Flavonoids have also been shown to inhibit cyclooxygenase, lipoxygenase, microsomal succinoxidase, and NADH oxidase [116]. Another oxidase, known as xanthine oxidase, is a molybdenum-containing enzyme and converts xanthine to uric acid. The transfer of an oxygen atom from the molybdenum core to xanthine is known to occur in this enzyme-catalyzed process [120].

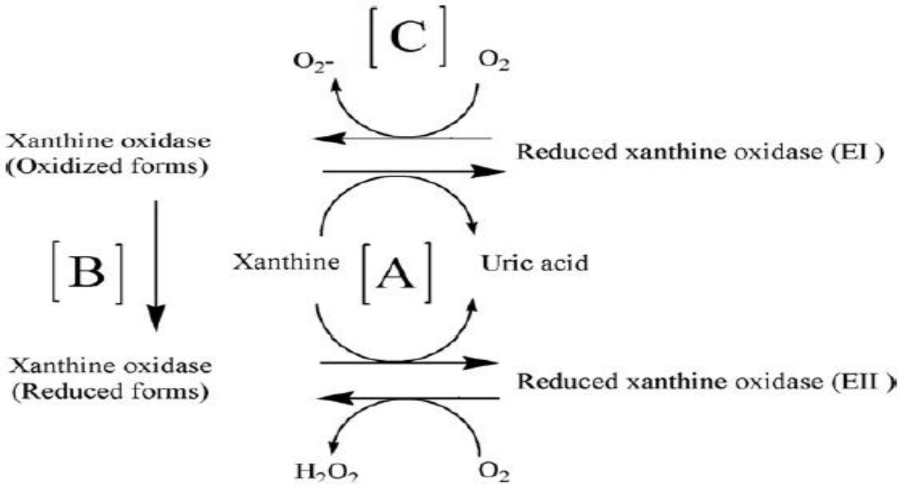


Fig. 6 The inhibition of the superoxide anion generation catalyzed by xanthine oxidase with antioxidants consisted of three reactions (A, B and C). [A] Inhibition of the xanthine oxidase reaction with antioxidants. [B] Reduction of the xanthine oxidase with antioxidants. [C] Scavenging of the superoxide anion with antioxidants [120]

Mitigation of oxidative stress caused by nitric oxide is another way flavonoids apply their antioxidant activity. Although nitric oxide (NO) is necessary for sustaining blood vessel dilatation, excessive levels can cause oxidative damage. NO is created by NO synthases catalyzing the oxidation of L-arginine. In numerous lipopolysaccharide-activated cell lines and cultures, flavonoids inhibited NO generation. This impact was most likely induced by flavonoid suppression of inducible NOS expression rather than inhibition of its activity [116, 121]. An increase in uric acid levels can lead to a surge in plasma total antioxidant capacity. There are significant differences in plasma or serum total antioxidant capacity and plasma flavonoids concentrations. Increased uric acid levels, which are a key contributor to plasma total antioxidant capacity, are likely to be responsible for the considerable rise in plasma total antioxidant capacity found after eating flavonoid-rich meals [122]. An increase in antioxidant properties of low molecular antioxidants may occur by their amalgamation with flavonoids.

UVA-induced cellular DNA damage was greatly reduced when flavonoids were combined with β-carotene during preincubation, and the effects were in the order of naringin > rutin > quercetin. According to the findings, combining - carotene with naringin, rutin, or quercetin may improve the safety of β-carotene [123].

As mentioned before, one of the most important factors is affecting the antioxidant activity of flavonoids is the structure of flavonoids. The presence of hydroxyl and glycosylated groups has a significant effect on the antioxidant properties of flavonoids. The presence of glycosylated groups reduces the antioxidant properties of flavonoids. On the other hand, the presence of hydroxy groups increases the antioxidant properties of flavonoids. For maximum free radical scavenging activity, flavonoids must have a hydroxy group at the 4' and 3' positions of the B ring, a conjugated double bond between carbon 2 and 3, an Oxo group at the 4 position of the C ring, a hydroxy group on carbon 3 in the C ring, and a hydroxy group on carbon 5 in the A ring (refer to Figure 2). Flavonoids, along with their hydroxy groups, act as free radical scavengers, and the presence of many hydroxy groups, especially in the B ring, increases their antioxidant activity. The hydroxyls of the B ring are the first active stations in traversing the oxidation chain. The three structural groups are responsible for determining the scavenging activity of free radicals and antioxidant activity of flavonoids: a catechol section in the B ring, a conjugated double bond at the positions 2 and 3, an oxo group with the carbonyl group function in the ring C, and the presence of hydroxy groups at the positions 3 and 5 [115, 124]. Hence, it is noteworthy that flavonoids can exhibit different antioxidant power according to their structure and its relation to the suitable mechanism of the antioxidant activity.

Flavonoids are classified as non-nutrients in the scientific food realm. They have typically been eliminated from food crops because of their inhibitory effects on digestive enzymes, astringency and bitterness, and poor absorption after intake. However, as a result of their inclusion in regular meals, several therapeutic benefits such as antioxidant properties in animal studies, the decrease of cardiovascular disease and high blood pressure, and antiallergic, anti-inflammatory, and anti-diabetic activities make them important. As a result, flavonoids are now considered third-order functional components (food factors) that have biological regulatory roles [125]. Flavonoids are also important in food preservation and industry. The phrase "sustainable intensification" was created by the Royal Society of London, which denotes current agricultural practices aiming at raising food production while also safeguarding biodiversity and environmental processes. Food waste minimization is one of the most critical elements of "sustainable intensification." As a result, there is a growing demand for postharvest storage technology and food preservatives research [126, 127]. Since today's consumers are concerned about the usage of chemically synthesized preservatives, natural products are being prioritized. At the same time, industries are putting a greater focus on the usage of plant-derived antioxidant and antibacterial components to improve shelf life. In this setting, the antioxidant activity of flavonoids may not only preserve food stability over time but also provide protection against necrotrophic fungi and food-borne diseases. The antioxidant mechanism of flavonoids in food systems is mainly connected to their capacity to prevent lipid autoxidation, which is a primary cause of food quality degradation and shelf-life reduction [128]. Flavonoids can donate hydrogen atoms to lipid radicals, resulting in more stable antioxidant radicals that are less susceptible to autoxidation. Antioxidant action mechanisms of flavonoids include direct scavenging of ROS, inhibition of ROS formation via chelation of trace elements (e.g., quercetin has iron-chelating and iron-stabilizing properties), or inhibition of free radical-generating enzymes (e.g., glutathione S-transferase, microsomal monooxygenase, mitochondrial succinoxidase, NADH oxidase), and activation of antioxidant defenses (e.g., upregulation of antioxidant enzymes with radical scavenging ability). A synergy of some of these mechanisms, such as radical scavenging activity along with some enzyme function inhibition, may also occur [129-131]. The capacity of flavonoids to lower the susceptibility of fresh fruits and vegetables to particular postharvest infections may also contribute to their antioxidant effect in extending shelf life [126, 132]. Flavonoids, exceptionally high hydroxylated anthocyanins, can prevent the growth of grey mold (produced by Botrytis cinerea), causing the dynamics of the ROS burst to be disrupted during infection. Flavonoids may bind and inactivate proteins and may form complexes with bacterial cell walls, giving them antibacterial action against a variety of pathogens [133-135]. Flavonoids have been employed in a variety of dietary applications due to their beneficial characteristics. They have been used as active antioxidant materials in the packaging of oxygen-sensitive foods to extend shelf life and improve bioactive component content [136]. They have also been used to minimize lipid oxidation in cooked pork patties and raw mackerel fillets [137]. Considering all mentioned information regarding the antioxidant potential of flavonoids, it is evident that, besides their health-promoting effects, they can be utilized as food additives to extend their shelf life.

4. CONCLUSION

As one of the significant subgroups of polyphenols, flavonoids are crucial secondary chemicals known as phytochemicals generated by plants that serve a variety of activities, including growth and development and stress resistance. The high demand and interest in the utilization of flavonoids in food processing, as well as their health-promoting effects, has resulted in the increased acknowledgment of positive aspects of flavonoids for human health. It is evident that as an important subset of the phytochemicals family, flavonoids possess a considerable antioxidant activity that is competitive with synthetic antioxidants. Flavonoids are abundant in vegetables, flowers, and seeds, and approaches to extract these compounds from these natural sources have been developed for use as food additives and preservatives. However, on a commercial scale, the extraction of flavonoids directly from the mentioned sources does not seem to be profitable. Hence, it seems that attempting to find a proper source for extraction, such as plant wastes as well as designing a high-performance extraction method, would be a critical step for these compounds to be applied on food products as preservatives.

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