

Selected Powerful Natural Antioxidants: Structure, Food Sources, Antioxidant Activities and Important Health Benefits

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Abstract

Numerous epidemiological studies indicate that consumption of antioxidant-rich foods is beneficial to human health and reduces the risks of dangerous diseases and premature aging. Among natural antioxidants some stand out for their powerful activity and health benefits and they are epigallocatechin gallate, quercetin, curcumin, resveratrol, hydroxytyrosol, astaxanthin, lycopene, dihydroquercetin, and lignans. Preclinical, clinical, and therapeutic studies of these antioxidants in their pure form or in their combination have shown positive health benefits. This review highlights basic information and interesting findings with their source, structure, antioxidant properties, and potential health benefits to human.

Keywords: natural antioxidants, foods, antioxidant activity, bioavailability, health benefits

1. Introduction

Epidemiological studies have demonstrated that consumption of antioxidant rich foods and beverages reduces the risks of dangerous diseases and premature aging in human (Preedy, 2010; Klein, 2014; Preedy, 2014; Waltson, Preedy, & Zibadi, 2014; Preedy, 2014; Yashin, Vedenin, & Yashin, 2016; Chu, 2012). Under excessive oxidative stress, the natural human antioxidant system is not able to neutralize the deleterious effects of free radicals which could damage cellular DNA, lipids, proteins, and other biomolecules that led to the development of chronic diseases and premature aging. Antioxidants are required to scavenge free radicals and prevent their actions *in vivo* to protect cells and tissues.

Several dietary antioxidants are primarily originated from fruits, vegetables, berries, spices, nuts, tea, coffee, cocoa, and red wine. Food databases of the total antioxidant content in various foods have been created during recent years and the intake of natural antioxidants in different countries have been evaluated (Yashin et al., 2010; Nemzer, Yashin, & Yashin, 2013; Wu et al., 2004). Halvorsen et al., (2006) evaluated and ranked 1120 food samples from USDA for total antioxidant activity and found that top 50 antioxidant rich foods are occupied by spices, fruits, vegetables, berries, chocolate, and nuts (Halvorsen et al., 2006). Along with proteins, fats, carbohydrates, vitamins, and trace elements, natural antioxidants are recognized as an important component of a healthy diet. In fact, antioxidant potential plays significant role in the marketing of antioxidant rich superfoods.

An antioxidant functions by transferring electrons, donating hydrogen, reducing peroxides, quenching singlet oxygen and superoxide, and chelating metal ion (Brewer, 2011; Nimese & Pal, 2015). Several *in vitro* antioxidant assays have been developed in continuation of the searching and identifying natural and safe antioxidants. Due to their differences in structures and reaction mechanisms of free radical several assays have been used to measure the antioxidant activities. For instance, ORAC (oxygen radical absorbance capacity), DPPH (diphenylpicrylhydrazyl), ABTS (2,2-azobis-(3-ethyl-benzothiazoline-6-sulfonate), (FRAP (ferric-reducing antioxidant power), superoxide anion radical scavenging, phospholipid peroxidation assays have been widely used as *in vitro* tests to determine the antioxidant potential for synthetic and natural products. In

most of the studies multiple assays were adopted to test the antioxidant capacity of number of plant extracts and phytochemicals as single antioxidant assay may not give conclusive information on antioxidant potential.

Antioxidant studies of fruits, vegetables, beverages, and functional foods have been attracting continuously for long time and the number of reports in this area increasing every year. Most of these reports covered the polyphenols content and their effect on antioxidant activities with their mechanism of action using appropriate antioxidant assays. These studies indicated the strong antioxidant activities arose due to the presence of certain polyphenolic and/or synergism of several antioxidant compounds (Brewer, 2011; Wu et al., 2004; Oroian & Escriche, 2015). Plant extracts and food matrices contain complex mixtures of polyphenols. Likewise, numerous compounds from these extracts have been reported to have potential antioxidant activities, many plant extract and food matrices are poorly characterized. However, among these natural antioxidant compounds very few have strong antioxidant activities. In this review we describe an overview of selected most powerful natural antioxidant compounds with their structure, source, bioavailability, antioxidant properties, and potential health benefits.

2. Powerful Natural Antioxidants

Antioxidants are subgrouped into three major groups such as polyphenols, vitamins, and carotenoids. In addition to these general group of antioxidant compounds some other nonphenolic compounds also showed promising antioxidant potential. Polyphenols are ubiquitous in plant species and more than 8000 phenolic compounds have been reported, many of which are major constituents of foods. Classification of polyphenols are based on the number of phenol rings and the nature of binding the rings to one another. Major groups of polyphenols constitute flavonoids, phenolic acids, phenolic alcohol, stilbenes, and lignans. Among them most common polyphenols are flavonoids that provide color and flavor to fruits and vegetables. Flavonoids are subgrouped into flavones (e.g., luteolin, tangeritin), flavonols (e.g., catechin, quercetin), flavanones (e.g., butin, naringin), flavanols (e.g., catechin, epicatechin gallate, epigallocatechin), anthocyanidins (e.g., petunidin pelargonidin, malvidin), and isoflavones (e.g., genistein, daidzein). Natural flavonoids exist as glycosides (sugar is attached) as well as aglycones forms. Most of the polyphenols exist in conjugated forms with one or more sugar residue linked to hydroxyl group.

The antioxidant potential of natural antioxidant depends on the structural composition of free hydroxyl (-OH) group in the flavonoid skeleton. Flavonoids with multiple hydroxyl groups show higher antioxidant activities compared to flavonoids with single hydroxyl group. However steric relationship and lipid/hydrophilic phase equilibrium also plays critical role towards the antioxidant activities (Brown & Kelly, 2007). The general mechanism of antioxidant activities of polyphenolic compounds undergoes inactivation of free radicals via transfer of hydrogen atom and electron. However, efficiency of *in vivo* and *in vitro* antioxidant activities depends on various factors such as structure, source, bioavailability of antioxidants, genetic, environmental, and physiological conditions.

Based on the reports on antioxidant activities of natural antioxidants very few have super strong antioxidant activity and have been used by consumers worldwide. We have listed nine such natural antioxidant compounds in the Table1 including their structure and major sources.

2.1 Epigallocatechin Gallate (EGCG) and other Catechins

Catechins are one of the major flavonoid compounds that constitute strong antioxidant activities. The common structural unit of catechin composed of a C₁₅ (C₆-C₃-C₆) skeleton containing 3 ring (A, B, and C) phenolic compounds where a double ring attached to a third ring (each phenyl ring has multiple hydroxyl group) by a single bond. In addition to the significant antioxidant properties tea catechins, they have the novel characteristic of trapping reactive carbonyl species. The ring A of the catechins is responsible for reactive carbonyl species trapping, and ring B contribute towards antioxidation (Wang & Ho, 2009).

Green tea is the major source of catechins containing 15 to 20% of dry weight (Yashin, Vedenin, & Yashin, 2016; Juneja, Kapoor, Okubo, & Rao, 2013). Black tea and oolong tea which are fully and partially fermented tea respectively, also contain a significant level of catechin compounds. However, due to differences in manufacturing process polyphenol contents in black tea and oolong tea are different from green tea. Nonfermented green tea products contain higher levels of total phenolics and catechins. EGCG is reported as the main active constituent of green tea which comprises 50 to 80% of the total catechin content. In addition to EGCG epicatechin gallate (ECG), epigallocatechin (EGC), epicatechin (EC) and catechin (C) are some other catechin available in tea. Other sources of catechins include grapes, red wine, cocoa, and dark chocolate. Dry red wine contains catechin (191 mg/L) and epicatechin (82 mg/L) at levels that are 4 to 6 times higher than in white wine. Cocoa and dark chocolate contain catechin and epicatechin only. In cocoa they make up to 40% of the total

polyphenol content. Catechins are also found in white and yellow tea which are not fermented.

Number of studies indicated catechin extract and purified fraction from all these natural resources exhibited significant antioxidant activity *in vivo*, *in vitro*, and in clinical studies. Recently He et al., (2018) studied the antioxidant potential of some catechins and reported that epigallocatechin gallate had the highest radical-scavenging activity and significant role to retard the ROS production because of the presence of hydroxyl and galloyl groups (He, Xu, Yang, & Wang, 2018). Grazeisek et al., (2018) reported in a study that catechins showed the highest activities in ABTS-scavenging capacity and FRAP assay (Grazeisek, Naparło, Bartosz, & Sadowska-Bartosz, 2018).

Green teas are being consumed for medicinal benefits for thousands of years. In recent decades, the benefits of green tea and EGCG alone were specifically studied in hundreds of epidemiological studies. Large body of literature are available on the health benefits of tea (Preedy, 2013; Powell, 2015; Yashin, Yashin, & Nemzer, 2012; Hayat, Iqbal, Malik, Bilal & Musthag, 2015; Wiejska, 2014). Green tea polyphenols are reported to play significant role in the prevention of cardiovascular diseases (Arab, Khan, & Lam, 2013; Grassi et al., 2013; Hodgson, 2008; Keske et al., 2015; Pang et al., 2015), reduction in low-density lipoprotein oxidation (Grassi et al., 2013), reduction in the risk of stroke and infarction (Hodgson, 2008), reduction of cholesterol levels (Kajimoto, Kajimoto, & Kakuda, 2003), and decrease in blood pressure (Liu et al., 2013). Several studies indicated the anticancer activities against the cancer in prostate, stomach, intestine, liver, breast, rectal, lung, kidney, and pancreatic (Brausi, Rizzi, & Bettuzzi, 2008; Borrelli, Capasso, Russo, & Ernst, 2004; Myung et al., 2009; Butler et al., 2015; Baba et al., 2012; Ogunleye, Xue, & Michels, 2010; Li, Yin, Wang, & Jiang, 2014; Arab & Il'yasova, 2003; Li et al., 2008; Carvalho, Jerónimo, Valentão, Andrade, & Silva, 2010; Shankar, Ganapathy, Hingorani, & Srivastava, 2008). Sabu et al., (2002) have reported that administration of green tea polyphenols increased glucose tolerance significantly when administered to normal rat and reduced serum glucose level in alloxan diabetic rats (Sabu, Smitha, & Kuttan, 2002). Moreover, green tea polyphenols containing catechin acted against chronic diseases (Balentine & Paetau-Robinson, 2000), hepatitis C (Lin et al., 2013) and B (Xu, Wang, Deng, Hu, & Wang, 2008), Epstein-Barr virus (Liu et al., 2013), influenza virus (Matsumoto, Yamada, Takuma, Niino, & Sagesaka, 2011), bacterium *Helicobacter pylori* (Stoicov, Saffari, & Houghton, 2009), and inflammation (Chatterjee, Chandra, Dey, & Bhattacharya, 2012; Sing, Akhtar, & Haqqi, 2010). It helped in protection from obesity (Rains, Agarawal, & Maki, 2011), improvement of mental abilities (Ide et al., 2014), beneficial effects in oral diseases (Kushiyama, Shimazaki, Murakami, & Yamashita, 2009), protection against Alzheimer's disease (Dragicevic et al., 2011), protection against urinary tract infections (Reygaert & Jusifi, 2013), human skin protection against UV radiation (Camouse et al., 2009). Interestingly galloyl moiety in catechins plays significant role towards the beneficial effects including lipid lowering effect (Ikeda, Tsuda, & Suzuki, 2005).

2.2 Quercetin

Quercetin is one of the most common flavonol compounds that comprised of an alcohol group on the C ring of flavonoid C15 skeleton. Quercetin is characterized by the presence of an ortho-dihydroxy or catechol group, a 2, 3-double bond, and 3, 5 hydroxyl substitution (Bors, Heller, Michel, & Saran, 1990). These special structural properties have featured quercetin, as an excellent antioxidant agent (Silva, Santos, Caroco, Rocha, Justino, & Mira, 2002; Rietjens, Boersma, van der Woude, Jeurissen, Schutte, & Alink, 2005).

Quercetin is highly abundant in fruits and vegetables. Onion is reported to have the highest level of quercetin (approx. 300 mg/kg) (Beecher, 1999). Other vegetables, such as broccoli, kale, apples, cranberries, yellow bell peppers, celery, tomatoes, blueberries, blackberries, raspberries, black currants, cherries, and apricots also have significant range of quercetin. Processing and storage could change the content of quercetin in food matrices. Ikou et al., (2001) found that frying and boiling cooking methods reduces the level of quercetin due to the thermal degradation and leaching to the water (Ikou et al., 2001). Long-term storage of foods was found to change their quercetin content. Efforts have been directed for enhancing nutraceutical bioaccessibility for quercetin. In order to improve the bio-accessibility of this hydrophobic nutraceutical formulated emulsion-based excipient food were prepared (Chen et al., 2018). Quercetin encapsulated in nanoparticle, for instance Zein/chitosan nanoparticles (ZCPs-Q) have also been prepared which improved its stability and water solubility and intracellular antioxidant activities (Ma, Yu, Yin, Tang, & Yang, 2018).

Quercetin shows potential anticarcinogenic, hepatoprotective, bacteriostatic, cardioprotective, anti-inflammatory, heavy metals chelating, and antioxidant properties (Russo, Spagnuolo, Tedesco, Billoto, & Russo, 2012). The chemical structure of quercetin confers it an outstanding antioxidant ability according to Bors et al., (1990) (Bors, Heller, Michel, & Saran, 1990). Quercetin protects DNA from oxidative damage occurred by the attack of free

radicals. The major beneficial health effects of quercetin-containing products are: inhibition of oxidative stress by protecting DNA molecules (Russo, Spagnuolo, Tedesco, Billoto, & Russo, 2012), anti-inflammatory activity (Boots et al., 2008), high therapeutic potential for reducing blood pressure (Larson, Symons, & Jalili, 2012), anti-cancer activity (Lamson & Brignall, 2000) against prostate cancer (Sharmila, et al., 2014) and breast cancer (Deng, Song, Zhou, Yuan, & Zheng, 2013), protection against Alzheimer's disease (Islam, Zaman, Jahan, & Chakraborty, 2013), reduction of oxidative stress after intense exercise (Gao et al., 2014); reduction of muscle disorders in athletes (Askari et al., 2013). Furthermore, quercetin improves immunity, has an anti-aging effect, and acts against obesity, diabetes, and cardiovascular diseases.

2.3 Curcumin

Curcumin is a polyphenolic compound with the molecular formula of $C_{21}H_{20}O_6$ containing α , β -diketo group, carbon-carbon double bonds, and phenyl rings with various hydroxyl and methoxy groups. It exhibits keto enol tautomerism. It is major component of turmeric and soluble in lipids. It is a unique antioxidant with significant antioxidant activity and reported to be an excellent free radical scavenger. Antioxidant activity of curcumin related strongly with the phenolic OH group. Studies on structure-activity relationship(s) for the antioxidant effects of curcumin are controversial. Whereas few group researchers claimed that the strong activity of curcumin is because of the presence of hydroxyl moiety, some other researchers proposed the involvement of the carbonyl groups. Barclay et al., (2000) reported that curcumin could donate H-atoms from the phenolic group (Barclay et al., 2000). In another study it was reported that curcumin is a strong H atom donor from the methylenic group rather than from the phenolic group (Jovanovic, Steenken, Boone, & Simic, 1999). Priyadarsini et al., (2003) have also proposed that the phenolic group plays active role for the free-radical-scavenging activity indicating the increased activity by the methoxy group (Priyadarsini et al., 2003). Thus, curcumin features unique chain breaking antioxidant ability which is correlated to the phenolic OH group and CH_2 group of the diketone moiety.

Curcumin is found in turmeric in significant amounts. Turmeric is one of the components of the curry spice mixture widely used in cooking. In Asian medicine, curcumin has been used for more than 4,000 years. It is non-toxic even at high doses. Consumption of up to 12 g/day is well tolerated. Curcumin can be detected in blood serum in 1.5-2 hours after consumption of turmeric. One major problem with curcumin is its lower bioavailability. To address this problem several formulations with nanoparticles, liposomes, micelles, and phospholipid complexes have been prepared (Peng et al., 2014; pawar et al., 2012; Ghosh et al., 2012, Yallapu, Dobberpuhl, Maher, Jaggi, & Chauhan, 2012; Gong et al., 2013; Pandelidou, Dima, Georgopoulos, Hatziantoniou, & Demetzos, 2011). The recommended consumption level of curcumin is 100 mg/day. Significant loss of spice ingredient was observed when the spices were subjected to heat treatments in cooking methods (Jayashree et al., 2016).

Curcumin's biological effects are summarized in several reports (Maheswari, Singh, Gaddipati, & Srimal, 2006; Aggarwal, Surth, & Shisodia, 2007; Goel, Kunnumakkara, & Aggarawal, Kumar, & Bharti, 2003). Curcumin is beneficial in cardiovascular diseases (Wu et al., 2004). It inhibits sclerosis (Coban et al., 2012) and reduces oxidation of low-density lipoproteins (Chen, 2006). It also neutralizes oxidative stress (Calaf et al., 2011) due to its strong antioxidative properties (Ak & Gulcin, 2008). It has strong anticancer activity (Sarvjeet & Ashok, 2006) against prostate cancer (Aggarwal, 2008) and melanoma. It is effective against Alzheimer's (Maheswari, Singh, Gaddipati, & Srimal, 2006) and Parkinson's disease (Goel, Kunnumakkara, & Aggarawal, 2008). In animal model oral administration of curcumin inhibited cancer in the colon, skin, stomach, liver, lung, duodenum, soft palate, and breasts of rodents (Rao, Rivenson, Simi, & Reddy, 1995). Moreover, Curcumin improved impaired wound healing in diabetic mice.

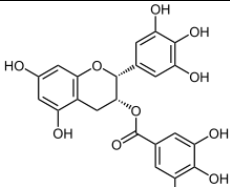
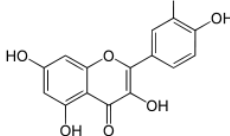
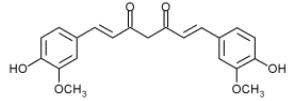
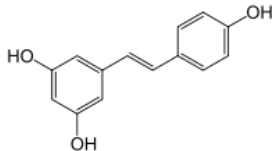
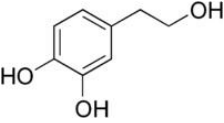
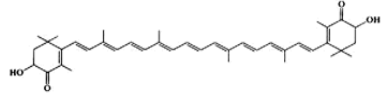

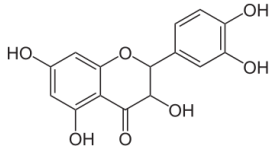
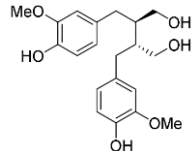
2.4 Resveratrol

Resveratrol is one of the major nonflavonoids phenolic compounds where two aromatic rings are joined by an ethane linkage. Resveratrol exists in monomeric, oligomeric or polymeric form of stilbenes. It is a natural phytoalexin in the fruits and vegetables such as peanuts, mulberries, grapes, red cabbage, spinach, and red wine. The French paradox of wellness and wine consumption is attributed to the effect of resveratrol (Ferreiers, 2012; Renaud, de Lorgeril, 1992; Vidalayur, Otani, Singal, & Maulik, 2006).

Resveratrol is currently receiving considerable attention worldwide because of its beneficial effects on the human health including significant antioxidant activity. Number of studies reported that resveratrol has strong antioxidant and radical scavenging capacity against DPPH, ABTS, DMPD, and superoxide radical and metal chelating activities. In the study Gü l ç in, (2010) found that compared to standard antioxidant resveratrol inhibited higher lipid peroxidation (89.1%) of the lipid peroxidation of linoleic acid emulsion than BHA, BHT,

α -tocopherol, and trolox (approximately 80%) at the concentration of 30 $\mu\text{g/ml}$. (Gülçin, 2010)

Table 1. Food sources of strong natural antioxidants

Antioxidant	Structural Formula	Food Sources	Analytical techniques
Epigallocatechin gallate		Green tea, oolong tea, grapes, wine, cocoa, & dark chocolate	RPHPLC, HPLC-UV, LC-ESI-MS/MS, UV-Vis spectroscopy, & NMR
Quercetin		Onion, apple, broccoli, kale, apples, cranberries, bell peppers, celery, tomatoes, & apricots	RPHPLC, HPLC-PDA, HPLC-UV, LC-MS/MS, Raman Spectroscopy, & NMR spectroscopy
Curcumin		Turmeric	HPLC-UV, HPTLC, Fluorescence UHPLC, UV-Vis spectroscopy, LC-MS/MS, & UPLC-MS/MS
Resveratrol		Japanese knotweed (<i>Polygonum cuspidatum</i>), red grapes, red wine, peanuts, mulberries, red cabbage, & spinach	HPLC-UV, HPLC-DAD, LC-MS/MS, SPME-GCMS, RPHPLC, & LC-DAD-FD-ED
Hydroxytyrosol		Olive, olive leaves, & olive oil	HPLC-UV, RP-HPLC-DAD, HPLC-MS, & LC-MS/MS
Astaxanthin		Algae, bacteria, fungi, yeast, salmon, lobster, trout, krill, shrimp, crayfish, red fish, & red fish roe	UV-Vis, RP-HPLC, HPLC-MS, LC-MS/MS, LC-APCI-MS, & LC-ESI-MS
Lycopene		Tomatoes, watermelons, wolfberry, papaya, pink-grapefruits, apricots, pink-guavas, red peppers, carrots, olives, & red grapefruit	UV-Vis, RP-HPLC, HPLC-MS/MS, & LC-MS/MS
Dihydroquercetin		Citrus fruits, onion, bark of Siberian larch, apples, larch, milk thistle, tea, cocoa, & vegetables	UHPLC-MS/MS, HPLC-UV, & LC-MS/MS
Lignans		Flax seed, pumpkin seed, poppy seed, sunflower seed, sesame seed, nuts, berries, wheat, oat, rye, coffee, tea, & wine	RPHPLC, HPLC-ESI-MS/MS, LC-MS/MS, & GC-MS

Cooking process such as roasting, boiling, and frying reduces the level of resveratrol. One of the big challenges for resveratrol is the low availability even after it is well absorbed and thus result in low plasma concentrations. In number of studies it was reported resveratrol as effective “therapeutic agent”, however clinical and *in vivo*

animal model studies indicated inconsistent results due to its low bioavailability showing sometime even 0% (Thazhath et al., 2016, De Vries, Strydom, Steenkamp, 2018). To enhance the bioavailability, better permeability and resistant to hydrolysis various formulation and alternative oral route have been prepared (Watkins, Wu, Zhang, Davis, & Xu, 2015, Ansari, Vavia, Trotta, & Cavalli, 2011).

Biological activity of resveratrol was investigated *in vitro* and *in vivo*. It showed positive cardiovascular health, antioxidant activities, and prevention of platelet aggregation. It has also been reported that resveratrol has chemopreventive effectiveness against initiation, promotion, and progression of carcinogenesis. The anticancer activity of resveratrol has been shown in many studies (Yashin, Chernousova, Trukhanov, Chertushkin, & Freidkina, 2001; Signorelli & Gidoni, 2005; Whitlock & Baek, 2012; Aggarwal et al., 2004) including its activity against breast cancer (Aggarwal et al., 2004), colon cancer (Wang, Li, & Meng, 2012), and rectal cancer (Miki et al., 2012). Resveratrol inhibits Epstein-Barr virus (De Leo et al., 2012), herpes virus (Docherty et al., 1999), and influenza virus (Mahady & Pendland, 2000). Resveratrol was shown to inhibit cell proliferation in a dose-dependent manner. Resveratrol actively reduces the growth of *Helicobacter pylori* in the stomach. It showed an anti-aging and neuroprotective effect (Baur & Sinclair, 2006; Aggarwal et al., 2004, Athar et al., 2007).

2.5 Hydroxytyrosol

Hydroxytyrosol is one of the most potent natural antioxidant compounds with o-diphenols compounds under the group of phenolic alcohol compounds. Compared to the tyrosol, hydroxytyrosol has one more OH group in the benzene ring and it contributes towards higher free radical scavenging and antioxidant activity. It is an amphipathic compound which has a water-soluble and fat-soluble component with aliphophilic end and hydrophilic end. This unique structural feature makes hydroxytyrosol a good transporter of substances and penetrate the cellular membrane in human body (Fernández-Bolaños, López, López-García, & Maset, 2012, Martínez, Ros, & Nieto, 2018).

Hydroxytyrosol is present in olives and olive oil, as well as in other vegetable oils. It attributes intense flavor and aroma. Being reported hydroxytyrosol, tyrosol, and oleuropein as main polyphenolic antioxidants in olive oil, hydroxytyrosol has the strongest antioxidant effects. Hydroxytyrosol is fifteen and three times more antioxidant than green tea coenzyme Q10 respectively (Richards, 2012). The antioxidant properties of hydroxytyrosol have been explained based on various molecular, cellular and animal model studies. With respect to superoxide anion Visioli et al., (1998) proved that hydroxytyrosol has potent scavenging activity of superoxide formation (Visioli, Bellemo, & Galli, 1998).

Virgin olive oil phenolic compounds are highly absorbed and showed bioavailability up to 70 to 99% depending on the age, hormonal status or gender of the patients. After ingestion they are absorbed in a dose-dependent manner. In a study with the administration of solution of hydroxytyrosol and tyrosol with olive and water Tuck et al., (2002) found higher bioavailability with olive oil compared to water (99% and 98% respectively in olive oil solution, 75% and 71% in aqueous solution) (Tuck & Hayball, 2002). Hydroxytyrosol is resistant to gastric juices and significantly bioavailable (Khymenets et al., 2016, Martínez, Ros, & Nieto, 2018).

Hydroxytyrosol possesses several pharmacological activities, such as antioxidant, anticarcinogenic, anti-inflammatory, and neuroprotective activities (Hu, He, Jiang, & Xu, 2014, Warleta, et al 2011, D'Angelo et al., 2005; Fabiani et al., 2002; Vazquez et al., 2010; Rodriguez Morato et al., 2015; Bulotta et al., 2014; Sun, Luo, & Liu, 2014). It has an exceptionally beneficial effect on the cardiovascular system (Bulotta et al., 2014). Consumption of hydroxytyrosol in regular way help to reduce cardiovascular diseases and diabetes mellitus (Merola, Castillo, Benavente-Garcia, Ros, & Nieto, 2017). Hydroxytyrosol is protective against neurodegenerative disorders Alzheimer or Parkinson's disease (Dexter & Jenner, 2013). It possessed antimicrobial capacity by inhibiting the growth rate of bacteria as *Escherichia coli*, *Candida albicans*, *Clostridium perfringens*, *Streptococcus mutans*, or *Salmonella enterica* (Medina, De Castro, Romero, & Brenes, 2006).

2.6 Astaxanthin

Astaxanthin is one of the strong natural carotenoid pigments and known as "the king of the carotenoids". Astaxanthin is a member of the xanthophylls and consists of two terminal rings joined by a chain of conjugated double bonds. Astaxanthin occurs as stereoisomers, geometric isomers, free and esterified forms because of the presence of the polyene bonds. In this oxygenated derivative molecule, it has two rings with hydroxyl and keto moieties with two asymmetric carbons in both ends and exist in esterified (one or both) forms by reacting with a fatty acid, protein or lipoprotein (Ambati, Phang, & Ravi, 2014).

Astaxanthin are naturally available in genus algae, bacteria, fungi, yeast, salmon, lobster, trout, krill, shrimp, and crayfish. The astaxanthin content in common salmon products has been measured by the U.S. Food and Drug Administration that ranges from 5.4 mg/kg to 40.4 mg/kg. Astaxanthin is also found in red fish roe. Another source of astaxanthin is a yeast, *Phaffia*, which grows on the bark of certain trees. Astaxanthin is found in its highest natural concentration in wild Pacific sockeye salmon in the range of 26-38 mg/kg flesh. Heat treatment reduce the level of astaxanthin while it is stable at 70-90 °C. Improved storage condition at 4 °C and 25 °C were developed by mixing the astaxanthin with cyclodextrin-water mixture (Yuan, Du, Jin, & Xu, 2013). Moreover lipid-based formulation of astaxanthin enhanced its bioavailability in human study (Olson, 2004).

Due to the unique structure of astaxanthin containing double bond, hydroxyl and keto group, it showed high antioxidant activity and even higher in comparison to other carotenoids such as lutein, lycopene, α -carotene and β -carotene (Naguib, 2004). In another study it was found that antioxidant activity of astaxanthin was 10 times higher than carotenoids including zeaxanthin, lutein, canthaxanthin, β -carotene and compared to α -tocopherol it was 100 times higher (Liu & Osawa, 2007). Whereas the oxo groups in astaxanthin result in high antioxidant activities the polyene chain as well as the terminal ring in astaxanthin traps radicals and scavenge radical's activity (Martin, Jagger, Ruck, & Schmidt, 1999). Astaxanthin protect the cell membrane from lipid peroxidation by scavenging the radicals at the outer and inner cell membranes (Ambati, Phang, & Ravi, 2014). In a study Augusti et al., (2012) found the elevation of antioxidant enzymes activities of superoxide dismutase and thioredoxin reductase in serum when astaxanthin were fed to rabbits (Augusti et al., 2012). Similar observations were reported Kamath et al., (2008) when ethanol-induced gastric ulcer rats were treated with astaxanthin (Kamath, Srikanta, Dharmesh, Sarada, & Ravisankar, 2008).

Many research studies have discussed the health benefits of astaxanthin (Higuera-Ciapara, Felix-Valenzuela, & Goyoolea, 2006; Querin, Huntley, Olaizola, & Haematococcus, 2003; Yang, Kim, & Lee, 2013; Yuan et al., 2011). Major health benefits include therapeutic efficacy in people with cardiovascular diseases (Fasset & Coombes, 2011), reduction of oxidative stress and inflammation processes, increase in immune function (Park et al., 2010), inhibition of cancer cell growth (Dore, 2005) specifically in neuroblastoma cancer (Ikeda et al., 2008), rectal cancer (Palloza et al., 2009), and skin cancer (Rao et al., 2013), protection from stomach ulcers (Murata et al., 2012), improvement of mental abilities (Katagiri, Satoh, Tsuji, & Shirasawa, , 2012), beneficial in eye diseases (Iwasaki & Tahara, 2006), protection of hepatic cells against damage (Curek et al., 2010), reduction of oxidative stress in overweight people (Choi et al., 2011), effect on insulin activity (Ishiki et al., 2013), and inhibition of oxidation of low-density lipoprotein (Iwamoto et al., 2000).

2.7 Lycopene

Lycopene is one of the major carotenoids among other 600 different carotenoids which could play crucial role in scavenging peroxy radicals. It is an acyclic isomer of beta carotene and contain a straight chain hydrocarbon with 11 conjugated and two non-conjugated double bonds. Due to the presence of these double bonds lycopene exist in cis-trans isomers.

Lycopene is found mainly in red fruits and vegetables such as tomatoes, watermelons, wolfberry, papaya, pink-grapefruits, apricots, pink-guavas, and peppers. In most of the natural resources it exists as trans isomerism. However, it can undergo cis-trans isomerisation with light heat and chemical reactions. Processing could significantly affect the bioavailability of lycopene by the trans to cis transformation. In a study it was found that lycopene from processed tomato juice in trans form is more bioavailable than raw tomato juice (Stahl & Sies, 1992). In human plasma trans lycopene are more bioavailable than cis isomers (Clinton et al., 1996).

During lipid peroxidation peroxy radical are generated and that could damage the lipids in the cell wall. Carotenoids play significant role in the protection from this damage of cellular membranes and lipoproteins by deactivating the peroxy radicals via resonance stabilized radical adducts. Lycopene showed stronger singlet oxygen quenching ability compared beta carotene which is another most abundant carotenoids. Number of research studies have been published on the effects of lycopene on human health (Gerster, 1997; Agarawal & Rao, 2000). Specific health benefits include beneficial in cardiovascular diseases (Gajendragadkar et al., 2014), reduction of the risk of heart attack (Ried & Fakler, 2011) and atherosclerosis (Kohlmeier et al., 1997), reduction of blood pressure and serum cholesterol (Devaraj et al., 2008), effective suppression of oxidative stress (Devaraj et al., 2008; Kaur, Chauhan, & Sandhir, 2011), anticancer activity (van Breeman & Pajkovic, 2008; Omoni & Aluko, 2005; Salman, Bergman, Djaldetti, & Besler, 2007; Ford & Erdman Jr, 2013; Seren et al., 2008), specifically, activity against prostate cancer (Giovannucci , 2002), rectal cancer (Tang et al., 2008), pancreatic cancer (Salman, Bergman, Djaldetti, & Besler, 2007), breast cancer (Chalabi et al., 2006), and bladder cancer (Helzlsouer, Comstock, & Morris, 1989), beneficial in the treatment of male infertility (Gupta & Kumar, 2002),

and beneficial in the treatment of Parkinson's disease (Kaur, Chauhan & Sandhir, 2011).

2.8 Dihydroquercetin

Dihydroquercetin, also known as taxifolin is a flavanonol compounds which has two hydroxyl phenolic groups at the meta and para- positions in the phenyl rings in the flavonoid's skeleton.

Taxifolin is considered as antioxidant-rich functional food. It is highly available in citrus fruits and onion. Dihydroquercetin has a high antioxidant activity with approximately 60,000 ORAC units (Yashin et al., 2018; Pillow, et al., 1999). Due to its conjugation behavior and resonance structure stability of phenolic rings it provides powerful radical-scavenging activity. In a study Topal et al., (2016) found that taxifolin had remarkable radical scavenging with DMPD, ABTS, superoxide, and DPPH radicals, and metal chelating activities. It has been reported that scavenging activity of taxifolin against superoxide anion is more than that of BHA, BHT, α -tocopherol, and Trolox (Topal et al., 2016).

Dihydroquercetin consumption has beneficial effects on human health such as: reduction in oxidative stress-related processes, specifically, in peroxide oxidation of cellular membrane lipids (Plotnikov, Aliev, Maslov, Vasileiv, & Tjukavkina, 2003; Yashin et al., 2018; Kilkkinen et al., 2003), slowing down of premature aging, protective activity on capillaries, strengthening blood vessel walls (including capillaries), slowing cancer progression (Maikoparova, 2010; Moreno-Franco et al., 2011), normalization of blood cholesterol and triglycerides, which helps in atherosclerosis prevention (Plotnikov et al., 2004), reduction of risk for stroke and heart attack (Plotnikov, Aliev, Maslov, Vasileiv, & Tjukavkina, 2003), prevention of dangerous diseases, such as cardiovascular diseases, cancer, and diabetes (Moreno-Franco et al., 2011), antidiabetic, antiallergic, diuretic, neuroprotective, and anti-inflammatory activities, positive effect on male and female reproductive system, reduction of chronic fatigue, improvement of mental and physical functions, and promoting burn wound healing (Teslekin, Zhambalova, Babenkova, Kelbanova & Tukavina, 1996).

2.9 Lignans

Lignans are the group of phenolic compounds that is derived from the propylbenzene (C6-C3) unit.

Flaxseed (*Linum usitatissimum L.*) is a major source of lignans. However other seeds, nuts, fruits, vegetables, coffee, tea, and wine also contain substantial amounts of lignans. Secoisolariciresinol diglucoside (SDG) is the major lignan present in flaxseed and it exist as component of a linear ester-linked complex. It has been observed that SDG is converted into enterolactone (ED) and enterodiol (EL) after its metabolism via the formation of secoisolariciresinol (SECO), a plant aglycon formed by the hydrolysis of SDG.

Flaxseed lignan secoisolariciresinoldiglucoside (SDG) and mammalian lignans enterodiol (ED) and enterolactone (EL) have been reported to play important role in protection from DNA damage and lipid peroxidation. In a study Hu et al., (2007) found that efficacy of lignans with the order of SDG > SECO >> ED > EL for DNA damage and SDG > SECO = ED = EL for liposome lipid peroxidation (Hu, He, Jiang, & Xu, 2007). Strong antioxidant activity of SDG and SECO were observed due to the presence of 3-methoxy-4-hydroxyl substituents in SDG while the mammalian lignan had only single hydroxyl group. The strong antioxidant activity of the mammalian lignans in an aqueous environment were appeared due to the ability of the benzylic hydrogen abstraction and resonance stabilized phenoxyl radicals.

In vitro and *in vivo* studies demonstrated that flaxseed lignan and its mammalian metabolites showed protective effects against several chronic diseases. (Yuan et al., 1999; Prasad, 2009; Thompson, Boucher, Liu, Cotterchio, & Kreiger, 2003). Interest towards lignans has been growing in recent years because of its significant antioxidant properties (Willfor et al., 2003; Yashin et al., 2017) and positive effects on human health (Adlercreutz, 2007), particularly, on cardiovascular diseases (Prasad, 2009; Maslov et al., 2016). It reduced the risk of cancer (Adlercreutz et al., 1992; Zhukova et al., 2010; Webb, & McCullough, 2005; Zhukova et al., 2010; Pojer, Mattivi, Jhonson & Stockley, 2013), especially hormone-dependent types, breast and ovarian cancer in women and prostate cancer in men. Recently, the ability of lignans to exhibit neural cell activity and stimulate neural cell repairing were also shown (Lores, Yashunsky, Nifantiev, & Schachner, 2014).

3. Conclusion

The review describes an overview of selected most powerful natural antioxidant compounds with their structure, source, bioavailability, antioxidant properties, and key healthcare effects. In addition to these selected antioxidant compounds several other antioxidant compounds have been reported with significant antioxidant activity such as phenolic acids in coffee and berries and anthocyanins in berries and fruits, isoflavones in soy, and proanthocyanidins in cranberries. From the recent studies on the powerful antioxidant compounds it was found that antioxidant activity of a natural antioxidant depends on the number of hydroxyl group in the

phenylring of the phenolic compounds as well as carbon carbon bonds in aliphatic skeleton. For few decades, efforts have been made by researchers to fill the knowledge gap between consumers and food nutrition in search for healthy diet. Information on such natural oxidants is expected to insight valuable source since current dietary guidelines recommend increasing the antioxidant rich foods. Despite the evidence of efficacy and safety of antioxidant compounds it has been found that most of the antioxidant compounds possessed limited bioavailability. Further studies to improve the bioavailability and medicinal value are needed for potential application.

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