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Review

Dietary food antioxidants and their radical scavenging activity: A review

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Abstract

Food antioxidants can prevent or/and delay free radical formation which is responsible for oxidative stress. Nowadays, natural remedy becomes the highest concern in many countries, as well as discouraging the intake of synthetic counterparts to avoid the burden of side effects on human health. Regular intake of dietary antioxidants could help to improve the fitness of the body, and subsequently make the body more competitive in its fight against diseases through enhanced immune response. The present review thus summarised recent knowledge on the dietary source of antioxidants, and also mechanism of action and functionalities on human health benefits. Due to the proven ability to restore mitochondrial function and cellular redox balance, food antioxidants also have great potential as natural therapies against COVID-19. However, the numbers of trials are still limited. There must be more tests with the hope that these compounds will mitigate the COVID-19 and similar outbreaks in the future.

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Introduction

The role of food antioxidants on human health can be expressed by using the famous quote "*let food be thy medicine, and medicine be thy food*" often ascribed to Hippocrates (400 BC). Antioxidants are a heterogeneous family of chemical substances that significantly inhibit or delay oxidation processes. Food antioxidants neutralise and/or inhibit the development of free radicals. The mechanisms of inhibition include scavenging reactive oxygen species (ROS), chelating metal ions, and quenching superoxide anion ($O_2^{\bullet -}$), all of which lead to the intervention of autoxidation reaction and/or diminish localised O_2 concentration (Brewer, 2011; Amarowicz and Shahidi, 2017).

For a long time, antioxidants have been extensively utilised in the food industries as a means of preventing lipid oxidation. In particular, lipid soluble antioxidants are commonly added as additives in the pharmaceutical and food industries (Lourenço *et al.*, 2019). Even at low concentrations, these antioxidants can potentially delay and/or prevent degradation reactions induced by the oxidation process. Antioxidants scavenge the formed free radicals, delay their chain reactions, and prevent unexpected degradation processes such as rancidity and browning, as well as inhibit the body stress and diseases induced by ROS (Baschieri *et al.*, 2017).

The effect of food antioxidants in reducing the oxidative effect is well established. Human body cells and tissues are uninterruptedly exposed to diversified stresses which lead to body stress resulting from the augmented exposure to oxidants, or reduced antioxidant efficacy of the system, or both (Lobo *et al.*, 2010). The consequence of oxidative stress is the generation of ROS, especially free radicals, which are more important than other compounds. These free radicals can act on lipids, proteins, and DNA, in both polar and non-polar sites, and play a role in the pathophysiology of diseases namely diabetes, atherosclerosis, neoplasia, inflammation, cancer,

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hypocholesterolaemia, hypertension, cardiovascular malfunctions, immunomodulatory disruption, hepatic and renal functions, and aging (Yashin *et al*., 2017; Incalza *et al.*, 2018).

Food antioxidant (*e.g.*, polyphenols, vitamins, *etc.*) molecular systems can work endogenously and exogenously to protect human body cells from free radicals. Although many studies (*in vitro* and *in vivo*) have been conducted recently, a new dimension and next-level research potential and application needs to be explored since it is a promising area of applied research, considering the industrial (*e.g.*, food, pharmaceutical, health industries, *etc*.) and human health aspects. Moreover, the recent outbreak of the COVID-19 pandemic led to millions of infections and causes huge death. The human immune response against SARS-CoV-2 of acute COVID-19 patients is mainly recognised as the activation of lymphocyte T cells (Thevarajan *et al*., 2020; Rodriguez *et al*., 2020). It has been reported that having a strong or better immune response might give us the capacity of a faster and stronger response against this infection, which can be achieved by dietary intake of food antioxidants.

In this context, it is imperative to strengthen our further understanding of food antioxidants as a natural remedy for human health. Therefore, the present review discussed the food antioxidants, the underlying mechanism of free radical production and inhibition process, as well as the prospect of food antioxidants as a natural remedy for preventing chronic inflammatory diseases and COVID-19.

Antioxidant compounds in food

The major food antioxidants include phenolic acids, flavonoids, phenolic diterpenes, carotenoids, tocopherol, and ascorbic acid (Figure 1).

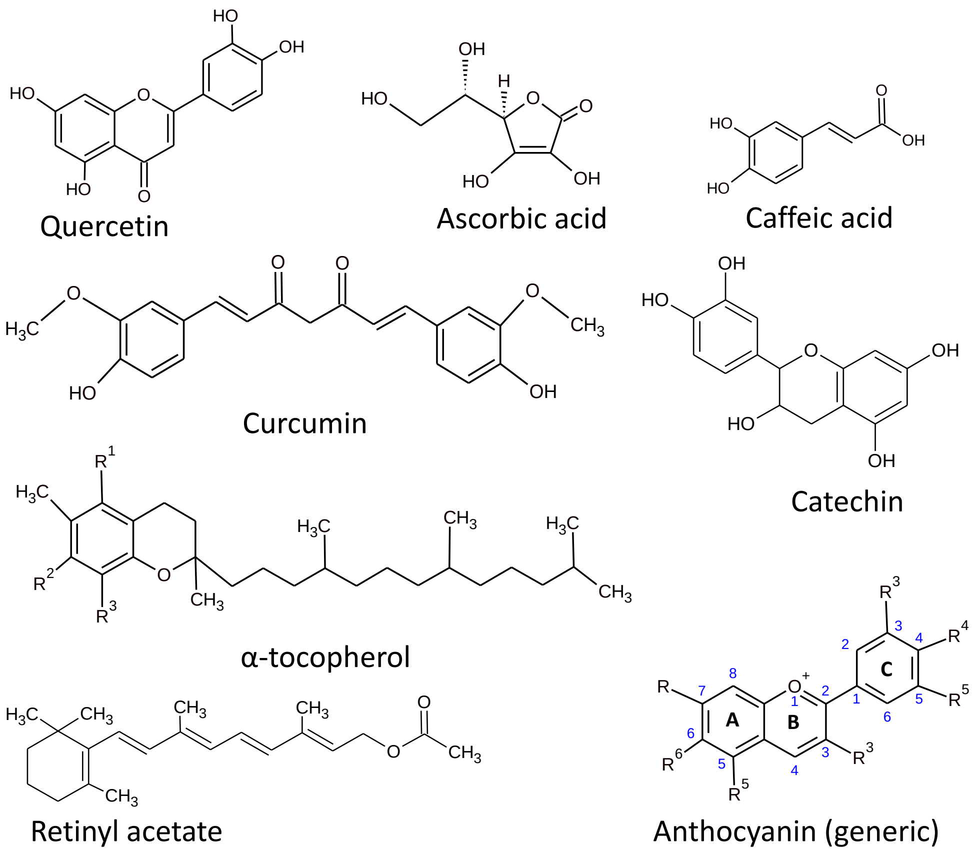

Figure 1. Structure of some antioxidant compounds commonly found in foods.

Phenolic acids (*e.g.*, gallic, protocatechuic, caffeic, and rosmarinic acids) may present as a free or bound form in plants. Phenolic acids can be divided into two subgroups such as hydroxybenzoic acids and hydroxycinnamic acids (Dai and Mumper, 2010). Unlike other phenolic compounds, these compounds are acidic in character due to the presence of one carboxylic group in their molecules (Haminiuk *et al.*, 2012). Hydroxybenzoic acids mostly occur as esters, having a C_6-C_1 structure such as gallic, vanillic, *p*-hydroxybenzoic, and syringic acid. On the other hand, hydroxycinnamic acids are aromatic compounds such as caffeic, ferulic, *p*-coumaric, and sinapic acid, and mainly present as derivatives by having a 3-carbon sidechain (C_6-C_3) (Teixeira *et al.*, 2014). Phenolic acids work by trapping free radicals, whereas flavonoids act by scavenging free radicals and chelating metal ions (Forman *et al.*, 2014).

More than 5,000 flavonoids have been identified. They mostly present as glycosides, aglycones, and partly as ester, rather than as free compounds. Flavonoids commonly consist of two aromatic rings connected by three carbons bridges to form an oxygenated heterocycle, or more precisely, phenylbenzopyran functionality, and a third heterocyclic ring (Haminiuk *et al.*, 2012; Durazzo *et al.*, 2019). Variation in substitution pattern on third ring structure defines the major flavonoid classes namely flavonols, isoflavones, flavanones, flavan-3-ols, flavones, and anthocyanin. Substitution to ring A and B includes oxygenation, alkylation, glycosylation, acylation, and sulphonation, and brings out a further variation within each class of flavonoids (Olszowy, 2019). Many of the antioxidative flavonoids are natural pigments such as anthocyanin and anthocyanidin. The dietary flavonoids possess good antioxidant properties as they are good scavengers of reactive nitrogen species (RNS) and ROS (Chen *et al.*, 2018).

Phenolic diterpenes and triterpenes are well-known antioxidants in food. The diterpene synthesis follows the terpenoids or mevalonate pathway, hence is composed of two isoprene (5-carbon backbone skeleton) units and triterpene consisting of three isoprene units. The isoprene units are the building block diterpene precursors such as geranylgeranyl pyrophosphate (GGPP). The GGPP goes through several conversion reactions namely cyclisation, aromatisation, and rearrangements along with the loss of the phosphate group and carbonium ion to form the diterpene subgroups (Habtemariam, 2016). Carnosic acid consists of well-known diterpenes featuring γ- and δ-lactone structures. In the presence of oxygen, it can easily be degraded *in vitro*, and form other compounds such as carnosol, rosmanol, epirosmanol, 7-methylepirosmanol, and methyl carnosate (Birtić *et al.*, 2015). Carnosic acid may also undergo enzymatic conversion *in vivo*, stimulated by singlet oxygen, to form rosmadial and other lactones such as rosmanol, isorosmanol, and 11,12-di-O-methylrosmanol (Zhang *et al.*, 2012). Phenolic diterpenes are also well reported for their antioxidant properties and therapeutic effects such as anti-inflammatory, antiproliferative, and antiangiogenic properties (Chun *et al.*, 2014; Petiwala and Johnson, 2015; Vo *et al.*, 2020).

Carotenoids are tetraterpene pigments with C_{40} skeleton, of which eight isoprene (C_5 skeleton) units are linked head-to-tail, except in the centre, which is linked tail-to-tail to give a symmetrical structure (Maoka, 2009). In nature, carotenoids are mainly found as a stable all-*trans* (-E) form and a small proportion of *cis* (-Z) isomers. In fruits and vegetables, about 850 carotenoids have been identified. They mainly belong to two classes: (a) carotenes - an unsaturated hydrocarbon (*e.g.*, β-carotene and lycopene), and (b) xynthophylls - oxygenated derivatives with hydroxyl, keto, epoxy, and aldehyde subunits (*e.g.*, β-cryptoxanthin, canthaxanthin, and violaxanthin) (Maoka, 2020). One of the most recognised properties of carotenoids is their antioxidant potential and precursor of vitamin A (Courraud *et al.*, 2013; Amengual, 2019).

Tocopherols are chemically 6-chromanol ring structures, having varying degrees of methylated at carbon positions of C_5, C_7, and C_8, and a side chain (saturated C_{16}) at C_2 position. Different isomers of tocopherol are available depending on the number and positions of methyl groups on the chromanol ring. The term vitamin E is commonly used for tocopherol and tocotrienols; both consist of α, β, γ, and δ form based on the degree of methylation (Pertuzatti *et al.*, 2015; Fritsche *et al.*, 2017). The antioxidant capacity of α-tocopherol has been studied extensively. Studies reported that α-tocopherols can play an important role in inhibiting tumour development and protecting membrane fatty acids from free radical action (Aykin-Burns *et al.*, 2019).

Ascorbic acid (AA) is a very strong and widely used food antioxidant. Since its discovery in the late 1920s, AA is one of the most celebrated chemical compounds ever found in food applications. If present in an adequate amount, AA can neutralise a variety of free radicals. This and its regeneration capability make it the perfect antioxidants for universal use (Arrigoni and De Tullio, 2002). All plants can synthesise AA at high rates following the Smirnoff-Wheeler pathway, whereas almost all animals synthesise AA *via* UDP-D-glucuronic acid, glucuronic acid/glucuronolactone, and L-gulonic acid/L-gulono-1,4-lactone pathway (Wang *et al.*, 2013). Ascorbic acid, a 6-carbon molecule structurally related to glucose, is a weak sugar acid. AA has strong reducing properties due to the moiety between its C_2 and C_3 carbons which easily donate two protons and electrons, and become a dehydroascorbic acid (DHA). It can donate hydrogen to an oxidising system on adjacent carbon atoms (Bilska *et al.*, 2019). Therefore, the antioxidant activity of AA encompasses a reducing agent, free radical scavenger, and metal ions (*e.g.*, Fe++) chelator (Brewer, 2011; Suliborska *et al.*, 2019; Bilska *et al.*, 2019).

Dietary source of food antioxidants

Plants develop their antioxidant systems naturally to control free radicals, lipid oxidation catalysts, and intermediate products of oxidation while they live under oxidative stress. Fruits, fresh vegetables, and legumes are the major sources of dietary antioxidants (Brewer, 2011; Haminiuk *et al.*, 2012; Yashin *et al.*, 2017). Seeds and cereals are the other good sources of antioxidants, and contain plenty of polyphenols, anthocyanins, and flavonoids (Xu *et al.*, 2020). Edible oils, such as extra virgin olive oil, sunflower oil, and canola oil are another source of food antioxidants (Xuan *et al.*, 2018; Negro *et al.*, 2019). Hydroxytyrosol, tyrosol, (+)-1-acetoxypinoresinol, (+)-pinoresinol, oleuropein, and decarboxylated dialdehyde derivatives of secoiridoids are the common antioxidant compounds in oils (Xuan *et al.*, 2018; Jimenez *et al.*, 2020). Extracts of oregano, rosemary, thyme, and basil have a high total phenolic content with antioxidative nature. Spices such as clove, cinnamon, red peppers, coriander, cumin, and dried herbal extracts are rich in antioxidant compounds (Yashin *et al.*, 2017; Leite *et al.*, 2018). Agro-industrial by-products such as peel, seed, and pomace are also cheap, and have rich sources of antioxidants (Hernández *et al.*, 2016).

Beverages such as milk, wines, tea, and coffee are also good sources of antioxidants. Wines are considered a good source of polyphenolic compounds (*e.g.*, anthocyanins), and all kinds of tea are rich in (+)epigallocatechin, (+)epicatechin, (+)gallocatechin, and (+)catechin (Novak *et al.*, 2010).

Bee products are another important source of antioxidants especially polyphenolic phytochemicals such as 4-dimethylaminobenzoic acid, apigenin, genistein, caffeic acid, *p*-coumaric acid, gallic acid, pinocembrin, tricetin, vallinic acid, chrysin, syringic acid, luteolin, chlorogenic acid, and quercetin (Laskar *et al.*, 2010; Alvarez-Suarez *et al.*, 2013). Moreover, some microorganisms especially probiotics show antioxidant activity such as *Lactobacillus* spp. (*L. fermentum* ME-3, *L. acidophilus*, *L. plantarum*, *L. casei*, *L. gasseri*, and *L. helveticus*), *Streptococcus* spp., *Bifidobacterium* spp. (*B. pseudocatenulatum*, *B. animalis*), and *Lactococcus* spp. (Mishra *et al.*, 2015; Fessard *et al.*, 2017).

Free radical and oxidative stress

Exogenous sources of free radicals are radiation, smoke, pollutants, and organic solvents, whereas the endogenous sites of free radicals are mitochondria, lysosomes, endoplasmic reticulum, and plasma membrane, where the oxygen consumption is high (Phaniendra *et al.*, 2015). The ultraviolet rays in solar radiation are the main exogenous cause that triggers the free radical production in the biological system, and are responsible for the haemolytic breakdown of bonds in molecules (Gutteridge and Halliwell, 2010). The visible light (blue and red parts) is needed for photosynthesis in the plant. The extra incident light energy creates active oxygen which oxidises plant cells. Therefore, the plant produces antioxidants (*e.g.*, vitamins C and E, anthocyanin, and carotene) for self-protection. Another exogenous factor that promotes the formation of free radicals is chemical intoxication (*e.g.*, drug toxicity). The toxicity of many drugs develops either by the conversion of drugs into free radicals or by their effect on the development of free radicals (Phaniendra *et al.*, 2015). Another cause of free radical formation is the presence of contaminants, additives, and pesticides in the food chain. During the processing or storage of foods, oxygen can oxidise carbon and hydrogen-rich ingredients or substances present in the foods. The oxygen molecule itself is reduced when it oxidises a molecule, and forms reactive intermediates, some of which act as free radicals (Arulselvan *et al.*, 2016; Santos-Sánchez *et al.*, 2019) as shown in Eqs. 1 - 5:

$$O_2 + H^+ + \mathrm{e} \rightarrow HO_2^* \ (hydroperoxyl\ radical) \quad \text{(Eq. 1)}$$

$$HO_2^* \rightarrow H^+ + O_2^{\circ -*} + H_2 (superoxide\ radical) \quad \text{(Eq. 2)}$$

$$O_2^- + 2H^+ + \mathrm{e} \rightarrow H_2O_2 \ (hydrozen\ peroxide) \quad \text{(Eq. 3)}$$

$$H_2O_2 + e \rightarrow OH^- + HO^* \ (hydroxyl\ radical) \quad \text{(Eq. 4)}$$

$$HO^* + H^+ + e \rightarrow H_2O \quad \text{(Eq. 5)}$$

Oxygen is a stable gas under normal conditions and has limited solubility in water. There are many

ROS in the biological system that act as biotic oxidants, among which the $O_2^{\bullet -}$ is the major oxidant. It simply forms $HO_2^{\bullet}$ by the addition of a proton, and becomes a very active oxidising agent. Sources and functions of free radicals generated in the biological system are briefly summarised in Table 1.

Table 1. Free radicals generated in biological systems.

Species	Function
Superoxide anion ($O_2^{\bullet -}$)	Acts as a reducing agent of iron complexes.
Hydroeroxyl ($HO_2^{\bullet}$)	Contributes to initiate fatty acid oxidation.
Hydroxyl ($HO^{\bullet}$)	Oxidises organic and inorganic compounds such as fats, proteins, carbohydrates, DNA, *etc.*
Alkyl ($R^{\bullet}$)	Takes part in the chain reaction of free radicals.
Alkoxyl ($RO^{\bullet}$)	Takes part in the chain reaction of free radicals.
Nitric oxide ($NO^{\bullet}$)	Helps in blood vessel and smooth muscle relaxation by stimulating protein kinase and guanylate cyclase activity.
Nitrogen dioxide ($NO_2^{\bullet}$)	Stimulates lipid oxidation, stabilisation reaction resulting in decreased concentration of plasma antioxidants (*e.g.*, ascorbic acid, tocopherol, *etc.*)
Peroxynitrite ($ONOO^{\bullet}$)	Contributes in nitration of tyrosine, loss of -SH of methionine, and formation of nitroguanine from DNA.
Carbonate ($CO_3^{\bullet -}$)	Oxidises organic compounds such as proteins, DNA, *etc*.
Nitrosoperoxycarbonate ($ONOOCO_2^{-}$)	Promotes nitration process of tyrosine *via* free radical and damage of oxyhaemoglobin.

Chemistry and working mechanism of antioxidant

Food antioxidants follow two principal reaction mechanisms for the neutralisation and/or inhibition of free radicals. The first mechanism is to neutralise the free radicals by donating electrons to the radicals, called the chain-breaking mechanism. The free radical becomes inactive after receiving electrons at the outer orbital since it is converted to an uncharged molecule or atom. The second mechanism is associated with the removal of ROS and RNS by quenching the catalyst chain reaction initiator (Fereidoon and Ying, 2010). Antioxidants can be categorised into two distinct groups based on their mode of action. The first category of food antioxidants is comprised of the chemical constituents (*e.g.*, tocopherols, gallusans, and dydrochinons) which interrupt the free radical propagation by donating hydrogen ions or relocating electrons to stabilise the radicals. The second category of antioxidants works through the synergistic effect of scavenging oxygen and chelating ions responsible for radical formation. The chain reaction of a free radical can be described as the following three steps (Fereidoon and Ying, 2010; Santos-Sánchez *et al*., 2019):

i. Initiation stage:

(1) $RH \rightarrow R^{\cdot} + H^{\cdot}$

(2) $R^{\cdot} \rightarrow R^{\cdot} + O_2$

(3) $2ROOH \rightarrow ROO^{\cdot} + RO^{\cdot} + H_2O$

ii. Propagation stage:

(4) $R^{\cdot} + O_2 \rightarrow ROO^{\cdot}$

(5) $ROO^{\cdot} + RH \rightarrow ROOH + R^{\cdot}$

(6) $R^{\cdot} + RH \rightarrow ROH + R^{\cdot}$

iii. Termination stage:

(1) $R^{\cdot} + R^{\cdot} \rightarrow R - R$

(2) $R^{\cdot} + ROO^{\cdot} \rightarrow ROOR$

(3) $ROO^{\cdot} + ROO^{\cdot} \rightarrow ROOR + O_2$

(4) $Antioxidants + O_2 \rightarrow oxidized\ antioxidants$

De Oliveira and Batista (2017) illustrated the two principal mechanisms of antioxidants actions into five classes: (a) scavenging of ROS directly, (b) neutralising radical by donating $H^{\bullet}$ species, (c) reducing ROS production by inhibiting oxidative enzymes, (d) chelating meatal ions that promote the conversion of $O_2^{\bullet-}$ and H_2O_2 into $HO^{\bullet}$, and (e) repairing the damage of cell components, as illustrated in Figure 2.

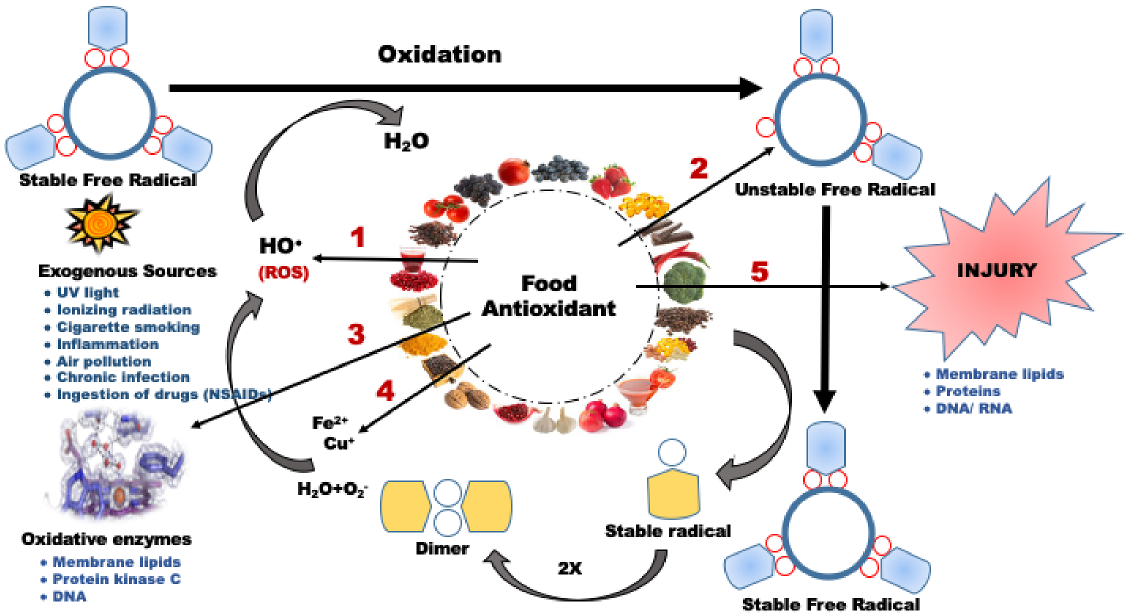

Figure 2. Working cellular mechanism of food antioxidants in the presence of various exogenous and endogenous factors.

Health benefits of antioxidant

Free radicals are called the enemy of the healthy cells; they attack cell outer membranes, eventually triggering the tissue injury and defects in genetic materials (*i.e.*, RNA and DNA) of the cells (Forman *et al*., 2014). This destructive effect of free radicals can be prevented with dietary antioxidants and/or antioxidant supplements. Calabrese *et al*. (2000; 2007) postulated the hormetic effect of chemical compounds more than couple of decades ago. Hormesis is a characteristics biological response shown when exposure to a substance or environmental agents. It shows biphasic responses, stimulation to low dose and inhibition to high dose. The hormetic effect has gained interest over the past decade, and it is postulated as the possible mechanism of action of some antioxidant polyphenols against neurodegenerative diseases (Calabrese *et al.*, 2000, 2010c). While excess ROS are toxic, regulated ROS, however, play an important role in cellular signalling pathway. The cellular stress response requires the activation of pro-survival pathways and the production of molecules with antioxidant, anti-apoptotic, or pro-apoptotic activities. The vitagenes, group of genes responsible for preserving cellular homeostasis during stress conditions, play a key role among the cellular pathways conferring protection against oxidative stress. It includes heat shock proteins (Hsps) which contribute to establishing a cytoprotective state in a wide variety of human diseases, including inflammation, cancers, aging, and neurodegenerative disorders (Zhang *et al.*, 2011). The potent inducers of vitagenes may facilitate the development of pharmacological strategies to maximise cell's antidegenerative mechanisms such as stress response, and thus cytoprotection (Calabrese *et al.*, 2010a, 2010b).

Consistent consumption of fruits and vegetables can significantly help in cognitive performance, and delay the converse age-linked deteriorations in brain functions by reducing the ROS and RNS formation. On the other hand, excessive calorie intake increases the risk of numerous miscellaneous long-lasting diseases by hormetic mechanism (Calabrese *et al.*, 2007; 2010c; Calabrese, 2013). The appropriate food with nutritive value is the strategic key for health intervention by foods including neurodegenerative diseases (Calabrese *et al.*, 2010a; Dattilo *et al.*, 2015). During food consumption, the interrelated factors such as age, sex, diet, exercise, genomic factors, and health status should be taken into consideration (Calabrese *et al.*, 2010c).

Food antioxidants and COVID-19

In early 2020, the eruption of COVID-19 due to the infection caused by SARS-CoV-2 appeared as a global pandemic, and has led to around 64.5 million infections and 1.5 million deaths. The characteristic of COVID-19 has a similarity with SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome) outbreaks (Galanakis, 2020). Several research studies on the recognition of human immune response have described the marked activation of lymphocyte T cells to respond against the virus, for instance, SARS-CoV-2 of acute COVID-19 patients (Thevarajan *et al*., 2020; Rodriguez *et al*., 2020). In a foremost effort, Mateus *et al*. (2020) have proven that some unexposed people have $CD4^+$ T cell memory which works against common cold coronavirus, but can also be cross-reactive to SARS-CoV-2. It has supported that having a strong immunity might give us the capacity to show up with a faster and stronger response. The genitive structure of previously reported SARS or MERS virus has similarities with the present SARS-CoV-2. The virus produces protease enzymes that play an essential role in controlling the replicase complex, consisting of a maximum of 16 viral subunits and many cellular proteins, as well as viral protein production (Nguyen *et al*., 2012). COVID-19 is related to cytokine storms and subsequent immunogenic damage to the endothelium and alveolar membrane (Liu *et al*., 2020).

Phytochemicals found in fruits, vegetables, legumes, cereals, and herbs have great potential to become therapeutic agents as they have an effective inhibitor of coronavirus protease (Adem *et al*., 2020). The antiviral activity of flavonoids (*i.e*., quercetin, quercitrin, epigallocatechin gallate, epicatechin gallate, gallocatechin-3-gallate, herbacetin, isobavachalcone, quercetin 3-β-d-glucoside, *etc*.) has been reported through the inactivation $3CL^{pro}$ (chymotrypsin-like protease) of SARS virus. Some of the polyphenols claimed as the beneficial dietary antioxidants for prevention and treatment of COVID-19 are shown in Figure 3. Therefore, flavonoids could be a potential supportive care agent for coronavirus (Yang *et al*., 2020). By binding with the active site and 3-OH galooyl group of $3CL^{pro}$, flavonoids inhibit the enzyme activity. Mainly, the hydrophobic and carbohydrate derivatives of flavonoids bind to the core structure and inhibit the activity of the virus (Jo *et al*., 2020; Ghosh *et al*., 2020).

Quercetin, a flavonol, is well known as an anticancer drug, treatment for diseases related to inflammation, and defence against viral disease (Batiha *et al*., 2020). Recently, a supercomputing-based *in silico* drug-docking study demonstrated that quercetin could inhibit the interaction between the receptor ACE-2 (angiotensin-converting enzyme-2) and the virus. The derivative of quercetin, quercetin-3-β-galactoside, is also considered effective against COVID-19 because this compound is the inhibitor of SARS-CoV $3CL^{pro}$, which shares similar features as SARS-CoV-2 (Sargiacomo *et al*., 2020). Curcumin, found in turmeric, is well known for its antioxidant, anticancer, antimutagenic, antiviral, and anti-inflammatory properties. From a molecular docking experiment with target receptors, it has been demonstrated that curcumin can bind with the receptor such as ACE-2, spike glycoprotein-RBD, and SARS-CoV-2 protease, hence reducing the viral infection (Yudi and Meiyanto, 2020). Others also reported that curcumin modulates characteristics of the lipid bilayer and viral S protein, thus inhibiting the virus from entering into cells (Zahedipour *et al*., 2020). It also stimulates the production of interferon to activate the host immunity. As an antioxidant, curcumin helps to neutralise free radicals and increase antioxidant enzyme production (Mrityunjaya *et al*., 2020). Therefore, considering the antioxidant, immune-boosting, anti-inflammatory, and anti-SARS-CoV-2 properties, quercetin and curcumin could be interesting protective and curative agents against COVID-19 (Quiles *et al*., 2020).

Hydroxytyrosol, a polyphenolic compound, has been reported for antioxidant, anti-inflammatory, and antimicrobial activity (Granados *et al*., 2010; Zoric *et al*., 2013). The activity of this compound is related to the removal of ROS. Hydroxytyrosol is also found effective against pulmonary fibrosis and influenza (Yamada *et al*., 2009; Liu *et al*., 2015). Hence, hydorxytyrosol could be a potential natural molecule to fight against COVID-19 infection (Quiles *et al*., 2020). Phytochemical, hesperidin, and rutin act through the inhibition of main protease (M^{pro}) of coronavirus (Adem *et al*., 2020). Herbal medicines such as ginseng root have long been utilised to prevent viral respiratory diseases (Im *et al*., 2016). Historical evidence of treatment against SARS influenza indicated that herbal formulas could be an

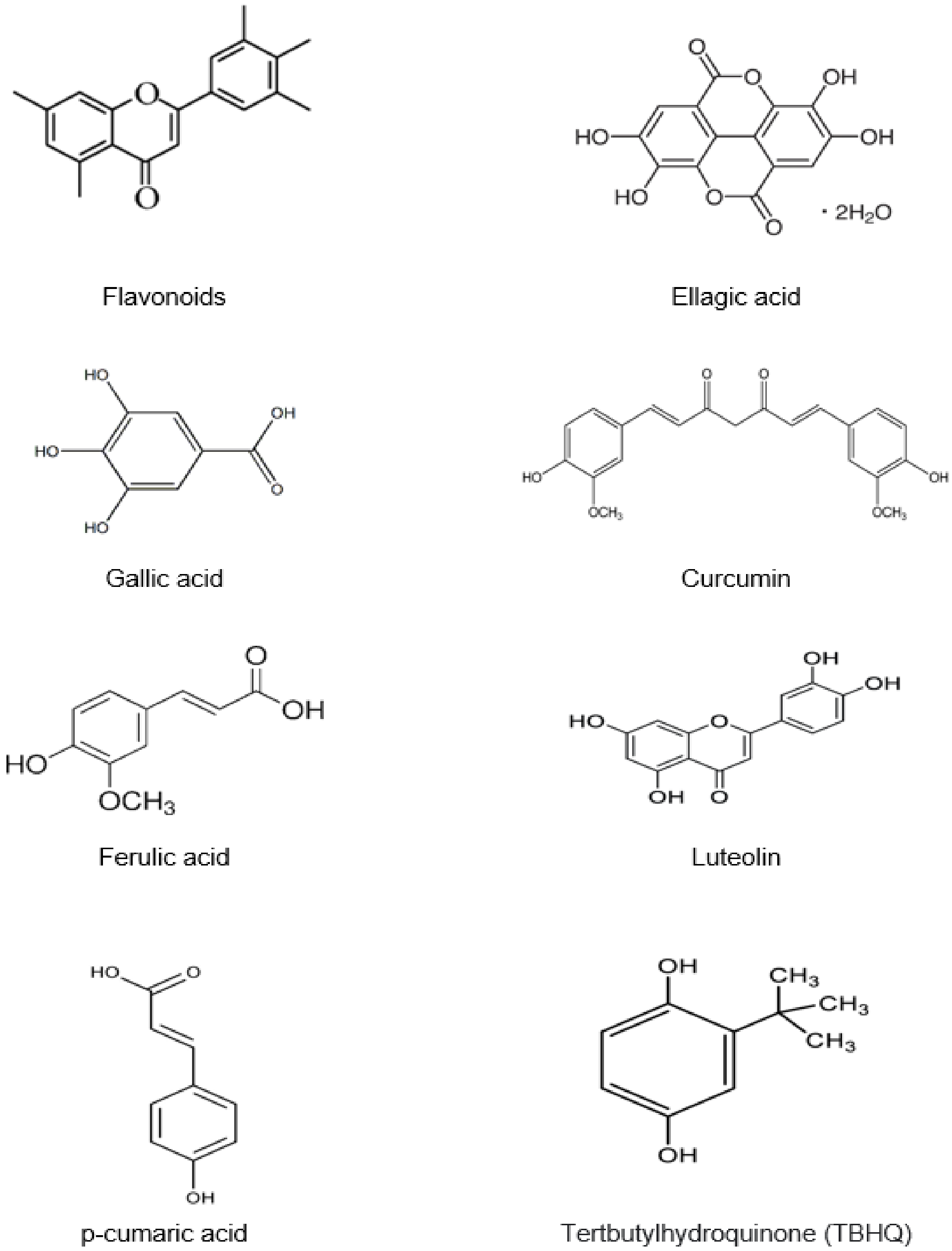

Figure 3. Chemical structures of some polyphenols claimed as beneficial dietary antioxidants for prevention and treatment of COVID-19.

alternative approach to prevent COVID-19 (Yang *et al*., 2020).

Ascorbic acid or vitamin C has a protective role of supporting immune function, and helping in the development and repair of body tissue (Jafari *et al*., 2019). Vitamin C has also been reported as a useful agent for immunomodulation against herpes and influenza (Colunga *et al*., 2020b). A recent study reported that vitamin C has proven effective for the treatment of 50 COVID-19 patients (Cheng, 2020). Another study has reported that high doses of intravenous administration of vitamin C (HIVC) can block several key components of cytokine storms, which is related to COVID-19 infection (Liu *et al*., 2020). The authors hypothesised that HIVC possibly will be useful in treating COVID-19 related acute respiratory distress syndrome (ARDS) and multiorgan dysfunction. Additionally, a combined application of curcumin, ascorbic acid, and glycyrrhizic acid (a triterpene) has also been suggested to regulate inflammatory and immune response related to COVID-19 infection (Chen *et al*., 2020). A synergistic effect of ascorbic acid and curcumin against COVID-19 is also reported by others (Colunga *et al*., 2020a). Considering the antioxidant, anti-inflammatory properties, and ability to defend against body exudative stress, food supplement rich in AA could be a preventive tool to combat COVID-19.

β-carotene, retinol (precursors of vitamin A), can play an important role to improve immune response and lower vulnerability to infections (Huang *et al*., 2018). α-tocopherol (vitamin E) also has an antioxidant and protective function against viral infections. Based on antioxidant, antiviral, and anti-inflammatory effects, other compounds such as cinnamaldehyde (cinnamon), allicin (garlic), piperine (black pepper), propolis (honey), lactoferrin (milk), (−)epigallocatechin-3-gallate (green tea), and theaflavin 3,3′ digallate (black tea) also have potential in combating COVD-19 (Chowdhury *et al*., 2020; Mrityunjaya *et al*., 2020). Traditional Chinese medicines such as *gan cao gan jiang*, *qingfei touxie fuzheng*, *sheganmahuang*, and *qingfei paidu* decoctions are also reported as beneficial in treating COVID-19 pneumonia patients (Arshad *et al*., 2020). Probiotics also play an important role in human health by maintaining gastrointestinal or lung microbiota. Scientific evidence supports that their supplementation can reduce lung infection; therefore, the supplementation of probiotics could also be interesting to reduce the COVID-19 infection (Olaimat *et al*., 2020; Infusino *et al*., 2020). Further randomised clinical trials (RCT) are needed to assess their ability to fight against coronavirus. In recent times, multiple studies have revealed that food antioxidant compounds have an immensely positive effect on immunomodulation. An *in vitro* evaluation showed that essential oils have protective influences on cell survival, and protect damages of lymphocytes (Valdivieso *et al*., 2019). Hence, extensive food antioxidant studies could help to improve human immune response and subsequently make us more competitive in the fight against COVID-19 or any unidentified disease.

Antioxidant compounds have long been studied for their important beneficial properties on human health. The available evidence regarding the potential use of food antioxidants suggests that these compounds provide positive support to human health by inhibiting and/or reducing ROS and other free radicals. Antioxidants from natural sources such as phenols, flavonoids, carotenoids, and vitamins have been reported to improve immune response against many infections and diseases. Several studies have already reported the effectiveness of some polyphenols, flavonoids, and vitamin C against COVID-19 infection. However, the statement needs to be properly supported by future random clinical trials. Therefore, extensive food antioxidant studies might be an interesting field of research to improve human immune response to fight against COVID-19 or any unidentified disease in the future.

Anti-inflammatory properties

Inflammation is an adaptive response triggered by noxious stimuli in response to infections and tissue injuries (Allegra, 2019). Based on inflammatory process and cellular mechanisms, inflammation can be divided into acute and chronic types. Acute inflammation persists for a short time to several days, whereas chronic inflammations cause chronic diseases such as metabolic and endocrine disorders, diabetic complications, pulmonary diseases, cancers, cardiovascular diseases, neurological disorders, autoimmune illnesses, arthritis, and inflammatory bowel diseases (Arulselvan *et al*., 2016). An inflammatory process occurring in tissue or cellular sites includes a series of instances such as dilation of venules and arterioles, increased permeability of vein and blood vessels, and blood flow with phagocytic leukocyte migrated to the surrounding cell and tissue which causes swelling, redness, pain, and warmth to the inflamed area (Incalza *et al*., 2018).

Non-steroidal anti-inflammatory drugs (NSAIDs) are generally prescribed for the treatment of inflammatory diseases. These drugs act through the inhibition of cyclooxygenase enzymes which make prostaglandins (PGs). The PGs are responsible for the swelling and pain of inflamed sites (Vane and Botting, 1998). The NSAIDs have been documented as having many side effects on human health. On the other hand, antioxidants play a role in inhibition of inflammation through protecting tissues from damage by ROS species and other free radicals, and also accelerate the wound healing process by controlling oxidative stress. It is well established that foods containing natural antioxidants such as polyphenols, flavonoids, carotenoids, and vitamins have anti-inflammatory properties. For example, antioxidants are usually applied to treat various types of brain inflammations such as oxidative stress in neurons, apoptosis, neurological damages, and neurodegenerative diseases (Warner *et al*., 2004). The brain cells are more vulnerable to oxidative injury due to their high metabolic activity and polyunsaturated lipid content (Roleira *et al*., 2010). Black rice (*Oryza sativa* L.) containing high levels of anthocyanin polyphenols have beneficial effects on wound healing in the skin by aiding in collagen synthesis (Palungwachira *et al*., 2019). Peluso *et al.* (2018) reported that anthocyanin from berries, and polyphenols from barley and sweet potato exhibit anti-inflammatory properties by improving the activity of antioxidant enzymes and/or neutralising the ROS. The biological properties of bioactive compounds assist in blocking major signalling pathways for the production of various pro-inflammatory mediators such as NF-κB and mitogen-activated protein kinases (MAPKs) (Arulselvan *et al*., 2016). Therefore, the intake of antioxidant compounds by adding plant-based foods in the daily diet can lead to living a healthy life.

Antidiabetic properties

Diabetes consists of hyperglycaemia and hyperlipidaemia. Oxidative stress can trigger the pathogenesis of type 2 diabetes by boosting insulin resistance or by harming insulin secretion (Montonen *et al*., 2004). Recent evidence indicates that dietary antioxidants have a protective effect against the progress of diabetes by inhibiting peroxidation chain reactions. The depletion of antioxidants owing to diabetes is well-documented (Montonen *et al*., 2004; Dembinska *et al*., 2008). Numerous studies have revealed a substantial reduction in plasma antioxidants in the course of diabetes. Diabetic patients frequently suffer from low levels of plasma antioxidants, especially in old age. Therefore, the therapeutic use of food antioxidants is a convincing approach for the prevention and treatment of diabetic complications.

Defence against cardiovascular diseases

Cardiovascular disease (CVD) is the most prevalent reason for premature death worldwide in recent years. Advanced research investigated the cardio-protective effect of food antioxidants. Foods rich in antioxidants such as fruits and fresh produces help in reducing body oxidative stress. The effects of food antioxidants on minimising cardiovascular risk factors such as hypertension, dyslipidaemia, and diabetes are well recognised (Duthie *et al*., 1989; Pellegrino, 2016).

Studies showed that the antioxidant molecules such as natural polyphenolic compound, resveratrol, are highly correlated with antihypertensive effect. The “French Paradox” implies that consistent intake of red wine (rich in resveratrol) is connected with the low occurrence of CVD among the Southwestern French population despite their high consumption of saturated fat-rich diets (Pellegrino, 2016; Griffiths *et al*., 2016). An important cardio-protective feature of resveratrol is associated with the minimisation of oxidative stress of the body (Pellegrino, 2016; Griffiths *et al*., 2016). Ascorbic acid and α-tocopherol have been demonstrated to down-regulate the activity of NADPH oxidase (nicotinamide adenine dinucleotide phosphate-oxidase, which is a foremost source of ROS in the vascular wall) and up-regulate endothelial NO synthase (eNOS) which ultimately help to reduce blood pressure (Rodrigo *et al*., 2008). The intake of fruits and vegetables, which are rich sources of food antioxidants, has antihypertensive effects.

Another CVD risk factor is dyslipidaemia, categorised as a preeminent fasting and postprandial plasmatic intensity of total triglycerides, as well as free fatty acids coupled with higher levels of LDL cholesterol and lower levels of HDL cholesterol. Disturbance of lipid metabolism are related with the overproduction of ROS, which in turn express the antioxidant status and lipoprotein levels of various organs (Hadi *et al*., 2005; Halperin *et al*., 2006).

Food antioxidants are key lipid-lowering agents. Literature showed that food antioxidants, especially monounsaturated and polyunsaturated fatty acids, and polyphenols in fruits and vegetables, could have positive impact on the lipid profile. Moreover, a regular consumption of fruits and vegetables is alleged to enforcing the capability of organisms to offset free radicals and also to have a better control of the lipid profile, which can positively regulate the main cardiovascular risk factors (Bahmani *et al*., 2015). Evidence suggests that in the absence of antioxidants, oxidative stress is one of the leading factors of cardiovascular risk.

Conclusion

Food antioxidants may have potential in future food formulation as a medicine to minimise the risk of various side effects and health complications. Since food antioxidants are prone to exogenous factors (*e.g*., oxygen and sunlight), it would be a challenge for food industries dealing with processed foods. For this reason, it is better to consider minimally processed food to meet the dietary antioxidant requirements. Natural antioxidants also can be a promising research area for pharmaceutical and nutraceutical industries in coming days. Although antioxidants can be used for both prevention and treatment of chronic inflammatory disease, it is better to use antioxidants as a preventive measure rather than cure due to its nature of working slowly in recovery from the inflammatory diseases. We should eat food (containing natural antioxidants) as our medicine; otherwise, we have to eat medicine as our food.

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