ΦYTON
REVISTA INTERNACIONAL DE BOTÁNICA EXPERIMENTAL
INTERNATIONAL JOURNAL OF EXPERIMENTAL BOTANY
Tech Science Press
871 Coronado Center Drive, Suite 200,
Henderson, Nevada, 89052, USA
www.techscience.com

Active compounds of medicinal plants, mechanism for antioxidant and beneficial effects

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Abstract. An increased interest in the antioxidant effects of medicinal plants has developed in recent years. Identifying antioxidant compounds present in medicinal plants and elucidating the mechanism by which they prevent oxidation have been the focus of the research community. We performed a systematic and exhaustive review aimed at analyzing the available data regarding the beneficial effects of secondary metabolites in plants. The result of this review is presented as a description of free radicals, as well as cellular and physiological oxidative stress, is provided. The origin and source of antioxidant compounds, and the cellular and molecular mechanism by which they exert antioxidant effects, have been reported. The absorption, distribution and, elimination of antioxidants are mentioned. The beneficial effects of secondary metabolites of medicinal plants in various high incidence disease conditions were also reviewed. Finally, disease states that benefit from antioxidant compounds includes diabetes, cancer, cardiovascular diseases, and liver, brain and, intestinal diseases.

Keywords: Antioxidants; Free radicals; Secondary metabolites; Polyphenols; Oxidative stress; Medicinal plants.

INTRODUCTION

Cells produce reactive oxygen species (ROS) in moderate concentrations as part of their normal physiological function. When ROS levels increase, modification to cellular components occurs (Birben et al., 2012), triggering a change in the balance between ROS production and antioxidant production. This leads to an increase in oxidative stress, alteration of cellular homeostasis and inadequate functioning of various cellular pathways, leading to apoptosis (Betteridge, 2000; Lobo et al., 2010; Venereo-Gutiérrez, 2002). Medicinal plants have been studied extensively due to the presence of beneficial antioxidants (Dueñas et al., 2015; Jadhav & Bhutani, 2002; Sathisha et al., 2011).

The natural antioxidants, more recently, have attracted considerable attention of users and researchers largely on account of adverse toxicological reports on some synthetic antioxidants and growing awareness among consumers (Ramalakshmi et al. 2007). In this context, among others, medicinal plants are being viewed as easily available and potent source of antioxidants as they contain a mixture of different chemical compounds that may act individually or in synergy to cure disease and improve health. A single plant may have a diversity of phytochemicals with different beneficial effects, ranging from bitter compounds that stimulate digestion system, phenolic compounds for antioxidant and many other pharmacological properties, antibacterial, and antifungal, tannins that work as natural antibiotics, diuretic substances, alkaloids, among others (Miguel 2010).

In this review (Fig. 1), we focus on the following aspects: the effects of free radicals, mainly cellular and physiological oxidative stress; the origin of plant-derived antioxidant, as well as their reported cellular and molecular mechanisms involved in free-radical scavenging. The absorption, and distribution of these components within the body as well as the elimination process. The beneficial effects of secondary metabolites from medicinal plants in various disease conditions such as diabetes, cancer, cardiovascular disease, and liver, brain, and intestinal diseases.

FREE RADICALS

Free radicals are molecules that have one or more unpaired electrons (Betteridge, 2000; Lobo et al., 2010; Pham-Huy et al., 2008; Valko et al., 2007). In biological systems, free radicals are derivatives of oxygen, nitrogen, and sulfur molecules.

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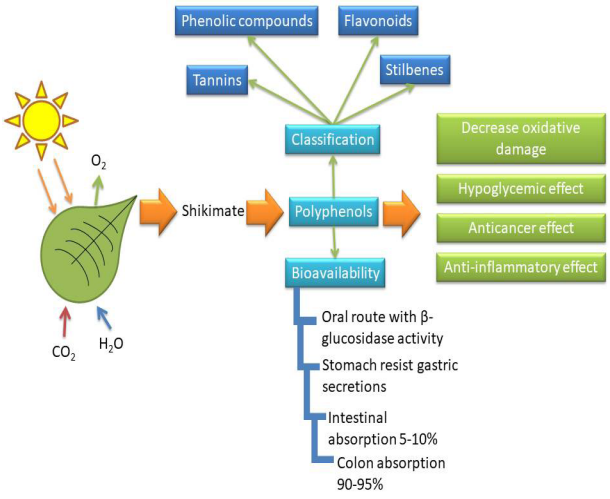

Fig. 1. Active compounds from medicinal plants, antioxidant and beneficial effects.

Depending on the molecular group, they are referred to as reactive oxygen species (ROS), reactive nitrogen species (RNS) and reactive sulfur species (RSS) (Jian-Ming et al., 2010).

Under normal physiological conditions, cells produce reactive oxygen species, including hydrogen peroxide (H_2O_2), the superoxide ion (O_2^-), and the hydroxyl radical (OH^-). The generation of free radicals represents a biological paradox as ROS can prevent diseases of the immune system and is essential for apoptosis (Betteridge, 2000; Lobo et al., 2010; Pham-Huy et al., 2008; Seifried et al., 2007; Sylvie et al., 2014; Valko et al., 2007; Venereo-Gutiérrez, 2002).

When the concentration of free radicals increases, damage to amino acids, proteins, lipids, and DNA can occur, affecting homeostasis and cellular function (Betteridge, 2000; Lobo et al., 2010; Seifried et al., 2007).

Oxidation and nitration of proteins, lipid peroxidation, DNA fragmentation, activation of caspases, and the expression of pro-inflammatory genes lead to apoptosis, necrosis, and cellular dysfunction, in addition to generating persistent inflammation (Oyenihi, 2014; Sylvie et al., 2014).

All aerobic organisms have defense mechanisms to protect against oxidative damage. Antioxidants are, by definition, compounds that have the ability to inhibit or prevent oxidation by electron donation (Al-Jaber et al., 2011; Lobo et al., 2010; Martínez-Flórez et al., 2002). Some of the actions of antioxidants include prevention or repair of the damage caused by ROS and RNS, as well as the elimination of free radicals (Al-Jaber et al., 2011, Pham-Huy et al., 2008; Venereo-Gutiérrez, 2002).

A mechanism by which antioxidants prevent oxidative stress is by the elimination of ROS molecules. Examples include reduced and oxidized glutathione, carotenoids, vitamin complexes E and C, flavonoids, and lipoic acid (Lobo et al., 2010; Nowotny et al., 2015; Venereo-Gutiérrez, 2002). Preventive antioxidants, which eliminate the formation of reactive oxygen species, act through mechanisms involving the reduction of hydroperoxides to alcohol and water, without generating free radicals (Lobo et al., 2010; Oyenihi, 2014).

A secondary mechanism is through antioxidant enzymatic activity; these enzymes include catalase, glutathione peroxidase, superoxide dismutase (Cu, ZnSOD, and MnSOD), and metal binding enzymes (Fe^{+2} and Cu^+). The transfer of an electron to hydrogen peroxide takes place via the Fenton reaction, creating a free hydroxyl radical, which can oxidize other molecules. The oxidized forms of these metals (Fe^{3+} and Cu^{2+}) are reduced, which generates a cycle of oxidation and reduction (Jian-Ming et al., 2010; Lobo et al., 2010, Nowotny et al., 2015; Oyenihi, 2014; Pham-Huy et al., 2008; Pignatelli et al., 2018; Sylvie et al., 2014).

The third mechanism is of vital importance, as it degrades ROS-damaged macromolecules, such as DNA proteases, lipases, among others. (Nowotny, 2015). Here the proteolytic enzymes, proteases, and peptidases present in the cytosol and mitochondria can rearrange, degrade, and remove proteins modified by oxidation, thereby preventing the accumulation of damage to macromolecules. Enzymes such as glycosylases and nucleases that can repair DNA damage are also included in this mode of action (Lobo et al., 2010; Oyenihi, 2014).

However, it is necessary to reinforce endogenous antioxidants through consuming a diet rich in antioxidant-containing foods, including fruits, vegetables, and plants (Billingsley & Carbone, 2018; Sylvie et al., 2014).

BIOSYNTHESIS OF COMPOUNDS WITH ANTIOXIDANT ACTIVITY

Plants synthesize several beneficial compounds via metabolism. The primary products of plant metabolism are proteins and cellulose. Secondary metabolic components include phenolic compounds, terpenoids, and nitrogen-containing compounds (Borrelli & Trono, 2016).

Products of secondary metabolism are classified according to the biosynthetic route. Secondary metabolites are classified as follows: polyphenols, phenolic compounds, terpenoids, steroids, and alkaloids (Al-Jaber et al., 2011; Bhooshan & Ibrahim, 2009; Bourgaud et al., 2011).

In plant cells, the synthesis of alkaloids and terpenes occurs in the plastid, whereas the production of sterols takes place in the endoplasmic reticulum. Amines and alkaloids are synthesized in the mitochondria. Water-soluble compounds are stored in vacuoles, and fat-soluble substances are stored in resin ducts, lacticifers, trichomes, and cuticles (Sepúlveda-Jiménez et al., 2003; Singh & Sharma, 2015).

The process of generating secondary metabolites begins in the shikimate pathway, which is a ubiquitous pathway in plants. It produces three essential aromatic amino acids: L-tryptophan, L-phenylalanine, and L-tyrosine, which the plant then uses to synthesize proteins that are crucial for plant growth, pigments generation, hormone and complex aromatic compound (alkaloids, phenylpropanoids, flavonoids) and production of cell wall components (Martínez-Flórez et al., 2002; Tzin & Galili, 2010). The malonate pathway produces condensed tannins and lignans via polymerization reactions (Borrelli & Trono, 2016; Valko et al., 2007).

During both photosynthesis and the pentose phosphate pathways, primary metabolic compounds are formed,

such as phosphoenolpyruvate (PEP) and D-erythrose-4-phosphate (E-4-P). The 3-deoxy-D-arabino-heptulosonate 7-phosphate (DAHP synthase) enzyme leads to the formation of shikimate. Then, by de-phosphorylation reactions, the chorismate metabolite is formed, which acts as an initiator in the synthesis of aromatic amino acids (Delgado-Vargas et al., 2000; Tzin & Galili, 2010). From chorismate, two metabolites are produced, the anthranilate precursor of tryptophan, and the prephenate precursor of phenylalanine and tyrosine (Fig. 2).

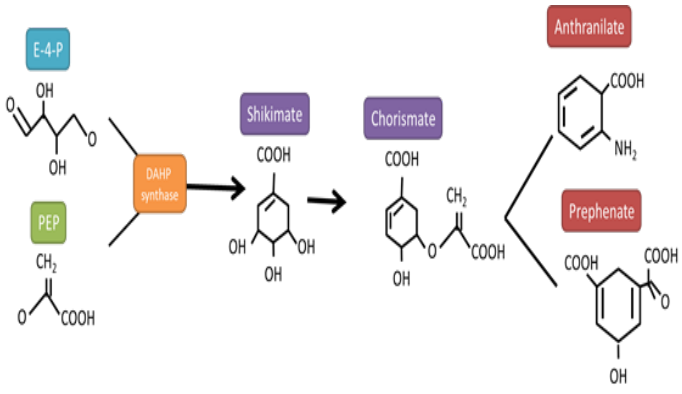

Fig. 2. Formation of the precursors of the secondary compounds. E-4-P: D-erythrose 4-phosphate. PEP: phosphoenolpyruvate. DAHP: 3-Deoxy-D-Arabino-Heptulosonate 7-Phosphate.

Tryptophan is catabolized to several secondary metabolites, including Indol-3-acetic, indole-glycosylates, phytoalexins, terpenoids, indole alkaloids, auxin, glucosinolates and tryptamine derivates. Phenylalanine is a precursor of phenylpropanoids, glucosinolates, cell wall lignin, salicylates, flavonoids, and anthocyanins. Finally, Tyrosine is a precursor of tocochromanol (tocopherols and tocotrienols), plastoquinones, isoquinoline alkaloids, and some phenylpropanoids (Fig. 3), (Delgado-Vargas et al., 2000; Martínez-Flórez et al., 2002).

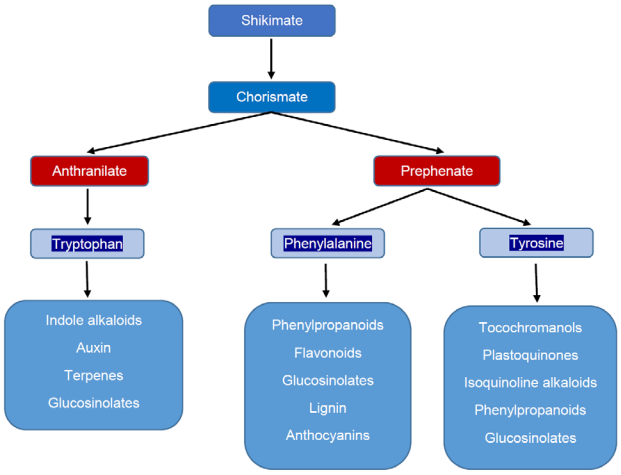

Fig. 3. Secondary metabolic compounds form from the Shikimate pathway.

The malonate and shikimate pathways produce flavonoids. Condensation and polymerization reactions produce tannins, lignans, cutin, and suberin. Terpenes and terpenoids are derived from a common precursor, isopentenyl diphosphate (IPP), which is ubiquitinated throughout the mevalonate pathway. Condensation of IPP with dimethylallyl pyrophosphate generates geranyl pyrophosphate, which is the precursor of monoterpenes. Nitrogen-containing compounds are derivatives of aliphatic amino acids; examples of these compounds are alkaloids and aliphatic glucosinolates (Borrelli & Trono, 2016; Jian-Ming et al., 2010). Polyphenols include different classes such as phenolic acids, flavonoids, stilbenes, and lignans (Fig. 4), all of which have beneficial health properties (Bhooshan & Ibrahim, 2000; Borrelli & Trono, 2016).

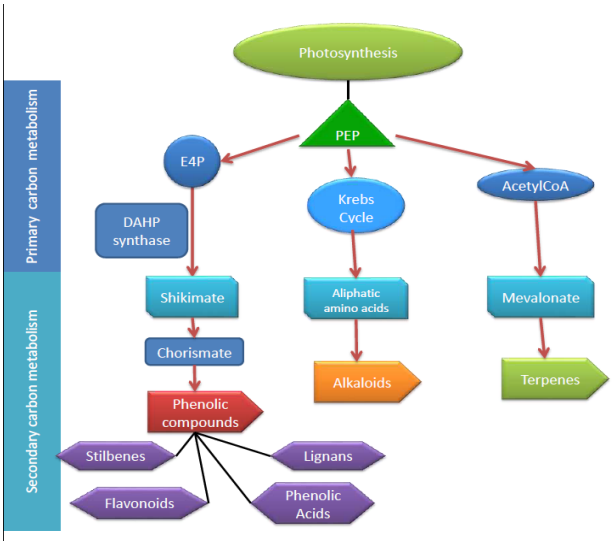

Fig. 4. Schematic representation of the biosynthesis of secondary metabolites. E4P, erythrose 4-phosphate; PEP, phosphoenolpyruvate.

Polyphenols can interact with receptors or enzymes involved in signal translation, thereby modifying cell oxidation and promoting an antioxidant condition (Bhooshan & Ibrahim, 2000; Matkowski, 2008). Apart from antioxidant capacity, polyphenols have chemoprotective properties which act to suppress cancer cells activity by inhibiting metabolic enzymes (Sylvie et al., 2014).

Flavonoids are produced as a protective mechanism against exogenous agents that affect the integrity of the plant (Martínez-Flórez et al., 2002). The chemical structure of flavonoids is a typical formula, $C_6C_3C_6$, which represents the number of carbons in each ring. Flavonoids contain two benzene rings, joined by a central chain of three carbon atoms (Borrelli & Trono, 2016; Martínez-Flórez et al., 2002; Matkowski, 2008). Different flavonoid classes can be identified depending on their structure: flavones, flavonols, flavanones, flavanols, flavones, isoflavonoids, proanthocyanidins (catechins) and anthocyanidins (Bhooshan & Ibrahim, 2009; Matkowski, 2008; Pham-Huy

et al., 2008). They can be hydroxylated in rings A and B, methylated in hydroxyl groups, phenylated, and glycosylated. Other modifications can form biflanonoids, lignans, oligomeric proanthocyanidins, and glycoside esters with other phenolics. Some flavonoids can be found in plants, such as phenolic acid in the form of glycosides (Peterson, 2010).

Phenols and flavonoids have free radical scavenging capacity; their antioxidant activity is attributed to redox properties, where they act as reducing agents, electron donors, or metal chelators (Al-Jaber et al., 2011; Sylvie et al., 2014; Tangney & Rasmussen, 2013). Formation begins with monolignols, which are derivatives of hydroxycinnamic acid. These are dimerized in lignans or polymerized in lignin structures. Lignans are stereospecific dimers of monolignols attached to carbon eight, in plants they are found as glycosides (Sin et al., 2015).

Terpenoids are derived from the fusion of 5 carbon units of isoprene. They are classified according to the number of units formed. Two different synthetic routes exist the mevalonate pathway in the cytoplasm and the DXP pathway in the plastids. Various products are generated in different areas of the cell. In the cytosol and endoplasmic reticulum, sesquiterpenes (C_{15}), triterpenes (C_{30}), and polyterpenes are produced, whereas isoprene, the monoterpenes (C_{10}), diterpenes (C_{20}), tetraterpenes (C_{40}) and prenylated quinones originate in the plastids (Sepúlveda-Jiménez et al., 2003).

Alkaloids are heterocyclic compounds synthesized from amino acids such as tryptophan, tyrosine, phenylalanine, lysine, arginine, and ornithine. They are divided into different alkaloids groups: isoquinoléic, quinolizidine, pyrrolizidine, tropánic and indole. The synthesis of alkaloids increases in response to the wound produced by insects. Betacyanins are chromo alkaloids of red-violet pigmentation, the antioxidant activity of betacyanins is higher than that of ascorbic acid, catechin, rutin, and α-tocopherol. They capture the excess ROS produced under stress to maintain the oxide-reduction state (Sepúlveda-Jiménez et al., 2003).

Other compounds with antioxidant activity that plants can present are β-carotenes, lycopene, tocopherols and, carotenoids. All of them are potent scavengers of free radicals (Matkowski, 2008; Peterson et al., 2010).

The polyphenol distribution is ubiquitous in plants. In the diet, they are the most abundant source of antioxidants, the food with the highest content of polyphenols are red wine, coffee, cocoa, tea, citrus fruits, berries, vegetables, cereals, and dry legumes (Valdés et al., 2015). To estimate the amount of polyphenols in the diet, the webpage called Phenol-Explorer 3.6 database contains more than 35,000 content values for 500 different polyphenols in over 400 foods (http://phenol-explorer.eu/).

BIOAVAILABILITY

The phenolic compounds in foods are in the form of esters, glycosides, polymers or as aglycones, so they need to be hydrolyzed for absorption (Dryden et al., 2006; Talavéra et al., 2003).

The digestion of polyphenols starts from the mouth, where the chewing process and the secretion of saliva, as well as the microbiota, have β-glucosidase activity, reducing them to simpler forms (Dueñas et al., 2015; Dryden et al., 2006).

In the stomach, glycosides resist gastric secretions, although there are reports that some compounds such as quercetin (Talavéra et al., 2003) and anthocyanins (Cardona et al., 2013) can be absorbed.

Dietary polyphenols reach the colon, where gut microbiota will react to produce aglycones, which facilitate the absorption and have higher activity in physiology than their food precursors (Dueñas et al., 2015). The intestinal absorption of polyphenols is 5-10% (Del Rio et al., 2013; Marín et al., 2015), the enzymes involved are β-glucosidase and lactase-phlorizin hydrolase, the latter located in the enterocyte membrane (Dueñas et al., 2015; Favari et al., 2013; Pietta et al., 2003), and showing a specificity for flavonoids O -β-D-glycosides (Angelino et al., 2017). However, they have no action on the compounds bound to rhamnose (Van Duynhoven et al., 2011). When a polyphenol reaches the intestine in its monomeric form or as a dimer structure, it is absorbed by passive diffusion into the interior of the enterocyte due to its lipophilic property (Angelino et al., 2017; Dueñas et al., 2015; Marín et al., 2015).

The more complex forms such as oligomeric and polymeric polyphenols (condensed or hydrolyzable tannins) reach the colon where they are degraded by the intestinal microbiota (Marín et al., 2015; Teng & Cheng, 2018), the percentage that reaches this region is 90-95% (Del Río et al., 2013; Marín et al., 2015). Plasma forms being different to those found in their sources. Absorption is affected by the chemical structure, degree of glycosylation, enterohepatic circulation and the percentage that reaches the colon (Pietta et al., 2003).

Polyphenols are metabolized in two stages: In phase I oxidation, reduction, and hydrolysis occur, leading to a reduction in the number of hydroxyl groups, adding sulfate, glucuronic acid or methyl groups to the structure, modifying the compound favoring an increase in polarity and its hydrophilic property (Marín et al., 2015). This makes the compound more soluble, facilitating excretion through the urine (Dryden et al., 2006). In the second phase conjugation processes occur, which can develop inside the enterocyte and the hepatocyte, generating as a product conjugated metabolites (methyl, glucuronide, and sulfate derivatives), which are released into the systemic circulation for distribution to organs and excretion by urine or feces (Bohn, 2014; Marín et al., 2015). Most measurements are limited because they are semi-quantitative because they do not take into account the balance between consumption and the elimination of these secondary compounds from plants (Pressman et al., 2017).

Once the compound reaches the intracellular level, through the SGLT1 transporters, the glycoside is hydrolyzed by the cytosolic β-glucosidase (CBG) (Angelino et al., 2017; Bohn, 2014; Favari et al., 2013). The compounds found intracellularly enter into detoxification processes where they undergo changes due to methylation, sulfation, and glucuronidation (Dryden et al., 2006; Favari et al., 2013; Van

Duynhoven et al., 2011) through enzymes such as catechol-O-methyltransferases (COMT), sulfotransferases (SULT) and uridine-5-diphosphate-glucuronosyltransferases (UGT), respectively (Angelino et al., 2017; Pietta et al., 2003) The other enzymes described are N-acetyl-transferases (NAT's), glutathione-S-transferases (GST's) and thiopurine-S-methyl-transferase (TPMT) (Dryden et al., 2006). Phase II enzymes biotransform this aglycone into conjugated metabolites (glucuronides, O-methyl ethers, and sulfates) within the enterocyte and in the liver (Dueñas et al., 2015; Marín, 2015).

Subsequently, the metabolites reach the periphery, where bind to plasma proteins (albumin), the affinity of polyphenols to proteins can be high as in the case of apigenin and quercetin (90%) and lower as epicatechin (10%) (Bhattacharyya et al., 2014). Hence, the compound can enter tissues (hepatic, stomach, intestinal and nephritic) where it is metabolized or transported to the target tissues (pulmonary, pancreatic, cerebral, cardiac and splenic) (Marín et al., 2015).

The metabolites reach the hepatocytes through the portal vein, where they undergo phase II metabolism to form glucuronide, methylated or sulfate metabolites, or a combination of these, and move on to the enterohepatic circulation, allowing re-uptake and solubility/serum bioavailability (Bohn, 2014; Pressman et al., 2017). Upon reaching the intestine through biliary secretion (Angelino et al., 2017; Del Rio et al., 2013; Ozdal et al., 2016). The process by which the metabolites are recycled into the intestinal lumen or peripheral blood to reach the liver is known as phase III metabolism. In this phase, the reflow or recycling of polyphenols is facilitated by the ATP-Binding-Cassette (ABC, membrane transporter), the multidrug resistance protein 2 (MRP-2, apical and lumen protein), and MRP-1 (basolateral transporter) (Dryden et al., 2006).

Finally, the elimination of these compounds is by biliary or urinary route (Del Rio et al., 2013; Marín et al., 2015; Ozdal et al., 2016; Van Duynhoven et al., 2011). It has also been reported that phenolic metabolites can be eliminated through feces (Dueñas et al., 2015; Pressman et al., 2017).

MOLECULAR MECHANISM OF SECONDARY METABOLITES

Sites of secondary metabolite functions vary by the compound (Singh & Sharma, 2015). Trans-resveratrol, a polyphenol found in red grapes and their derivatives (Dueñas et al., 2015; Huang & Manning, 2008) increase the activity of SIRT1 (sirtuin 1 or NAD-dependent sirtuin-1 deacetylase) a molecule related to longevity, and it is downregulated in cells that have high insulin resistance. SIRT1 promotes the deacetylation of Foxo1 (Forkhead box protein O1, member of a transcription factor family). The acetylation status of Foxo1 is reduced, and at the same time, there is transcriptional activation of glucose transport 4 (GLUT4) that leads to a decrease in insulin resistance (Yu et al., 2008).

Resveratrol can activate AMP-activated protein kinase (AMPK), which phosphorylates TSC2 (tuberous sclerosis complex 2) by inhibiting mTOR (Huang & Manning, 2008; Yu et al., 2008). It has been described that curcumin also inhibits Akt / mTOR signaling, by preventing Akt phosphorylation, this decreases the activation of the S6K protein (ribosomal kinase S6) producing effects similar to resveratrol (Goel et al., 2001). In cancer, resveratrol binds directly to cyclooxygenase (COX-2), inhibiting the production of prostaglandins (PGE) and producing an anti-inflammatory effect (Queipo-Ortuño et al., 2012). Curcumin has been shown to inhibit COX-2 mRNA expression (Peralta-Pérez & Volke-Sepúlveda, 2012).

In most secondary metabolites, an antioxidant capacity has been identified, as well as the mechanism of free radicals elimination (Peterson et al., 2010). In its role as a signal molecule, ROS can induce the expression of antioxidant enzymes that regulate free radical levels. The production of superoxide dismutase, ascorbate peroxidase and ascorbic acid, α-tocopherol, carotenoids, anthocyanins, and betacyanins are all promoted by ROS. This shows that the secondary metabolites contribute to the maintenance of the oxidation-reduction state of plant cells (Sepúlveda-Jiménez et al., 2003).

At the end of the 20th century, it was suggested that only flavonoids and polyphenols present in red wine, as well as other products (tea, coffee, fruits, vegetables, and chocolate), have antioxidant activity (Bhooshan & Ibrahim, 2009; Jadhav & Bhutani, 2002; Tangney & Rasmussen, 2013). Now it is known that secondary metabolites can eliminate free radicals and mitigate the effects of oxidative stress (Al-Jaber et al., 2011).

Epigallocatechin-3-gallate (EGCG), a polyphenol that acts in the NF-κB pathway, inhibits the signaling and expression of inflammatory proteins, resulting in anti-inflammatory effects. Carotenoids and flavonoids, neutralize hydrogen peroxide and, superoxide radical. Alpha-tocopherol is a lipid-soluble antioxidant that can eliminate the superoxide radical and protect lipids from peroxidation (Re et al., 1999).

Different methods can quantify secondary metabolites with antioxidant activity. It is essential to correctly measure antioxidant levels to determine the antioxidant capacity. Among the most used methods is the ABTS radical measurement test (Ou & Hampsch-Woodill, 2001). ABTS calculates the oxygen radical absorption capacity (ORAC) (Brand-Williams et al., 1995). To evaluate the total antioxidant potential (TRAP) (Matough et al., 2012) methods exist to determine the reduction of the DPPH radical (Matough et al., 2012), and the quantification of the plasma iron reduction capacity (FRAP) (Yu et al., 2006).

EFFECTS OF OXIDATIVE STRESS AND THE PROTECTIVE EFFECT OF POLYPHENOLS

Diabetes and Pancreas

In diabetes mellitus, ROS levels increase due to oxidation of glucose, changes in antioxidant-radical concentration, as well as a decrease of low molecular weight antioxidants (GSH, vitamin E, SOD) (Busik et al., 2008; Volpe et al.,

2018). In hyperglycemia, ROS are generated by stimulating an increase in mitochondrial respiration (Oyenihi, 2014; Valko et al., 2007; Xiao & Högger, 2015; Yu et al., 2006). Free radicals generation in diabetes is produced by non-enzymatic glycation (products of advanced glycation), increased lipid peroxidation, which affects enzyme damage, cellular pathways, and an increase in insulin resistance. The mitochondria play an important role in the generation of reactive oxygen species, during oxidative metabolism, generating mainly the superoxide radical, which can be fused with hydrogen peroxide to form peroxynitrite, which can damage beta cells (Betteridge, 2000; Kim et al., 2016; Xiao & Högger, 2015).

Numerous reports are suggesting the hypoglycemic effect of polyphenols that are generated through the inhibition of pancreatic enzymes such as α-amylase and α-glucosidase, as well as through hydroxylation, glycosylation, and methylation (Bhooshan & Ibrahim, 2009). Stimulating insulin secretion can also protect the cell against toxicity caused by hyperglycemia (Dolado & Nebreda, 2008).

Cancer, tumors, and role of flavonoids

It has been described that in cancer, ROS are tumorigenic due to their ability to increase cell proliferation and migration, as well as to induce DNA damage causing genetic lesions that lead to tumor progression (Lobo et al., 2010; Seifried et al., 2007; Valko et al., 2007). The reduction of NADPH oxidase (Nox 4 and 5) is a source of ROS production favoring the survival and growth of tumor cells of pancreas and lung respectively. Reactive oxygen species activate Akt by inhibiting phosphatases and PTEN: gene homolog of phosphatase and suppressed tensor of chromosome 10, preventing the activation of phosphoinositol 3-kinase (PI3K) (Ohkawa et al., 1979). It has been shown that hyperactivation of Akt increases metabolic activity in the mitochondria and inhibits the transcriptional activity of FoxO, which increases ROS levels (Sin et al., 2015).

Polyphenols can inhibit tumor growth and metastasis, when combined with other macromolecules (ascorbic acid, lysine, proline or arginine) or with other polyphenols, due to their antioxidant capacity, favoring a decrease in pro-oxidant effects and favoring an antioxidant state inhibiting MMP-9 and VEGF (De Marchi et al., 2013). Another mechanism described is through the inhibition of different kinases such as cyclin-dependent kinase (CDC2), inhibition of PKC, PI3K / Akt and MEK1, and inhibiting MAPK / ERK pathway (Ras-Raf-MEK-ERK pathway) acting from lipid rafts, thus inhibiting the cancer progression (Rasouli et al., 2017; Vita, 2005).

Cardiovascular Diseases

In cardiovascular disease (CVD) the generation of ROS is increased, while the bioavailability of nitric oxide (NO) decreases. The damage of ROS in CVD in the vascular wall where lipid peroxidation products can accumulate as well as increase the induction of pro-inflammatory genes, that are favored by NADPH oxidase-1. In the mitochondria, the deficiency of antioxidant enzymes promotes the onset of CVD. Mitochondrial dysfunctions can be caused by DNA damage mainly affecting complex I of the mitochondrial respiratory chain (Quiñones et al., 2012; Valko et al., 2007).

Other problems triggered by free radicals are the generation of the oxidized low-density proteins (LDL), which increases the inflammatory state and promotes the development of atherosclerosis (Lobo et al., 2010; Pham-Huy et al., 2008; Seifried et al., 2007; Tangney & Rasmussen, 2013).

A reduction of CVD is generated by flavonoids, anthocyanidins, isoflavone flavonols, flavones, lignin, and proanthocyanidins has been documented (Matkowski, 2008; Rasouli et al., 2017). The consumption of anthocyanidins (blueberries and strawberries), reduces hypertension by 5-8% since structurally the B-hydroxylated and methoxylated ring can be factors that trigger vasodilation. Similarly, the consumption of grape juice for 14 days is associated with dilation of the brachial (humeral) artery in adults with the coronary disease (Huang & Manning, 2008; Sathisha et al., 2011). The consumption of cocoa (176 mg / dL), significantly increases endothelial dilation, 2 hours after its administration (Quiñones et al., 2012).

Polyphenols have antihypertensive, atherogenic (formation of plaque in blood vessels), and anti-inflammatory effects, as well as the ability to inhibit platelet aggregation and activation. The mechanisms through which they act include decreasing LDL oxidation (Bhooshan & Ibrahim, 2009; Duthie et al., 2000; Rodriguez-Ramiro et al., 2016), and inflammatory cytokines (IL-6, IL-1, IL-8, TNFα), triglyceride and cholesterol production. Increased HDL levels and vasodilation occur via enhancement of bioavailability and bioactivity of NO. A decrease in endothelin (ET-1) and angiotensin-converting enzyme (ACE) inhibitor levels are also known to take place. Tea polyphenols prevent platelet adhesion and aggregation by inhibiting cyclooxygenase and reducing cyclic adenosine monophosphate as well as the response of prostaglandin I2 (PGI2). The vasodilatory effect of tea has been described by the accumulation effect of NO (Rodriguez-Ramiro et al., 2016).

Other effects of polyphenols in cardiovascular tissue are the increase in NO and eNOS and decrease in iNOS, PDE, and ACE levels (Favari et al., 2013)

Hepatoprotective Effects

Polyphenols reduce in the risk of non-alcoholic fatty liver disease (NAFLD), through the reduction in *de novo* lipogenesis, through the protein SREBP-1c, by increasing the β-oxidation of fatty acids, and by increasing antioxidant defense via the nuclear factor erythroid-2 (NF-E2) (Nie et al., 2015).

Nie et al. (2015) studied the hepatoprotective effect of apple peel in rats with acute hepatic toxicity with carbon tetrachloride (CCl_4). The mechanism through which the CCl_4 damages the liver is through the generation of free radicals that react with oxygen (O_2) forming trichloromethyl peroxyl, a compound capable of destroying fatty acids from the cell membrane (lipid peroxidation) (Rahman, 2007). The apple peel in a dose of 250 and 500 mg/kg of body mass showed the ability to exert hepatoprotective effects in *in vivo* models, due to the high amount of polyphenols (Dumont &

Beal, 2011). Similarly, Favari et al. (2013) tested the possible hepatoprotective effect before CCI_4 of the aqueous extract of dandelion *(Taraxacum officinale)*, which reduced the enzymes alanine aminotransferase, alkaline phosphatase, as well as serum bilirubin, lipid peroxidation. In addition to exhibiting an antioxidant effect by favoring expression of the antioxidant enzyme catalase and glutathione peroxidase. Enzyme expression occurs as a result of a high concentration of polyphenols (Dumont & Beal, 2011; Favari et al., 2013; Rahman, 2007).

Effects on the Brain

ROS are involved in the cellular lesions observed in neurodegenerative diseases such as Alzheimer's disease, in which oxidative damage can affect the deposition of amyloid plaque, as well as generate protein cross-linking and the aggregation of the β-amyloid protein and also a decrease expression of superoxide dismutase (MnSOD). In Parkinson's disease, it has been reported that the oxidation of dopamine produces semiquinone and that the metabolic acceleration of dopamine caused by monoamine oxidase-B can induce the formation of hydrogen peroxide, superoxide, and hydroxyl radicals. In this same disease, it has been seen that oxidative stress is a factor that initiates the loss of dopaminergic neurons (Pham-Huy et al., 2008; Vauzour, 2012; Vauzour, 2017).

Polyphenols can exhibit anti-neuroinflammatory properties by blocking the release of cytokines (IL-1β, TNF-α), and antioxidant properties by inhibiting the production of NO and PGE_2, decreasing the activation of NADPH oxidase, and preventing the formation of reactive oxygen species (ROS) (Schaffer & Halliwell, 2012). It has been described that polyphenols are present in the brain at low concentrations (1 nmol/g tissue), being enough to affect neuron pathways. They show the ability to cross the blood-brain barrier since the polyphenol interacts with membrane proteins facilitating transport through the lipid bilayer. Polyphenols can interact directly with neurotransmitters in signaling cascades of various kinases such as MAPK, PI_3K, and PKB (Flores et al., 2016).

It has been reported that pre-treatment of mice with polyphenols reduces the negative impact of cardiovascular events and that these compounds can increase blood flow, which can provide the brain with a considerable amount of oxygen and glucose (Bhattacharyya et al., 2014). In cortical neurons, polyphenols activate the Akt pathway which generates the inhibition of proteins involved in cell death (caspases 9, 3 and ASK1) and the hippocampus. Also by modulation of the Akt pathway, polyphenols have been implicated in the expression of proteins associated with the cytoskeleton (Arc/Arg31) (Schaffer & Halliwell, 2012), which leads to morphological changes in dendritic spines density morphology and outgrowth and synaptic conduction, producing a cognitive improvement (Flores et al., 2016). Recent studies show that some polyphenols can delay brain aging in addition to improving memory and preventing cognitive impairment by activating AMPK and NRF_2, which induce the expression of antioxidant enzymes, and also they activate CREB and increase of BDNF in the hippocampus (Vauzour 2012; Flores et al., 2016).

Intestinal Effects

In intestinal diseases such as ulcerative colitis and Crohn's disease, an increase in reactive oxygen species and a decrease in antioxidant levels have been described. This contributes to increasing pathogenic mechanisms, which potentiate immune reactions mediated by inflammatory leukocytes, thereby increasing tissue damage. The superoxide radical and hydrogen peroxide is the main molecules secreted by phagocytes, which accumulate in the site of inflammation causing lipid peroxidation (Kaulmann & Bohn, 2016).

Dryden et al. (2006) reported a decrease in intestinal inflammation after consuming green tea leaves, and found in their analyzes a decrease in tumor necrosis factor alpha (TNF-α), intracellular adhesion molecule-1 (ICAM-1) and inhibits the activation of the nuclear factor kappa B (NF-κB), also generating an increase in the levels of Hemo-oxygenase-1 (HO-1) (Ozdal et al., 2016). Another disease that affects enterocytes is cholera, which generates an intracellular accumulation of cAMP that results in severe diarrhea (Crespy et al., 2002). It has been reported that polyphenols in the enterocyte favor increased production of SOD and GPx, which may constitute a form of cell protection (Ahmed-Nasef et al., 2014). The effect of oral administration of polyphenols from the apple in cases of acute diarrhea during cholera disease has been commented in the literature, showing that it can be used as a therapeutic and precautionary measure, by demonstrating the inhibition of cholera decreases ADP ribosylation and fluid accumulation induced by the toxin (Crespy, 2002).

CONCLUSION

The findings presented on the antioxidant potential of medicinal plants corroborate the presence of compounds with antioxidant activity such as polyphenols (flavonoids, phenols, terpenoids, alkaloids), which present the ability to interact with free radicals, improving the homeostasis between oxidative stress and antioxidant status. The different interactions with gene expression factors, inhibition or activation of receptors to favor homeostasis or the improvement of a cell with critical damage, are properties that reveal the possible applications of these compounds in complementing current treatments or as tools to prevent the appearance of diseases. These aspects open a field of study on medicinal plants to increase knowledge and investigate their use.

ACKNOWLEDGMENT

This study was partially supported by grant CIC-UMSNH

2018 given to Bertha Fenton-Navarro Ph.D. This article corresponds to partial fulfillment for the requirements for the Master´s degree in Health Sciences, UMSNH for Francisco Orozco Montes. The authors have declared no conflict of interest.

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