Send Orders for Reprints to reprints@benthamscience.ae

Current Drug Targets, **2018**, *19*, 97-110

REVIEW ARTICLE

Pharmacology and Toxicology of Polyphenols with Potential As Neurotropic Agents in Non-communicable Diseases

Agustín R. Miranda[1,2], Claudia Albrecht[1,3], Mariela V. Cortez[1] and Elio A. Soria[1,*]

[1]*Instituto de Investigaciones en Ciencias de la Salud, Universidad Nacional de Córdoba, CONICET, FCM (Enrique Barros, Ciudad Universitaria, CP 5014), Córdoba, Argentina;* [2]*Instituto Nacional del Cáncer, Ministerio de Salud de la Nación (Av. Julio A. Roca 781 10°, CABA), Buenos Aires, Argentina;* [3]*Centro de Investigaciones en Nutrición Humana, Escuela de Nutrición, Facultad de Ciencias Médicas, Universidad Nacional de Córdoba (Enrique Barros, Ciudad Universitaria, CP 5014), Córdoba, Argentina*

ARTICLE HISTORY

Received: June 15, 2016
Revised: September 08, 2016
Accepted: December 09, 2016

DOI:
10.2174/1389450117666161220152336

Abstract: ***Background:*** The central nervous system (CNS) is involved in organic integration. Nervous modulation *via* bioactive compounds can modify metabolism in order to prevent systemic non-communicable diseases (NCDs). Concerning this, plant polyphenols are proposed as neurotropic chemopreventive/therapeutic agents, given their redox and regulating properties.

Objective: To review polyphenolic pharmacology and potential neurological impact on NCDs.

Method: First, polyphenolic chemistry was presented, as well as pharmacology, *i.e.* kinetics and dynamics. Toxicology was particularly described. Then, functional relevance of these compounds was reviewed focusing on the metabolic CNS participation to modulate NCDs, with data being finally integrated.

Results: Oxidative stress is a major risk factor for NCDs. Polyphenols regulate the redox biology of different organic systems including the CNS, which participates in metabolic homeostasis. Polyphenolic neurotropism is determined by certain pharmacological characteristics, modifying nervous and systemic physiopathology, acting on several biological targets. Nonetheless, because these phytochemicals can trigger toxic effects, they should not be recommended indiscriminately.

Conclusion: Summing up, the modulating effects of polyphenols allow for the physiological role of CNS on metabolism and organic integration to be utilized in order to prevent NCDs, without losing sight of the risks.

Keywords: Antioxidant, bioavailability, cancer, central nervous system, chemoprevention, flavonoid, functional food, metabolism, oxidative stress, phytochemical, side effect, toxicity.

1. INTRODUCTION

In recent years, interest in investigating the functional properties of food has grown exponentially, especially related to the prevalence reduction of non-communicable diseases (NCDs). Plant derivatives show a protective effect regarding health, attributed to various nutrients and phytochemicals with antioxidant activity. The emphasis on understanding the antioxidant capacity of these compounds is founded on the fact that oxidative stress is a biological process proposed as etiological factor of NCDs [1, 2]. This stress occurs when the rate of formation of free radicals overcomes the activity of protective systems. Under physiological conditions, these aggressors are controlled by the integrated and harmonious action of enzymes generated evolutionarily and can also be modulated by dietary substances such as vitamins, minerals, and phytochemicals agents. Among these, the most important group corresponds to the polyphenols, which act directly and indirectly in different biological systems [3, 4]. Concerning this, these compounds can act on centers of the central nervous system (CNS) involved in systemic regulation of metabolic homeostasis, which in turn modifies the risk of developing NCDs. Nonetheless, exogenous interventions are not free of risks. Thus, polyphenol toxicology should be considered before realizing any health recommendations. In this sense, this work revises pharmacological and toxicological effects of neurotropic polyphenols on NCDs.

2. PHENOLIC COMPOUNDS

There are more polyphenols in the diet than any other antioxidant, with consumption reaching up to 1 g/d [5, 6]. The main sources are fruits and vegetables, significant concentrations are also found in juices, tea, coffee, wine, cereals, and chocolate [7, 8]. This group of compounds has diverse and complex chemical structures and their health effects are determined by the amount consumed and their bioavailability [5].

*Address correspondence to this author at the INICSA, Enrique Barros, Ciudad Universitaria, Córdoba 5014, Argentina; Tel\Fax: +5493514334020; E-mail: easoria@fcm.unc.edu.ar

1389-4501/18 $58.00+.00

These phytochemicals are secondary plant metabolites and are generally involved in defending against ultraviolet radiation or pathogen aggression [8, 9]. They can be classified into different groups based on the number of phenol rings they contain and the structural elements connecting these rings together. These differences define: phenolic acids, flavonoids, stilbenes, and lignans, with the first two groups being the major ones (Fig. **1**). In addition to this diversity, polyphenols can be associated with various carbohydrates and organic acids, or even with other polyphenols [3].

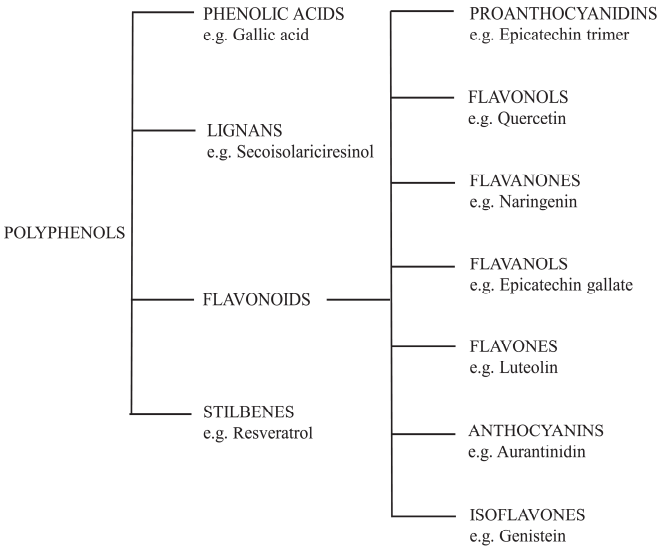


Fig. (1). Classification of polyphenols.

Phenolic acids constitute about a third of dietary phenols, they are found in plants either in free or bonded forms [10, 11]. Structurally they vary due to the differences in the number and positions of hydroxyl groups on the aromatic ring [12]. They are divided into two subgroups: hydroxybenzoic acids and hydroxycinnamic acids [13]. Hydroxybenzoic acids include: gallic, p-hydroxybenzoic, protocatechuic, vanillic and syringic acids. They have the C6-C1 structure in common. On the other hand, hydroxycinnamic acids are aromatic compounds with a C6-C3 structure, including: caffeic, ferulic, sinapic, and p-coumaric acids [13, 14].

This group of phenolic acids presents prominent antioxidant activity, which neutralizes free radicals and other reactive species [15, 16]. Gallic acid (3,4,5-trihydroxybenzoic acid) and its esters are used as antioxidant additives in food and pharmaceutical industries, given that they protect against oxidative damage induced by reactive species and free radicals [17]. Chlorogenic acids are a number of hydroxycinnamic acids (caffeic, ferulic, coumaric, sinapic) esterified with quinic acid [18, 19].

Chlorogenic acids are found in cell walls, esterified to polysaccharides. They are biosynthesized from phenylalanine and tyrosine [20], these acids are precursors of lignin and they affect the texture and plasticity of plants. Chlorogenic acids offer protection against microorganisms, ultraviolet light, herbivore damage and physical damage [21, 22]. Coffee, fruits, herbs, tea and vegetables are the main dietetic sources of chlorogenic acids [23].

Flavonoids are a very large group of polyphenolic compounds distributed in the plant kingdom characterized widely by possessing a benzo-γ-pyran structure [24]. Chemically they share a structure consisting of two aromatic rings (A and B) linked by three carbon atoms forming an oxygen heterocycle (C ring). These can be divided into six sub-classes according to the heterocycle involved: flavonols, flavones, isoflavones, flavanones, anthocyanidins, and flavanols (catechins and proanthocyanidins) [3].

The antioxidant activity of flavonoids emerges from a combination of iron chelating properties and scavenging of reactive oxygen species (ROS), in addition to inhibition of enzymes, such as lipoxygenase, cyclooxygenase, myeloperoxidase and NADPH oxidase; thus preventing ROS formation and organic hydroperoxides [25].

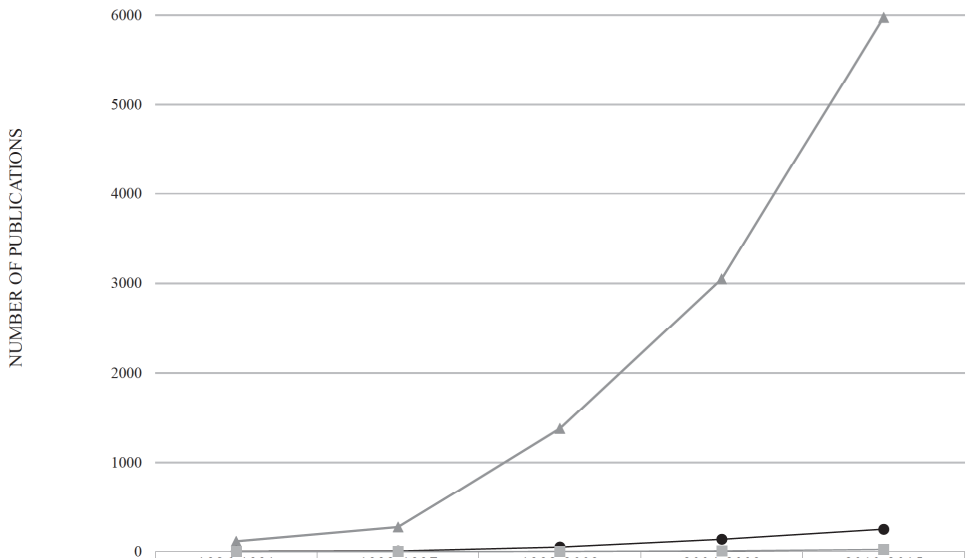
Some flavonoids, such as catechins, epicatechins, and epigallocatechins, reduce the production of free radicals by inhibiting xanthine oxidase (XO), an enzyme that catalyzes the oxidation of hypoxanthine and xanthine to uric acid [26].

3. PHARMACOKINETICS OF PHENOLIC COMPOUNDS

Although scientific publications about polyphenols have grown in the last years, there are fewer works about their bioavailability, mainly in the brain (Fig. **2**). *In vitro*, polyphenols demonstrated potential of playing a useful role in the prevention of chronic diseases [27]. However, adequate amounts must reach the tissues to be effective [28].

Ingested soluble compounds are metabolized in the gastrointestinal tract. Before being absorbed, polyphenols are cleaved into aglycone and glycoside. Glycoside has increased water solubility and is rapidly absorbed, while aglycone can take up to three hours to be absorbed [29]. Free aglycones, such as quercetin, genistein and simple compounds such as ferulic, caffeic, and p-coumaric acids are absorbed through the mucosa of the small intestine and stomach in varied degrees [30, 31]. Enzymatic digestion (small intestine) and bacterial fermentation of carbohydrates (large intestine) could possibly release phenolic compounds bound to fiber. Free aglycone is absorbed in the colon, to be then conjugated with glucuronic acid or sulfate in the liver and excreted *via* urine [31, 32].

Bioavailability varies widely among polyphenols [6, 33]. Depending on the type of polyphenol, total plasma concentration of their metabolites range from 0 to 4 mM after an intake of 50 mg of aglycone equivalent [34]. The polyphenols with the highest absorption rates in humans are isoflavones and gallic acid, followed by catechins, flavanones and quercetin glycosides, with different kinetics. Polyphenols that show less absorption are proanthocyanidins and anthocyanins. Data for other polyphenols is still too limited. The plasma kinetics also differs between polyphenol classes. Peak concentrations are reached between approximately 1 to 5.5 hours depending on the intestinal absorption site [3, 35, 36].



	1986-1991	1992-1997	1998-2003	2004-2009	2010-2015
"Polyphenols"	115	276	1379	3048	5975
"Polyphenols" AND "Bioavailability"	4	6	51	138	250
"Polyphenols" AND "Bioavailability" AND "Brain"	0	0	1	9	24

Fig. (2). Number of publications found for the search terms "Polyphenols", "Polyphenols" AND "Bioavailability" or "Polyphenols" AND "Bioavailability" AND "Brain" in PubMed. The search field tag was limited to "Title/Abstract".

4. PHARMACODYNAMICS OF PHENOLIC COMPOUNDS

Phenolic compounds have several biological targets, such as cellular receptors, membrane constituents, intracellular redox-related pathways, and transcription factors [37] (Table **1**). Phenols can act on these targets as agonists, antagonists, inverse agonists, or partial agonists, determining distinct biological responses [38]. In this sense, they can modulate neuron activity of different centers involved in the regulation of systemic metabolism [39] (Fig. **3**).

Polyphenols may regulate food intake and satiety. There is evidence of their pro-anorectic effects, which involve down-regulation of neuropeptide Y and agouti-related protein, with up-regulation of pro-opiomelanocortin and cocaine/amphetamine-regulated transcript in hypothalamic neurons (arcuate nucleus) [40, 41]. Furthermore, other extrahypothalamic pathways have been described, such as the serotonergic effect that increases serotonin production in the raphe nuclei with the consequent activation of the 5-HT_{2C}R and 5-HT_{1B}R receptors in the hypothalamus [42]. Also, some of the antidepressant effects of polyphenols support this serotonergic activation [43]. Experimental treatment with Ginkgo extracts increased both serotonin reuptake and prefrontal dopaminergic transmission [44, 45]. Acute and chronic exposure to curcumin favors the concentrations of serotonin, norepinephrine and dopamine by inhibiting monoamine oxidase [46].

Dopamine, another relevant neurotransmitter, is a mediator involved in food intake; it is associated with serotonin to determine feeding behavior (duration, frequency and meal size) [47]. Concerning this, polyphenols modulate dopaminergic activity, *e.g.* the protective effect on dopamine-synthesizing neurons of curcumin derivatives [48]. Moreover, it has been found that the flavone oroxylin A inhibits dopamine reuptake, while pycnogenol decreases D_2 receptors leading to higher dopamine levels [49, 50]. Polyphenols have additional effects on other food intake regulators. They promote the activity of tyrosine-tyrosine YY3-36 pancreatic peptide, glucagon-like peptide-1, an insulin-like growth factor-1, whereas ghrelin and leptin levels are decreased [51-58]. As consequences, insulin resistance, glycemia and metabolism-related inflammation are improved by these phytochemicals [59-62]. Overall, polyphenols enhance metabolic homeostasis by targeting multiple sites of action: prefrontal cortex (behavior), hypothalamus, nucleus accumbens, amygdala, brain stem (nucleus of the solitary tract), adipose tissue, pancreas, and gastrointestinal tract, modulating several hormones and neurotransmitters.

5. TOXICOLOGY OF PHENOLIC COMPOUNDS

Most studies of polyphenols have been designed to define their benefits, but the evidence about their toxicity is scarce (Fig. **4**). Concerning this, pharmacological doses of these compounds may have deleterious effects in certain susceptible populations [63].

5.1. Pro-oxidant Activity

Although several studies have promoted dietary polyphenols as antioxidants, there is increasing evidence about pro-oxidative polyphenols [64, 65]. In this regard, tea catechins, including epigallocatechin-3-gallate, are unstable under cell culture conditions, with the consequent generation of hydrogen peroxide, which can induce oxidative stress in cancer cells [66-69]. In a previous study, biological oxidation by polyphenols from American plants, such as *Ilex paraguariensis* A. St.-Hil., *Aspidosperma quebracho-blanco* Schltdl. or *Lantana grisebachii* Stuck., was confirmed in murine spleen of BALB/C females after their oral intake, given that levels of these compounds are highly correlated to levels of lipid peroxides (Spearman's 85% correlation, $p<0.005$) [70].

Table 1. Biological effects of polyphenols.

Antioxidant Effects	*Anti-inflammatory Effects*
Radical scavenging	Increase of IL-12
Inhibition of lipid peroxidation	Inhibition of cyclooxygenase and lipoxygenase
Inducible nitric oxide synthase decrease	Regulation of neutrophil signaling
Decrease of xanthine oxidase	Inhibition of VCAM
Inhibition of cyclooxygenase and lipoxygenase	Increase of CD11b
Increase of the activity of antioxidant enzymes: Catalase, hemeoxygenase-1, glutathione peroxidase and superoxide dismutase	Inhibition of NF-kB activation
Inhibition of NF-kB activation	Inhibition of ERK1/2
Inhibition of transcription factors: Sp1, AP-1, STAT1, STAT3 and FOXO1	Inhibition of p38 protein.
	Inhibition of Phospholipase A2
Anti-proliferative effects	Activation of Peroxisome proliferator activated receptors
Suppression of tissue inhibitors of metalloproteinases-2	Inhibition of TNF-α
Expression of functional p21WAF1	Induce NAG-1 expression
Prevention of Ras/JNK activation	
Negative regulation of NFkB	*Anti-aggregating effects*
Induce NAG-1 expression	Decrease of platelet activation factor
Inhibition of VEGF signaling	Inhibition of related acetyl transferases
Reduced expression of the matrix metalloproteinases	Inhibition of thrombin induced phosphorylation of p38MAPK and ERK1/2
Reduced expressions of CD31	Inhibition of tyrosine phosphorylation of platelet proteins
Inhibition of the activity of DNA methyltransferase	Reduction of intracellular Ca2+ level
Prevention of ERKs, PDK1 and p90RSK activation	Suppression of prostaglandin D2
Stabilization of tumor suppressor protein p53	Suppression of Thromboxane A2
Altered expression of Bcl-2 family members	
Activation of initiator caspases	*Anti-atherosclerotic and anti-angiogenic effects*
Inhibition of Bcl-X_L and Bcl-2	Inhibition of the expression of adhesion molecules: ICAM-1, VCAM-1 and E-Selectin
Inhibition on telomerase	Increase of endothelial nitric oxide synthase
Inhibition FAS receptor	Inhibition of phosphodiesterases in smooth muscle
	Inhibition of the fibroblast growth factors
	Inhibition of the vascular endothelial growth factor

AP-1: Activator protein 1; Bcl-2: Apoptosis regulator Bcl-2; Bcl-XL: B-cell lymphoma-extra-large; CD-31,11b: cluster of differentiation 31 and 11b; ERK: extracellular signal–regulated kinases;; FOXO1: Forkhead box protein O1; ICAM: Intercellular Adhesion Molecule 1; IL-12: Interleukin 12; JNK: c-Jun NH2-terminal kinase; NAG-1: nonsteroidal anti-inflammatory drug-activated gene 1; NF-kB: Nuclear factor kappa-light-chain-enhancer of activated B cells; p21WAF1: cyclin-dependent kinase inhibitor p21; p38MAPK: P38 mitogen-activated protein kinases; p90RSK: p90 kDa ribosomal S6 kinases; PDK1: phosphoinositide-dependent kinase 1; STAT1-3: Signal transducer and activator of transcription 1 and 3; TNF-α: tumor necrosis factor α ; VCAM: vascular adhesion molecule; VEGF: Vascular endothelial growth factor.

5.2. Hepatotoxicity and Nephrotoxicity

There is evidence about the hepatotoxic potential of certain polyphenols. Treatment with epigallocatechin-3-gallate in rats reduces hepatocyte viability. Cell death is associated with increased production of reactive oxygen species and reduced glutathione depletion [71]. Laboratory studies in rodents and dogs have supported the toxic effects of high doses of preparations derived from green tea [72]. High doses of polyphenols can induce hepatotoxicity and nephrotoxicity [73, 74]. Particularly, hepatic and renal toxicity appear to be correlated with the bioavailability of epigallocatechin-3-gallate [75]. Recent studies in humans have also shown that fasting increases its bioavailability [6, 76].

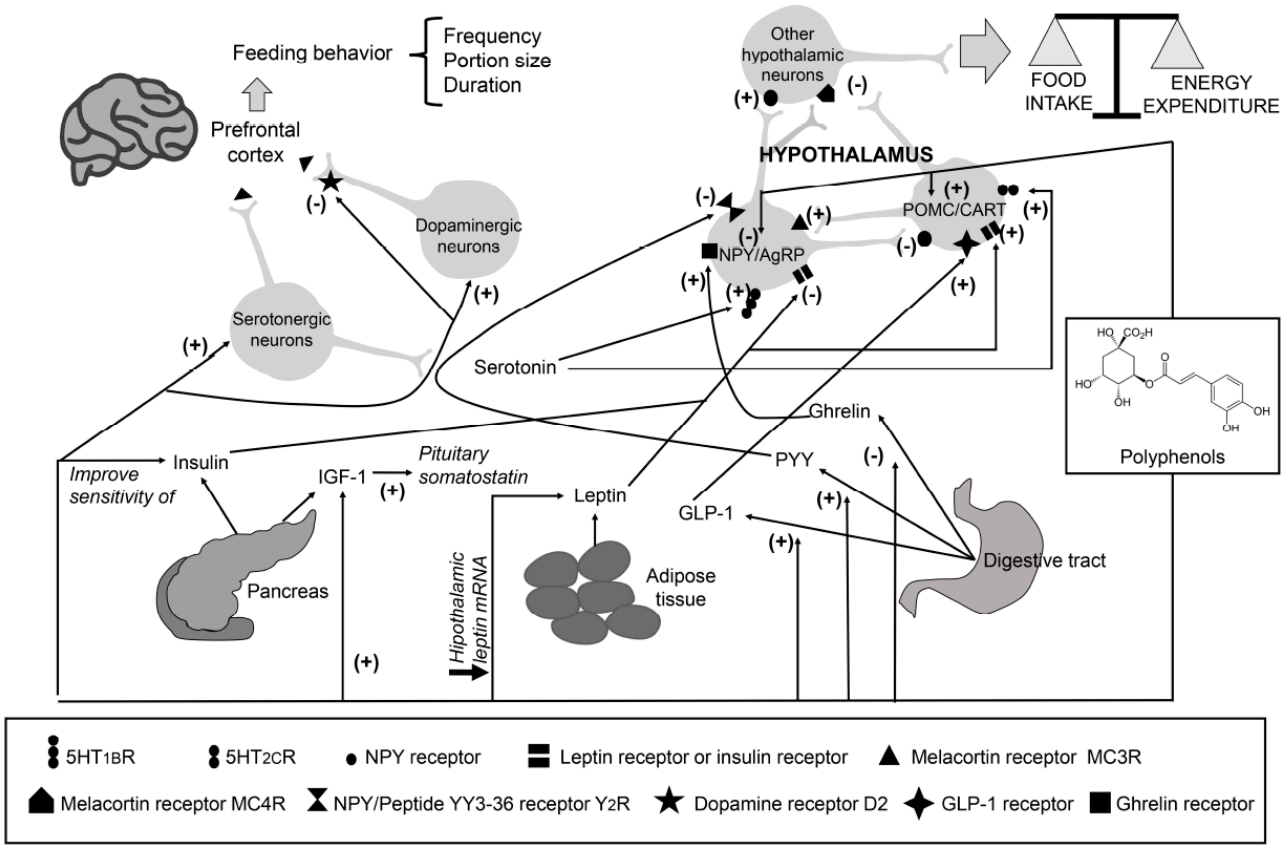


Fig. (3). Metabolic regulation by neurotropic polyphenols (AgRP: agouti-related protein. NPY: Neuropeptide Y. POMC: pro-opiomelanocortin. CART: cocaine- and amphetamine-regulated transcript. PYY: peptide YY3-36. GLP-1: glucagon-like peptide-1. IGF-1: insulin-like growth factor-1).

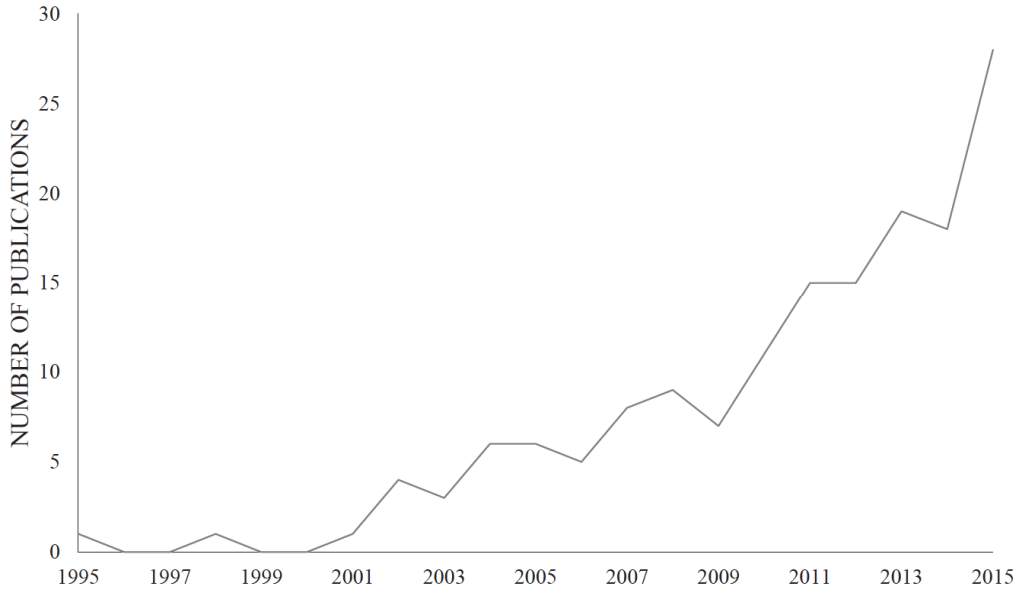


Fig. (4). Number of publications found for the search terms “Polyphenols” AND “Side effect” in PubMed. The search field tag was limited to “Title/Abstract”.

5.3. Carcinogenicity

Some polyphenols may have genotoxic, carcinogenic effects at high doses [77, 78]. Caffeic acid, for example, induces the development of tumors in the stomach and kidneys of rats and mice [79]. In addition, catechols are postulated to mediate the induction of renal tumors by estradiol. Quercetin inhibits methylation of catecholestrogen and increases renal levels of 2- and 4-hydroxyestradiol by 60-80%. This can

result in a higher imbalance in catecholestrogen redox homeostasis and estradiol-induced carcinogenesis [80, 81].

Finally, it has been reported that catechins promote tumor development in the colon of male rats and although quercetin can reduce the proliferation of cancer cells at high doses, some studies have found that it stimulates cell proliferation at low doses [82, 83].

5.4. Other Side Effects

Several flavonoids can inhibit thyroid peroxidase and interfere with the biosynthesis of the thyroid hormone (free radical iodination) [84-86]. This is thought to be one of the causes of endemic goiter in West Africa, where millet is a staple [86, 87].

Isoflavones have estrogen-like activity [88, 89]. Due to this activity, polyphenols may present both beneficial and adverse effects [89-91]. Exaggerated consumption has been associated with reduced fertility in animals and anti-luteinizing effects in premenopausal women [92-94], although anti-tumor effects are still seen [95-97]. Also, isoflavones can produce anti-androgenic effects, impairing sexual development, as well as causing male and female infertility [98, 99].

The consumption of polyphenols can also have anti-nutritional effects [100]. Excessive consumption of polyphenols can increase the risk of iron depletion with a negative impact on iron absorption [100-102]. In addition, proanthocyanidins and ellagitannins have been considered anti-nutritional compounds, particularly in animal nutrition, as these are able to interact with certain proteins and inhibit various enzymes, *e.g.* α-glucosidase and α-amylase [103, 104].

Studies in cell lines with purified flavonoids (including quercetin, luteolin, and kaempferol) have suggested that maternal consumption of flavonoids produces inhibition of topoisomerase II in the fetus, which could increase the risk of leukemia in newborns [105, 106]. The most potent inhibitors were quercetin and fisetin.

6. NON-COMMUNICABLE DISEASES

The World Health Organization (WHO) defines NCDs as pathologies of chronic evolution, representing an epidemic whose increase is due to an aging population and modern lifestyles characterized by physical inactivity and malnutrition. The main NCDs are: diabetes, cardiovascular diseases, cancer, chronic respiratory disease and kidney disease. They are characterized by sharing the same risk factors: tobacco consumption, malnutrition, sedentary lifestyle, and excessive alcohol consumption [107].

These risk factors trigger four metabolic/physiological changes that increase the risk of NCDs: high blood pressure, obesity, hyperglycemia and hyperlipidemia [107]. WHO studies indicate that by the year 2020, 75% of deaths worldwide will be attributable to such diseases [107, 108]. NCDs are preventable, thus public policy actions involving intervention, promotion, prevention, and treatment are effective [109].

Given that obesity is a risk factor for NCDs, it is pertinent to promote the incorporation of dietary compounds that modulate weight gain [110]. Current nutrition is oriented towards promoting the consumption of biologically active compounds that provide additional benefits. Based on this premise, the concept of Functional Foods arises: foods that naturally possess or have added bioactive components such as carotenoids, lipids, and polyphenols. In this sense, their regular consumption has a positive association with decreased risk for NCDs [111].

7. OXIDATIVE STRESS

The human body maintains a constant redox balance, preserving the homeostasis between the production of pro-oxidant factors of cellular metabolism and antioxidant defense systems [112, 113]. Oxidative stress refers to a situation of serious imbalance between the production of reactive species and antioxidant defense [114, 115]. Sies in 1991 defined it as "an alteration in the pro-oxidant/antioxidant balance in favor of the former, leading to potential harm" [116]. Oxidative stress can result from:

- A decrease in antioxidants. For example: mutations affecting antioxidant defense enzymes, toxic agents depleting these defenses, or the lack of dietary antioxidants.
- Increased production of reactive species, especially reactive oxygen species (ROS) and reactive nitrogen species (RNS). This happens in exposure to high levels of reactive toxins, or substances that are metabolized to generate ROS, as well as by excessive activation of natural systems, such as the inappropriate activation of phagocytes in chronic inflammatory diseases [117].

When levels of free radicals and reactive species cannot be offset by antioxidant defense systems, cell damage and death occur [118]. This is the physiopathological mechanism of many diseases, such as NCDs [119]. Free radicals are atoms or molecules containing one or more unpaired electrons. This characteristic makes them highly reactive and able to damage other molecules, which become reactive leading to an oxidative cascade in cells and tissues [113, 120].

Oxidative stress, in its most severe form, causes serious disturbances in cell metabolism such as: DNA rupture, increased concentration of intracellular calcium, changes in membrane transport of ions and specific proteins, and lipid peroxidation [113]. The reversibility or lack thereof, of the damage depends on factors like the duration of the stress, the effectiveness of antioxidant defenses of the organism, age, nutritional status, and genetic factors involved in encoding antioxidant systems [115].

ROS are the final products of oxygen used by the cells. They are responsible for the detrimental oxidative stress causes in biological systems [121]. ROS are formed during aerobic mitochondrial respiration in which oxygen undergoes an incomplete, one-electron reduction generating reactive and unstable molecules such as superoxide anion, hydrogen peroxide, and hydroxyl radical [122]. It is currently known that other reactive species besides ROS exist, including: reactive iron species, reactive copper species, and RNS [113].

Ninety percent of intracellular ROS are of mitochondrial origin [123]. Other endogenous sources include the peroxisomal β-oxidation of fatty acids, the activation of phagocytes, and the action of certain enzyme systems such as cytochrome P450. Certain external stimuli generate ROS, such as pro-inflammatory factors, environmental toxins, UV light, ionizing radiation, *etc* [124].

Although the deteriorating effects of excessive ROS production are well known, low concentrations are essential to ensure proper functioning of intracellular processes and signaling mechanisms. In this sense, they modulate migration, proliferation, survival, and apoptosis [122].

8. ANTIOXIDANT DEFENSE

The body has antioxidant defense systems responsible for minimizing the formation of ROS as well as eliminating them; however, they are not completely effective [115]. This antioxidant protection system is composed of enzymes and low molecular weight compounds. A biological antioxidant is defined as a substance, present at low concentrations compared to an oxidizable substrate, which inhibits or retards the oxidation of said substrate [125]. Antioxidants prevent other molecules from binding to oxygen by interacting faster with free radicals and ROS [126].

There are different ways of classifying antioxidants:

I. By position [127]:

- Membrane antioxidants (α-tocopherol)
- Intracellular antioxidants (superoxide dismutase, catalase, glutathione peroxidase).
- Plasma antioxidants (β-carotene, ascorbic acid, ceruloplasmin, transferrin).

II. By nature [128]:

- Enzymatic antioxidants (superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase).
- Non-enzymatic antioxidants: subdivided into nutrients (Carotenoids, polyphenols, ascorbic acid) or metabolites (glutathione, albumin, bilirubin).

III. By their effect on lipid peroxidation:

- Preventive: those that block the initial production of free radicals (catalase, glutathione peroxidase).
- Disruptors: those involved in the propagation of lipid peroxidation (superoxide dismutase, vitamin E, uric acid).

8.1. Endogenous Enzymatic System

Catalase is the predominant component of the antioxidant system [129]; it is responsible for catalyzing the decomposition of hydrogen peroxide generated by cellular metabolism into water [130]. It also has peroxidative activity [131]. Catalase is present predominantly in the peroxisomes and mitochondria. The levels of catalase are high in liver and kidneys, lower in epithelial and connective tissue, and practically null in nervous tissue [132]. For the catalytic reaction, the donor is another hydrogen peroxide molecule. To accomplish this function, the enzyme must present its tetrameric form [133]. In peroxidative reactions, the enzyme can use methanol, ethanol, formic acid, phenol, or formaldehyde as hydrogen donors. This function can be performed by monomers, dimers and tetramers [133].

Glutathione peroxidase is a selenium-dependent enzyme that uses reduced glutathione and reduces peroxides in cytosol (erythrocytes) and lysosomes (neutrophils, macrophages and other cells of the immune system) [134]. Three forms of glutathione peroxidase have been categorized: the cellular form, which has more affinity for hydrogen peroxide than the lipoperoxide; the extracellular form, it has similar affinity for both substrates; and the PH form which has specific affinity for lipid peroxides [126].

Superoxide dismutase is group of metalloenzymes distributed widely throughout in the body. They utilize different metals as cofactors: copper, zinc, magnesium, and iron [126]. These enzymes catalyze the conversion of superoxide into hydrogen peroxide and molecular oxygen [135].

8.2. Exogenous Antioxidants

In recent years, interest in researching plant-derived compounds with antioxidant capacity and their implications in human health has been growing constantly. Bioactive compounds in fruits and vegetables are able to interact with other compounds in redox reactions. Dietary antioxidants are defined as substances in foods that significantly decrease the adverse effects of reactive species generated in normal physiological processes [136]. Dietary antioxidants are biocompounds that cannot be synthesized by animals, and therefore must be acquired in the diet [137]. Of these substances, the following stand out:

- Tocopherols (Vitamin E): lipophilic antioxidant that neutralizes reactive species and protects lipids from peroxidation to protect cell membranes [138].
- Ascorbic acid (Vitamin C): Vitamin involved in multiple metabolic reactions. It is a water-soluble antioxidant that neutralizes free radicals and inhibits lipid peroxidation. It also promotes regeneration of α-tocopherol [139].
- Carotenoids: Natural compounds with lipophilic properties. There are about 500 identified types of carotenoids, β-carotene being the most important. They possess antioxidant properties [140].
- Selenium: Transient essential element with important antioxidant power. It reacts along with vitamin E in the process of neutralizing free radicals. It is also essential to the functioning of the glutathione peroxidase enzyme [141].

Also, other antioxidants are found in different plant species, denominated phenolic compounds, for example: isoflavones, flavonoids, quercetin, and other polyphenols [142].

9. NCD MODULATION BY PHENOLIC COMPOUNDS

Phenolic phytochemicals include a large group of compounds that have been extensively studied as preventive agents for chronic diseases such as cancer, arteriosclerosis, and neurological disorders [143, 144].

Oxidative stress is a major contributing factor in cardiovascular disease. Clinical studies have shown significant positive associations between oxidative stress and inflammation, as well as indicators of vascular damage such as impaired endothelial function [145, 146].

Dietary polyphenols seem to be effective in cardioprotection [147], in this context, they reduce the size of atherosclerotic lesions and increase serum paraoxonase activity (antioxidant enzyme associated with HDL) [148-150].

Induction of protective factors, such as nitric oxide and the endothelium-derived factor, has been proposed as the mechanism of action. This promotes vasodilatation and prevents platelet activation [151]. Also, phenolic compounds can improve the function of vascular smooth muscle and tend to maintain the redox balance [152, 153]. Polyphenol treatments are associated with reduced expression of NADPH oxidase, a vascular source of superoxide anions, as well as reduced action of the angiotensin system [154, 155]. Decreased oxidative stress prevents degradation of nitric oxide by superoxide anion, along with vasoconstrictive and pro-inflammatory responses. Therefore, the actions of polyphenols on endothelial and smooth muscle cells can promote vascular health [156].

Polyphenols are potentially neuroprotective through their ability to inhibit and modulate several neurodegenerative processes [157]. The proposed mechanisms of action inhibit inflammation, lipid peroxidation, endothelial activation, and modulate nitric oxide activity [157, 158].

Among them, catechins suppress neuroinflammation and inhibit activation of microglia and astrocytes associated with the production of mediators related to neuronal apoptosis [159]. Catechins also have a protective effect against neurotoxins involved in the development of Parkinson's disease [160]. Furthermore, catechin derivatives can delay the occurrence of neurodegenerative disorders such as Alzheimer's disease [161, 162]. Quercetin exerts significant protection against ischemic injury [163, 164]. Anthocyanins reduce oxidative stress associated with age and improve cognitive function [165, 166].

Furthermore, polyphenols have shown potential of possessing chemopreventive activity. Chemoprevention is defined as pharmacological intervention used to stop or reverse the process of cancer development before invasion and metastasis occur [167]. Although the health benefits of polyphenols come from their antioxidant effects, this cannot explain all ones, such as specific inhibition of signal transduction [168].

Dietary polyphenols can interfere with the initiation, development, and progression of cancer through modulation of various cellular processes, such as: cell cycle arrest by inhibiting cyclins, induction of apoptosis through the liberation of cytochrome C, caspase activation and up or down regulation of members of the family of anti-apoptotic proteins, inhibition of proliferation and survival signaling, modulation of inflammation (cyclooxygenase-2, tumor necrosis factor, *etc.*), and deletion of key proteins involved in angiogenesis and metastasis [169].

Diets rich in polyphenols are epidemiologically associated with a lower risk of developing cancer [170-172]. Fruit consumption is linked to a lower risk of cancers of the digestive and urinary tracts [173-175]. Intake of whole grain foods is also associated with a reduced risk of developing colorectal cancer [176].

Numerous studies in cell cultures and animal models have been performed to assess the ability of specific edible plants to prevent cancer [177, 178]. This chemopreventive activity has been demonstrated for green tea, black tea, and their constituents in different tissues of animal models: skin, lung, oral cavity, esophagus, stomach, liver, pancreas, bladder, small intestine, colon, mammary and prostate gland tumors [179-181].

In light of the high levels of polyphenols in the diet, the biological activity of these compounds is an important topic for scientific research. The chemopreventive potential of these compounds compels the design of future studies based on discovering the mechanism. This could facilitate a better understanding of the potential beneficial dietary polyphenols [182].

There is increasing evidence to suggest that plant polyphenols may help combat the risk factors linked to the development of metabolic syndrome [183]. Among the polyphenols associated with prevention of metabolic syndrome, epigallocatechin-3-gallate has shown benefits because it inhibits the nuclear factor kappa-light-chain-enhancer of activated B cells, increases the production of nitric oxide, vasodilatation, and induces apoptosis of adipocytes [184, 185]. It also interferes with the regulation of insulin secretion and blood pressure [186-188].

Finally, polyphenols may have implications for the treatment of chronic respiratory diseases [189]. It is known that oxidative stress is involved in the pathogenesis of asthma and chronic obstructive pulmonary disease. It can also be associated with resistance to therapy in some clinical forms of exacerbations and remodeling of the airways [190]. Resveratrol present in red wine, has antioxidant and anti-inflammatory properties that inhibit inflammatory cytokine release from alveolar macrophages [191, 192].

10. METABOLIC INVOLVEMENT OF THE NERVOUS SYSTEM

Energy metabolism is defined as the set of processes and physicochemical reactions involved in attaining and transforming energy from food intake to maintain vital cell functions [193]. The mechanisms involved in maintaining weight stability and body composition are very complex. They respond to central control, represented by the different brain regions (cerebral cortex, hypothalamus and brainstem) and peripheral control from the digestive organs and endocrine system [194, 195].

Brain regions are interconnected through a network of neural circuits communicating the satiety and appetite centers, emitting both afferent and efferent signals that determine intake regulation. Among these centers are hypothalamic regions such as the arcuate nucleus, paraventricular nucleus, the ventromedial and lateral hypothalamic areas, and extra hypothalamic regions such as the nucleus of the solitary tract, which belongs to the brainstem [196]. Also, various peripheral modulators are involved in controlling

intake, especially the digestive tract, liver, and adipose tissue [197]. Food consumption is influenced by social, psychological, and environmental factors [198].

The relationship between the various regulatory components of energy homeostasis and intake is mediated *via* nerve signals, hormones, neuropeptides, nutrients, and metabolites [199]. Meanwhile, stomach distension and contractions produce gastric satiety signals and decreased appetite, in addition to specific neuroendocrine and metabolic signals [200]. In this regard, certain orexigenic and anorexigenic factors, such as ghrelin, insulin, leptin, *etc*., are generated in the gastrointestinal tract in function of nutritional status [201]. These signals interact with central neuropeptides involved in the regulation of appetite and energy expenditure such as: neuropeptide Y, agouti-related protein, orexin, melanin-concentrating hormone, proopiomelanocortin, and transcribers related to cocaine and amphetamines, corticotrophin-releasing hormone, among others [193].

Therefore, nutritional, nervous, endocrine, and metabolic signals produced by different organs and systems regulating energy homeostasis are released in response to the nutritional and metabolic state of the body. The integration of this conglomerate stimuli influences weight stability and body composition through regulation of the energetic balance, with the gastrointestinal tract and the central nervous system interacting through specific nerve signals [193, 202].

11. NEUROTROPIC PHENOLIC COMPOUNDS

Phenolic bioavailability in the central nervous system depends on the ability of these compounds to cross the blood-brain barrier [203]. With studies confirming this ability, polyphenols with higher lipophilicity as well as those of small molecular weight and size, polar polyphenols and their metabolites, achieve higher concentrations in encephalic tissue. They include anthocyanins, cyanidin glycosides, penidins, and cyanidin [204].

Also, permeability of certain polyphenols (*e.g.* flavonoids) is influenced by efflux transporters, such as P- glycoprotein and their stereochemistry [205]. A non-region-specific accumulation below 1 nmol per tissue gram has been proposed [204, 206], including quercetin, epigallocatechin-3-gallate and catechin [207-209].

Then, these phytochemicals exert the redox bioactivities previously described. In this regard, anthocyanins and flavonoids are neuroprotective antioxidants [210, 211]. Furthermore, they can modulate physiology of neurons and glial cells, thus modifying neurotransmission and neuroimmune response [210-213]. In consequence, phenolics might affect the metabolic involvement of the nervous system. Concerning this, resveratrol and curcumin are ligands of cannabinoid receptors by acting as antagonists/inverse agonists, which give them the capacity to reduce body weight and adjust energetic metabolism [214]. Additionally, resveratrol, a neurotrophic agent, affects behavior and improves of neuroendocrine recovery [215]. Meanwhile, a tetrahydroxystilbene glycoside regulates different molecular pathways in hippocampus, which are relevant for nervous functions [216]. Another interesting target of polyphenols is the brain derived neurotrophic factor, given its participation structural and functional characteristics of the central nervous system [217].

Despite their numerous health benefits, these biomolecules are also risky. In fact, both low and excessive levels of polyphenols in different areas of the encephalon can break redox homeostasis leading to tissue damage [218]. Moreover, preliminary data suggest that an elevated dose of chlorogenic acid triggers neurotoxicity [219]. Thus, equilibrium is a major concern to obtain positive effects.

CONCLUSION

Phenolic compounds modulate redox state of nervous cells and their tissue environment, which can functionally modify neurotransmission. If it happens in nervous centers involved in metabolic regulation, several systemic effects can be triggered in order to restore homeostasis and prevent NCDs. Thus, psychoneuroimmunoendocrine modulation by polyphenols might be an integrative approach to combat these pathologies, which requires further assessment.

Nonetheless, researchers and physicians should be objective and careful in order to avoid overdose and side effects. Furthermore, scientific literature is mainly focused on beneficial effects, but pharmacokinetic and toxicological studies are scarce with neurotoxicological potential of polyphenols possibly being underestimated.

Further studies are encouraged to confirm therapeutic potential of neurotropic polyphenols, in order to identify their plant sources, bioactivity and biological risks after use.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors acknowledge the support of CONICET and SECYT (UNC), Argentina.

REFERENCES

[1] Halliwell B. Reactive oxygen species in living systems: source, biochemistry, and role in human disease. Am J Med 1991; 91: 14-22.

[2] Halliwell B. Oxidation of low-density lipoproteins: questions of initiation, propagation, and the effect of antioxidants. Am J Clin Nutr 1995; 61: 670-77.

[3] Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. Am J Clin Nutr 2004; 79: 727-47.

[4] Diplock AT. Antioxidant nutrients and disease prevention: an overview. Am J Clin Nutr 1991; 53: 189-93.

[5] Scalbert A, Johnson IT, Saltmarsh M. Polyphenols: antioxidants and beyond. Am J Clin Nutr 2005; 81: 215-17.

[6] Bohn T. Dietary factors affecting polyphenol bioavailability. Nutr Rev 2014; 72: 429-52.

[7] Ismail T, Calcabrini C, Diaz A, *et al.* Ellagitannins in Cancer Chemoprevention and Therapy. Toxins 2016; 8: 151.

[8] Zamora-Ros R, Knaze V, Rothwell J, *et al.* Dietary polyphenol intake in Europe: the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Eur J Nut 2015; 55: 1359-75.

[9] Orlikova B, Legrand N, Panning J, Dicato M, Diederich M. Anti-inflammatory and anticancer drugs from nature. Cancer Treat Res 2014; 159: 123-43.
[10] Acosta-Estrada B, Gutiérrez-Uribe J, Serna-Saldívar S. Bound phenolics in foods, a review. Food Chem 2014; 152: 46-55.
[11] Robbins RJ. Phenolic acids in foods: an overview of analytical methodology. J Agric Food Chem 2003; 51: 2866-87.
[12] Gross GG. In: secondary plant products: A comprehensive treatise; E E Conn, Ed. Londres: Academic press, INC 2016; Vol. 7: pp 301-16.
[13] Ignat I, Volf I, Popa VI. A critical review of methods for characterization of polyphenolic compounds in fruits and vegetables. Food Chem 2011; 126: 1821-35.
[14] Gonçalves J, Silva C, Castilho P, Câmara J. An attractive, sensitive and high-throughput strategy based on microextraction by packed sorbent followed by UHPLC-PDA analysis for quantification of hydroxybenzoic and hydroxycinnamic acids in wines. Microchem J 2013; 106: 129-38.
[15] Pająk P, Socha R, Gałkowska D, Rożnowski J, Fortuna T. Phenolic profile and antioxidant activity in selected seeds and sprouts. Food Chem 2014; 143: 300-6.
[16] Gülçin I. Antioxidant activity of food constituents: an overview. Arch Toxicol 2012; 86: 345-91.
[17] Badhani B, Sharma N, Kakkar R. Gallic acid: a versatile antioxidant with promising therapeutic and industrial applications. RSC Advances 2015; 5: 27540-557.
[18] Oboh G, Agunloye O, Adefegha S, Akinyemi A, Ademiluyi A. Caffeic and chlorogenic acids inhibit key enzymes linked to type 2 diabetes (*in vitro*): a comparative study. J Basic Clin Physiol Pharmacol 2015; 26: 165-70.
[19] Tekale S, Jaiwal B, Padul M. Identification of metabolites from an active fraction of Cajanus cajan seeds by high resolution mass spectrometry. Food Chem 2016; 211: 763-9.
[20] Cha M, Kim H, Kim B, Ahn J. Synthesis of Chlorogenic Acid and p-Coumaroyl Shikimates from Glucose Using Engineered Escherichia coli. J Microbiol Biotechnol 2014; 24: 1109-17.
[21] Cheynier V, Comte G, Davies K, Lattanzio V, Martens S. Plant phenolics: recent advances on their biosynthesis, genetics, and ecophysiology. Plant Physiol Biochem 2013; 72: 1-20.
[22] Dixon RA, Paiva NL. Stress-induced phenylpropanoid metabolism. Plant Cell 1995; 7: 1085.
[23] Marin C, Puerta G. Contenido de ácidos clorogénicos en granos de Coffea arabica L y C canephora según el desarrollo del fruto. Cenicafé 2008; 59: 7-28.
[24] Cartaya O. Influencia de diferentes variables experimentales en la composición del complejo de bioflavonoides del limón (CBL). Cultivos Tropicales 2013; 23: 97-100.
[25] Garrido G, Ortiz M, Pozo P. Fenoles y flavonoides totales y actividad antioxidante de extractos de hojas de Lampaya medicinalis F. Phil. J Pharm Pharmacogn Res 2013; 1: 30-8.
[26] Adarmes Ahumada HH, Dörner C, Galleguillos M. ¿Qué son los flavonoides ya qué se debe su efecto protector? TecnoVet 2006; 12: 14-8.
[27] Alvarez-Suarez JM, Giampieri F, Battino M. Honey as a source of dietary antioxidants: structures, bioavailability and evidence of protective effects against human chronic diseases. Curr Med Chem 2013; 20(5): 621-38.
[28] Tomás Barberán FA. Los polifenoles de los alimentos y la salud. Alim Nutr Salud 2003; 10(2): 41-53.
[29] Chávez Mendoza A. Efectos del tratamiento periodontal coadyuvado con polifenoles en las condiciones clínicas de pacientes obesos con periodontitis crónica. PhD Thesis. Mexico City Instituto Politecnico Nacional 2012.
[30] Liu, JY, Lee KF, Sze CW, *et al.* Intestinal absorption and bioavailability of traditional Chinese medicines: a review of recent experimental progress and implication for quality control. J Pharm Pharmacol 2013; 65(5): 621-33.
[31] Palafox-Carlos H, Ayala-Zavala JF, González-Aguilar GA. The role of dietary fiber in the bioaccessibility and bioavailability of fruit and vegetable antioxidants. J Food Sci 2011; 76(1): 6-15.
[32] María MJA, Fernando RE. Componentes fenólicos de la dieta y sus propiedades biomedicinales. Rev Hor Med 2007; 7(1): 23-31.
[33] D'Archivio M, Filesi C, Varì R., Scazzocchio B, Masella R. Bioavailability of the polyphenols: status and controversies. Inter J Mol Sci 2010; 11(4): 1321-42.
[34] Pimpao RC, Ventura MR, Ferreira R B, Williamson G, Santos C N. Phenolic sulfates as new and highly abundant metabolites in human plasma after ingestion of a mixed berry fruit purée. Br J Nutr 2015; 113(03): 454-63.
[35] Qiao J, Kong X, Kong A, Han M. Pharmacokinetics and biotransformation of tea polyphenols. Curr Drug Metab 2014; 15(1): 30-6.
[36] Clifford MN, van der Hooft JJ, Crozier A. Human studies on the absorption, distribution, metabolism, and excretion of tea polyphenols. Am J Clin Nutr 2013; 98(6): 1619-30.
[37] Defagó MD, Soria EA. Onconutrition: Redox chemoprevention by functional biomolecules and biomarker assessment. En: Rahman A, Zaman K (Eds.). Topics in Anti-Cancer Research (vol. 2). Sharjah, Emiratos Árabes Unidos: Bentham Science Publishers, 2013, pp. 522-552.
[38] Velázquez BL, Lorenzo P, Moreno A, Lizasoain I, Leza JC, Moro MA, Portolés A. Farmacología Básica y Clínica, 18th ed., Médica Panamericana, Madrid 2008.
[39] Lin LC, Wang MN, Tseng TY, Sung JS, Tsai TH. Pharmacokinetics of (-)-epigallocatechin-3-gallate in conscious and freely moving rats and its brain regional distribution. J Agric Food Chem 2007; 55(4): 1517-24.
[40] Kim SJ, Lee YH, Han MD, *et al.* Resveratrol, purified from the stem of Vitis coignetiae Pulliat, inhibits food intake in C57BL/6J Mice. Arch Pharm Res 2010; 33: 775-80.
[41] Myoung HJ, Kim G, Nam KW. Apigenin isolated from the seeds ofPerilla frutescens britton var crispa (Benth.) inhibits food intake in C57BL/6J mice. Arch Pharm Res 2010; 33: 1741-6.
[42] Lam DD, Garfield AS, Marston OJ, Shaw J, Heisler LK. Brain serotonin system in the coordination of food intake and body weight. Pharmacol Biochem Behav 2010; 97(1): 84-91.
[43] Xu Y, Wang Z, You W, *et al.* Antidepressant-like effect of trans-resveratrol: involvement of serotonin and noradrenaline system. Eur Neuropsychopharmacol 2010; 20: 405-13.
[44] Yoshitake T, Yoshitake S, Kehr J. The Ginkgo biloba extract EGb 761® and its main constituent flavonoids and ginkgolides increase extracellular dopamine levels in the rat prefrontal cortex. Br J Pharmacol 2010; 159(3): 659-68.
[45] Ramassamy C, Christen Y, Clostre F, Costentin J. The Ginkgo biloba extract, EGb761, increases synaptosomal uptake of 5-hydroxytryptamine: in-vitro and ex-vivo studies. J Pharm Pharmacol 1992; 44(11): 943-45.
[46] Sanmukhani J, Anovadiya A, Tripathi CB. Evaluation of antidepressant like activity of curcumin and its combination with fluoxetine and imipramine: an acute and chronic study. Acta Pol Pharm 2011; 68(5): 769-75.
[47] Meguid MM, Fetissov SO, Varma M, *et al.* Hypothalamic dopamine and serotonin in the regulation of food intake. Nutr 2000; 16(10): 843-57.
[48] Harish G, Venkateshappa C, Mythri RB, *et al.* Bioconjugates of curcumin display improved protection against glutathione depletion mediated oxidative stress in a dopaminergic neuronal cell line: implications for Parkinson's disease. Bioorg Med Chem 2010; 18(7): 2631-8.
[49] Yoon SY, de la Peña I, Kim SM, *et al.* Oroxylin A improves attention deficit hyperactivity disorder-like behaviors in the spontaneously hypertensive rat and inhibits reuptake of dopamine *in vitro*. Arch Pharm Res 2013; 36(1): 134-40.
[50] Khan MM, Hoda MN, Ishrat T, *et al.* Amelioration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced behavioural dysfunction and oxidative stress by Pycnogenol in mouse model of Parkinson's disease. Behav Pharmacol 2010; 21(5-6): 563-71.
[51] Panickar KS. Effects of dietary polyphenols on neuroregulatory factors and pathways that mediate food intake and energy regulation in obesity. Mol Nutr Food Res 2013; 57(1): 34-47.
[52] Bagul PK, Middela H, Matapally S, *et al.* Attenuation of insulin resistance, metabolic syndrome and hepatic oxidative stress by resveratrol in fructose-fed rats. Pharmacol Res 2012; 66: 260-8.
[53] Zhang J, Chen L, Zheng J, *et al.* The protective effect of resveratrol on islet insulin secretion and morphology in mice on a high-fat diet. Diabetes Res Clin Pract 2012; 97(3): 474-82.
[54] Roussel AM, Hininger I,Benaraba R, *et al.* Antioxidant effects of a cinnamon extract in people with impaired fasting glucose that are overweight or obese. J Am Coll Nutr 2009; 28: 16-21.
[55] Chen S, Li J, Zhang Z, *et al.* Effects of resveratrol on the amelioration of insulin resistance in KKAy mice. Can J Physiol Pharmacol 2012; 90: 237-42.

[56] Hlebowicz J, Hlebowicz A, Lindstedt S, *et al*. Effects of 1 and 3 g cinnamon on gastric emptying, satiety, and postprandial blood glucose, insulin, glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, and ghrelin concentrations in healthy subjects. Am J Clin Nutr 2009; 89: 815-21.

[57] Dao TM, Waget A, Klopp P, *et al.* Resveratrol increases glucose induced GLP-1 secretion in mice: a mechanism which contributes to the glycemic control. PLoS One 2011; 6: e20700.

[58] Weickert MO, Reimann M, Otto B, *et al.* Soy isoflavones increase preprandial peptide YY (PYY), but have no effect on ghrelin and body weight in healthy postmenopausal women. J Negat Results Biomed 2006; 5: 11.

[59] McLaughlin JM, Olivo-Marston S, Vitolins MZ, *et al.* Effects of tomato- and soy-rich diets on the IGF-I hormonal network: a crossover study of postmenopausal women at high risk for breast cancer. Cancer Prev Res (Phila.) 2011; 4: 702-10.

[60] Shen CL, Cao JJ, Dagda RY, *et al.* Green tea polyphenols benefits body composition and improves bone quality in long-term high-fat diet-induced obese rats. Nutr Res 2012; 32: 448-57.

[61] Lu C, Zhu W, Shen CL, Gao W. Green tea polyphenols reduce body weight in rats by modulating obesity-related genes. PLoS One 2012; 7: e38332.

[62] Gruendel S, Garcia AL, Otto B, *et al*. Carob pulp preparation rich in insoluble dietary fiber and polyphenols enhances lipid oxidation and lowers postprandial acylated ghrelin in humans. J Nutr 2006; 136: 1533-8.

[63] Schilter B, Andersson C, Anton R, *et al.* Guidance for the safety assessment of botanicals and botanical preparations for use in food and food supplements. Food Chem Toxicol 2003; 41(12): 1625-49.

[64] Murakami A. Dose-dependent functionality and toxicity of green tea polyphenols in experimental rodents. Archiv Biochem Biophys 2014; 557: 3-10.

[65] Lambert JD, Sang S, Yang CS. Possible controversy over dietary polyphenols: benefits *vs* risks. Chem Res Toxicol 2007; 20(4): 583-5.

[66] Odiatou EM, Skaltsounis AL, Constantinou AI. Identification of the factors responsible for the *in vitro* pro-oxidant and cytotoxic activities of the olive polyphenols oleuropein and hydroxytyrosol. Cancer Lett 2013; 330(1): 113-21.

[67] Valdés A, García-Cañas, Koçak E, Simó C, Cifuentes A. Foodomics study on the effects of extracellular production of hydrogen peroxide by rosemary polyphenols on the anti-proliferative activity of rosemary polyphenols against HT29 cells. Electrophoresis 2016.

[68] Weisburg JH, Weissman DB, Sedaghat T, Babich H. *In vitro* cytotoxicity of epigallocatechin gallate and tea extracts to cancerous and normal cells from the human oral cavity. Basic Clin pharmacol toxicol 2004; 95(4): 191-200.

[69] León-González AJ, Auger C, Schini-Kerth VB. Pro-oxidant activity of polyphenols and its implication on cancer chemoprevention and chemotherapy. Biochem pharmacol 2015; 98(3): 371-80.

[70] Miranda AR, Leonangeli S, Cittadini MC, Canalis AM, Albrecht C, Soria EA. In: Weight and redox effects of infusive phytoextracts on overweight female mice treated for fifteen days, Proceedings of the 3° Reunión Internacional de Ciencias Farmacéuticas, Córdoba, Argentina, September 18-19, 2014; IJPSR 2015; pp 171-72.

[71] Galati G, Lin A, Sultan AM, O'Brien PJ. Cellular and *in vivo* hepatotoxicity caused by green tea phenolic acids and catechins. Free Radic Biol Med 2006; 40(4): 570-8.

[72] Ramachandran B, Jayavelu S, Murhekar K, Rajkumar T. Repeated dose studies with pure Epigallocatechin-3-gallate demonstrated dose and route dependant hepatotoxicity with associated dyslipidemia. Toxicol Rep 2016; 3: 336-45.

[73] Cottart CH, Nivet-Antoine V, Laguillier-Morizot C, Beaudeux JL. Resveratrol bioavailability and toxicity in humans. Mol Nutr Food Res 2010; 54(1): 7-16.

[74] Yang CS, Sang S, Lambert JD, Lee MJ. Bioavailability issues in studying the health effects of plant polyphenolic compounds. Mol Nutr Food Res 2008; 52(1): 139-51.

[75] Chow HS, Hakim IA, Vining DR, *et al.* Effects of dosing condition on the oral bioavailability of green tea catechins after single-dose administration of Polyphenon E in healthy individuals. Clin Cancer Res 2005; 11(12): 4627-33.

[76] Deneo–Pellegrini H, De Stefani E, Boffetta P, *et al.* Maté consumption and risk of oral cancer: Case-control study in Uruguay. Head Neck 2013; 35(8): 1091-95.

[77] Catterall F, Souquet JM, Cheynier V, *et al.* Differential modulation of the genotoxicity of food carcinogens by naturally occurring monomeric and dimeric polyphenolics. Environ Mol Mutagen 2000; 35(2): 86-98.

[78] Lin CL, Chen RF, Chen JYF, *et al.* Protective effect of caffeic acid on paclitaxel induced anti-proliferation and apoptosis of lung cancer cells involves NF-κB pathway. Inter J Mol Sci 2012; 13(5): 6236-45.

[79] Zhu BT, Liehr JG. Inhibition of Catechol O-Methyltransferase-catalyzed O-Methylation of 2-and 4-Hydroxyestradiol by Quercetin possible role in estradiol-induced tumorigenesis. J Biol Chem 1996; 271(3): 1357-63.

[80] Zhu BT, Liehr JG. Quercetin increases the severity of estradiol-induced tumorigenesis in hamster kidney. Toxicol Appl Pharm 1994; 125(1): 149-58.

[81] Hirose M, Hoshiya T, Mizoguchi Y, Nakamura A, Akagi K, Shirai T. Green tea catechins enhance tumor development in the colon without effects in the lung or thyroid after pretreatment with 1, 2-dimethylhydrazine or 2, 2′-dihydroxy-di-n-propylnitrosamine in male F344 rats. Cancer Lett 2001; 168(1): 23-9.

[82] van der Woude H, Gliszczyńska-Świgło A, Struijs K, Smeets A, Alink GM, Rietjens IM. Biphasic modulation of cell proliferation by quercetin at concentrations physiologically relevant in humans. Cancer Lett 2003; 200(1): 41-7.

[83] Giuliani C, Di Santo S, Bucci I, *et al*. In: The flavonoid quercetin inhibits thyroid function in rats. Non-neoplastic Thyroid Disorders, Proceedings of The Endocrine Society's 95th Annual Meeting and Expo, San Francisco, USA, June 15–18, 2013; Endocrinol Rev 2013, 34.

[84] Ferreira ACF, Lisboa PC, Oliveira KJ, Lima LP, Barros IA, Carvalho DP. Inhibition of thyroid type 1 deiodinase activity by flavonoids. Food Chem Toxicol 2002; 40(7): 913-17.

[85] Doerge DR, Sheehan DM. Goitrogenic and estrogenic activity of soy isoflavones. Environ Health Perspect 2002; 110(3): 349.

[86] Eastman CJ, Zimmermann MB. The iodine deficiency disorders. In: Thyroid disease manager 2009. Reference: Available from: http://www.thyroidmanager.org/chapter/the-iodine-deficiency-disorders.

[87] Setchell KD. Phytoestrogens: the biochemistry, physiology, and implications for human health of soy isoflavones. Am J Clin Nutr 1998; 68(6): 1333-46.

[88] Clifton-Bligh PB, Nery ML, Clifton-Bligh RJ, *et al.* Red clover isoflavones enriched with formononetin lower serum LDL cholesterol—a randomized, double-blind, placebo-controlled study. Eur J Clin Nutr 2015; 69(1): 134-42.

[89] Ososki AL, Kennelly EJ. Phytoestrogens: a review of the present state of research. Phytother Res 2013; 17(8): 845-69.

[90] Setchell KD, Cassidy A. Dietary isoflavones: biological effects and relevance to human health. J Nutr 1999; 129(3): 758-67.

[91] Fernandez-Lopez A, Lamothe V, Delample M, Denayrolles M, Bennetau-Pelissero C. Removing isoflavones from modern soy-food: Why and how? Food Chem 2016; 210: 286-94.

[92] Mahalingam S, Gao L, Gonnering M, Helferich W, Flaws JA. Equol inhibits growth, induces atresia, and inhibits steroidogenesis of mouse antral follicles *in vitro*. Toxicol Appl Pharmacol 2016; 295: 47-55.

[93] Cassidy A, Bingham S, Setchell KD. Biological effects of a diet of soy protein rich in isoflavones on the menstrual cycle of premenopausal women. Am J Clin Nutr 1994; 60(3): 333-40.

[94] Lephart ED. Modulation of Aromatase by Phytoestrogens. Enzyme Res 2015; 2015: 594656.

[95] Wang X, Wang G, Li X, *et al.* Suppression of rat and human androgen biosynthetic enzymes by apigenin: Possible use for the treatment of prostate cancer. Fitoterapia 2016; 111: 66-72.

[96] Krazeisen A, Breitling R, Möller G, Adamski J. In: Flavonoids in Cell Function; Buslig B, Manthey J, Ed. Florida USA: Springer Science & Business Media 2013; 151-208.

[97] Nagao T, Yoshimura S, Saito Y, Nakagomi M, Usumi K, Ono H. Reproductive effects in male and female rats of neonatal exposure to genistein. Reprod Toxicol 2011; 15(4): 399-411.

[98] Delclos KB, Bucci TJ, Lomax LG, *et al.* Effects of dietary genistein exposure during development on male and female CD (Sprague-Dawley) rats. Reprodu Toxicol 2001; 15(6): 647-63.

[99] Roos N, Sørensen JC, Sørensen H, *et al*. Screening for anti-nutritional compounds in complementary foods and food aid prod-

ucts for infants and young children. Matern Child Nutr 2013; 9(1): 47-71.
[100] Temme EH, Van Hoydonck PG. Tea consumption and iron status. Eur J Clin Nutr 2002; 56(5): 379-86.
[101] Zijp IM, Korver O, Tijburg LB. Effect of tea and other dietary factors on iron absorption. Crit Rev Food Sci Nutr 2000; 40(5): 371-98.
[102] Lesjak M, Hoque R, Balesaria S *et al.* Quercetin inhibits intestinal iron absorption and ferroportin transporter expression *in vivo* and *in vitro*. PloS one 2014; 9(7): e102900.
[103] McDougall GJ, Stewart D. The inhibitory effects of berry polyphenols on digestive enzymes. Biofactors 2005; 23(4): 189-95.
[104] Santos Buelga C, Scalbert A. Proanthocyanidins and tannin like compounds–nature, occurrence, dietary intake and effects on nutrition and health. J Sci Food Agriculture 2000; 80(7): 1094-117.
[105] Puumala SE, Ross JA, Aplenc R, Spector LG. Epidemiology of childhood acute myeloid leukemia. Pediatr blood cancer 2013; 60(5): 728-33.
[106] Strick R, Strissel PL, Borgers S, Smith SL, Rowley JD. Dietary bioflavonoids induce cleavage in the MLL gene and may contribute to infant leukemia. PNAS 2000; 97(9): 4790.
[107] World Health Organization. Preventing chronic diseases: a vital investment. WHO global report. Ginebra, Suiza, 2005. Available at: http://www.who.int/chp/chronic_disease_report/en/ [accessed June 06, 2016].
[108] World Health Organization. Cause specific mortality and morbidity. WHO Statistics 2010. Ginebra, Suiza, 2010. Available at: http://www.who.int/gho/publications/world_health_statistics/EN_WHS10_Full.pdf. [accessed June 06, 2016].
[109] Browson R, Remington P, Wegener M. Chronic Disease Epidemiology and Control. 3rd Ed. Washington DC: American Public Health Association 2006.
[110] Peña M, Bacallao J. La obesidad y sus tendencias en la Región. Rev Panam Salud Publica 2001; 10(2): 45-78.
[111] Lutz M, León AE. In: Alimentos saludables y funcionales: la tendencia actual. Aspectos nutricionales y saludables de los productos de panificación; Luttz M & León AE Ed. Valparaíso: Universidad de Valparaíso 2009: pp 14-16.
[112] Poljsak B, Šuput D, Milisav I. Achieving the balance between ROS and antioxidants: when to use the synthetic antioxidants. Oxid Med Cell Longev. 2013; 2013: 956792.
[113] Martínez CD, Vargas CR, Arancibia SR. Estrés oxidativo y neurodegeneración. Rev Fac Med UNAM 2003; 46(6): 229-35.
[114] Zacarías-Flores M, Sánchez-Rodríguez MA, Correa-Muñoz E, Arronte-Rosales A, Mendoza-Núñez, VM. Postmenopausal symptoms severity enhancement oxidative stress in metabolic syndrome women's. Ginecol Obstet Mex 2014; 82(12): 796-806.
[115] Halliwell B. Role of free radicals in the neurodegenerative diseases. Drugs Aging 2001; 18(9): 685-716.
[116] Sies, H. Oxidative stress: from basic research to clinical application. Am J Med 1991; 91: 31-8.
[117] Beckman KB, Ames BN. The free radical theory of aging matures. Physiol Rev 1998; 78: 547-81.
[118] Liochev SI. Reactive oxygen species and the free radical theory of aging. Free Radic Biol Med. 2013; 60: 1-4.
[119] Ferrari CK, Percário S, Silva JC, da Silva TE. An apple plus a nut a day keepS the doctors away: antioxidant capacity OF foods and THEIR health benefits. Curr Pharm Des 2016, 22(2): 189-95.
[120] Afanas'ev I. Signaling and damaging functions of free radicals in aging—free radical theory, hormesis, and TOR. Aging Dis 2010; 1(2): 75-88.
[121] Schieber M, Chandel NS. ROS function in redox signaling and oxidative stress. Curr Biol 2014; 24(10): 453-62.
[122] Marotte C, Noemi Zeni S. Reactive oxygen species on bone cells activity. Acta Bioquim Clin Latinoam 2013; 47(4): 661-74.
[123] Sohal RS, Weindruch R. Oxidative stress, caloric restriction, and aging. Science 1996; 273: 59-63.
[124] Filaire E, Toumi H. Reactive oxygen species and exercise on bone metabolism: Friend or enemy? Joint Bone Spine 2012; 79(4): 341-6.
[125] Satyanarayana U, Chakrapani U. Biochemistry, 4th edition. India: Elsevier Health Sciences: 2013.
[126] Venereo Gutiérrez JR. Daño oxidativo, radicales libres y antioxidantes. Rev Cubana Med Milit 2002; 31(2): 126-33.
[127] Singh B, Bhickta S, Gupta R, Goyal S, Gupta RR. Antioxidants the powerful new weapons in the fight against periodontal diseases. Dental Journal of Advance Studies 2013; 1(2): 85-90.
[128] Flora G, Gupta D, Tiwari A. Toxicity of lead: a review with recent updates. Interdiscip Toxicol 2012; 5(2): 47-58.
[129] Pomatto LCD, Raynes R, Davies KJ. The peroxisomal Lon protease LonP2 in aging and disease: functions and comparisons with mitochondrial Lon protease LonP1. Biol Rev Camb Philos Soc 2016. [Epub ahead of print].
[130] Baskin S, Salem H. Oxidants, antioxidants and free radicals. Washington, DC: Taylor & Francis 1997.
[131] Apanasets O, Grou CP, Van Veldhoven PP, *et al.* PEX5, the Shuttling Import Receptor for Peroxisomal Matrix Proteins, Is a Redox-Sensitive Protein. Traffic 2014; 15(1): 94-103.
[132] Céspedes Miranda EM, Hernández Lantigua I, Llópiz Janer N. Enzimas que participan como barreras fisiológicas para eliminar los radicales libres: II. Catalasa. Rev Cubana Invest Biomed 1996; 15(2): 0-0.
[133] Srivastava SK, Ansari NH. The peroxidatic and catalatic activity of catalase in normal and acatalasemic mouse liver. Biochim Biophys Acta 1980; 633(3): 317-22.
[134] Dias FA, Gandara AC, Perdomo HD, *et al.* Identification of a selenium-dependent glutathione peroxidase in the blood-sucking insect Rhodnius prolixus. Insect Biochem Mol Biol 2016; 69: 105-14.
[135] García Triana B, García Morales O, Clapes Hernández S, Rodes Fernández L, García Piñeiro JC. Enzimas que participan como barreras fisiológicas para eliminar los radicales libres: I. Superóxido dismutasas. Rev Cubana Invest Biomed 1995; 14(1): 0-0.
[136] Prior RL. Oxygen radical absorbance capacity (ORAC): New horizons in relating dietary antioxidants/bioactives and health benefits. J Funct Foods 2015; 18: 797-810.
[137] Marri V, Richner H. Immune response, oxidative stress and dietary antioxidants in great tit nestlings. Comp Biochem Physiol A Mol Integr Physiol 2015; 179: 192-6.
[138] Surai PF. Natural antioxidants in avian nutrition and reproduction. Nottingham: Nottingham University Press, 2002.
[139] Lane DJ, Richardson DR. The active role of vitamin C in mammalian iron metabolism: Much more than just enhanced iron absorption! Free Radic Biol Med 2014; 75: 69-83.
[140] Chinembiri TN, du Plessis LH, Gerber M, Hamman JH, du Plessis J. Review of natural compounds for potential skin cancer treatment. Molecules 2014; 19(8): 11679-721.
[141] Liu F, Cottrell JJ, Furness JB, *et al.* Selenium and Vitamin E together improve intestinal epithelial barrier function and alleviate oxidative stress in heat stressed pigs. Exp physiol 2016; 1-10.
[142] Avello M, Suwalsky M. Radicales libres, antioxidantes naturales y mecanismos de protección. Atenea 2006 (494): 161-72.
[143] Larrauri M, Quiroga PR, Asensio CM, *et al.* In: Composición química y actividad antioxidante de tegumento de maní obtenido por diferentes procesos industriales, Proceedings, XXVIII Jornada Nacional de Maní 20013. General Cabrera, Córdoba. Argentina.
[144] Chasquibol SN, Lengua CL, Delmás I, *et al.* Alimentos funcionales o fitoquímicos, clasificación e importancia. Rev Per Quím Ing Quím 2003, 2(5):9-20.
[145] Kim YW, Byzova TV. Oxidative stress in angiogenesis and vascular disease. Blood 20014; 123(5): 625-31.
[146] Lusis AJ. Atherosclerosis. Nature 2000. 407(6801): 233–41.
[147] Vilahur G, Padró T, Casaní L, *et al.* El enriquecimiento de la dieta con polifenoles previene la disfunción endotelial coronaria mediante la activación de la vía de Akt/eNOS. Rev Esp Cardiol 2015; 68(3):216-25.
[148] Gonzalez-Santiago M, Martin-Bautista E, Carrero JJ, *et al.* One-month administration of hydroxytyrosol, a phenolic antioxidant present in olive oil, to hyperlipemic rabbits improves blood lipid profile, antioxidant status and reduces atherosclerosis development. Atherosclerosis 2006; 188(1): 35-42.
[149] Zagayko AL, Kravchenko GB, Krasilnikova OA, Ogai YO. Grape polyphenols increase the activity of HDL enzymes in old and obese rats. Oxid Med Cell Longev 2013; 2013: 593761.
[150] Aviram M, Rosenblat M, Gaitini D, *et al.* Pomegranate juice consumption for 3 years by patients with carotid artery stenosis reduces common carotid intima-media thickness, blood pressure and LDL oxidation. Clin Nutr 2004; 23(3): 423-33.
[151] Kane MO, Sene M, Anselm E, Dal S, Schini-Kerth VB, Augier C. Role of AMP-activated Protein Kinase in NO-and EDHF-mediated

Endothelium-dependent Relaxations to Red Wine Polyphenols. Indian J Physiol Pharmacol 2015; 59(4): 369-79.
[152] Ndiaye M, Chataigneau M, Lobysheva I, Chataigneau T, Schini-Kerth VB. Red wine polyphenol-induced, endothelium-dependent NO-mediated relaxation is due to the redox-sensitive PI3-kinase/Akt-dependent phosphorylation of endothelial NO-synthase in the isolated porcine coronary artery. FASEB J 2005; 19(3): 455-57.
[153] Huang J, Feresin R, Zhao Y, Pourafshar S, Arjmandi BH, Salazar G. (2016). Black Berry Polyphenol Reduce Nox1 Function to Inhibit Senescence in Vascular Smooth Muscle Cells. FASEB J 2016; 30(1): 420-22.
[154] Spanier G, Xu H, Xia N, *et al.* Resveratrol reduces endothelial oxidative stress by modulating the gene expression of superoxide dismutase 1 (SOD1), glutathione peroxidase 1 (GPx1) and NADPH oxidase subunit (Nox4). J Physiol Pharmacol 2009; 60(4): 111-16.
[155] Actis-Goretta L, Ottaviani JI, Fraga CG. Inhibition of angiotensin converting enzyme activity by flavanol-rich foods. J Agric Food Chem 2006; 54(1): 229-34.
[156] Andriantsitohaina R, Auger C, Chataigneau T, *et al.* Molecular mechanisms of the cardiovascular protective effects of polyphenols. Br J Nutr 2012, 108 (09): 1532-49.
[157] Bhullar KS, Rupasinghe HP. Polyphenols: multipotent therapeutic agents in neurodegenerative diseases. Oxid Med Cell Longev 2013; 2013: 891748.
[158] Basli A, Soulet S, Chaher N, *et al.* Wine polyphenols: potential agents in neuroprotection. Oxid Med Cell Longev 2012; 2012: 805762.
[159] Li R, Huang YG, Fang D, Le WD. (−) Epigallocatechin gallate inhibits lipopolysaccharide-induced microglial activation and protects against inflammation-mediated dopaminergic neuronal injury. J Neurosci Res 2004; 78(5): 723-31.
[160] Vauzour D, Ravaioli G, Vafeiadou K, Rodriguez Mateos A, Angeloni C, Spencer JP. Peroxynitrite induced formation of the neurotoxins 5-S-cysteinyl-dopamine and DHBT-1: implications for Parkinson's disease and protection by polyphenols. Archiv Biochem Biophys 2008; 476(2): 145-51.
[161] Schaffer S, Asseburg H, Kuntz S, Muller WE, Eckert GP. Effects of polyphenols on brain ageing and Alzheimer's disease: focus on mitochondria. Mol Neurobiol 2012; 46(1): 161-78.
[162] Mandel S, Youdim MB. Catechin polyphenols: neurodegeneration and neuroprotection in neurodegenerative diseases. Free Radic Biol Med 2004; 37(3): 304-17.
[163] Yao RQ, Qi DS, Yu HL, Liu J, Yang LH, Wu XX. Quercetin attenuates cell apoptosis in focal cerebral ischemia rat brain *via* activation of BDNF–TrkB–PI3K/Akt signaling pathway. Neurochem Res 2012; 37(12): 2777-86.
[164] Pandey AK, Hazari PP, Patnaik R, Mishra AK. The role of ASIC1a in neuroprotection elicited by quercetin in focal cerebral ischemia. Brain Res 2011; 1383: 289-99.
[165] Shih PH, Chan YC, Liao JW, Wang MF, Yen GC. Antioxidant and cognitive promotion effects of anthocyanin-rich mulberry (Morus atropurpurea L.) on senescence-accelerated mice and prevention of Alzheimer's disease. J Nutr Biochem 2010; 21(7): 598-605.
[166] Varadinova MG, Docheva-Drenska DI, Boyadjieva NI. Effects of anthocyanins on learning and memory of ovariectomized rats. Menopause 2009; 16(2): 345-49.
[167] Sporn MB. Carcinogenesis and cancer: Different perspectives on the same disease. Cancer Res 1991; 51: 6215-8.
[168] Kang NJ, Shin SH, Lee HJ, Lee KW. Polyphenols as small molecular inhibitors of signaling cascades in carcinogenesis. Pharmacol Ther 2011; 130(3): 310-24.
[169] Ramos S. Cancer chemoprevention and chemotherapy: dietary polyphenols and signalling pathways. Mol Nutr Food Res 2008; 52(5): 507-26.
[170] Lall RK, Syed DN, Adhami VM, Khan MI, Mukhtar H. Dietary polyphenols in prevention and treatment of prostate cancer. Int J Mol Sci 2015; 16(2): 3350-76.
[171] Khan N, Mukhtar H. Dietary agents for prevention and treatment of lung cancer. Cancer Lett 2015; 359(2): 155-64.
[172] Levi F. Cancer prevention: epidemiology and perspectives. Eur J Cancer 1999; 35(14): 1912-24.
[173] Bradbury KE, Appleby PN, Key TJ. Fruit, vegetable, and fiber intake in relation to cancer risk: findings from the European Prospective Investigation into Cancer and Nutrition (EPIC). Am J Clin Nutr 2014; 100(1): 394-98.
[174] Turati F, Rossi M, Pelucchi C, Levi F, La Vecchia C. Fruit and vegetables and cancer risk: a review of southern European studies. Br J Nutr 2015; 113(2): 102-10.
[175] La Vecchia C, Tavani A. Fruit and vegetables, and human cancer. Eur J Cancer Prev 1998; 7(1): 3-8.
[176] Vainio H, Weiderpass E. Fruit and vegetables in cancer prevention. Nutr Cancer 2006; 54(1): 111-42.
[177] Surh YJ. Cancer chemoprevention with dietary phytochemicals. Nat Rev Cancer 2003; 3(10): 768-80.
[178] Lee KW, Lee HJ. Biphasic effects of dietary antioxidants on oxidative stress-mediated carcinogenesis. Mech Ageing Dev 2006; 127(5): 424-31.
[179] Yang CS, Wang H. Cancer therapy combination: green tea and a phosphodiesterase 5 inhibitor?. J Clin Invest 2013; 123(2): 556-58.
[180] Yang CS, Maliakal P, Meng X. Inhibition of Carcinogenesis by Tea. Annu Rev Pharmacol Toxicol 2002; 42(1): 25-54.
[181] Katiyar SK, Elmets CA. Green tea polyphenolic antioxidants and skin photoprotection. Int J Oncol 2001; 18(6): 1307-13.
[182] Lambert JD, Hong J, Yang GY, Liao J, Yang CS. Inhibition of carcinogenesis by polyphenols: evidence from laboratory investigations. Am J Clin Nutr 2005, 81(1): 284-91.
[183] Cherniack EP. Polyphenols: planting the seeds of treatment for the metabolic syndrome. Nutrition 2011; 27(6): 617-23.
[184] Lin J, Della-Fera MA, Baile CA. Green Tea Polyphenol Epigallocatechin Gallate Inhibits Adipogenesis and Induces Apoptosis in 3T3-L1 Adipocytes. Obes Res 2005; 13(6): 982-90.
[185] Li HL, Huang Y, Zhang CN, *et al.* Epigallocathechin-3 gallate inhibits cardiac hypertrophy through blocking reactive oxidative species-dependent and-independent signal pathways. Free Radic Biol Med 2006; 40(10): 1756-75.
[186] de Bock M, Derraik JG, Brennan CM, *et al.* Olive (Olea europaea L.) leaf polyphenols improve insulin sensitivity in middle-aged overweight men: a randomized, placebo-controlled, crossover trial. PloS one 2013; 8(3): e57622.
[187] Munir KM, Chandrasekaran S, Gao F, Quon MJ. Mechanisms for food polyphenols to ameliorate insulin resistance and endothelial dysfunction: therapeutic implications for diabetes and its cardiovascular complications. Am J Physiol Endocrinol Metab 2013; 305(6): 679-86.
[188] Li C, Allen A, Kwagh J, *et al.* Green tea polyphenols modulate insulin secretion by inhibiting glutamate dehydrogenase. J Biol Chem 2006; 281(15): 10214-21.
[189] Conte E, Fagone E, Fruciano M, Gili E, Iemmolo M, Vancheri C. Anti-inflammatory and antifibrotic effects of resveratrol in the lung. Histol Histopathol 2015; 30(5): 523-29.
[190] Gimeno JC, Sánchez EJM. Fármacos antioxidantes para el asma. AFT 2009; 7(2): 91-6.
[191] Biswas S, Hwang JW, Kirkham PA, Rahman I. Pharmacological and dietary antioxidant therapies for chronic obstructive pulmonary disease. Curr Med Chem 2013, 20(12): 1496-530.
[192] Culpitt SV, Rogers DF, Fenwick PS, *et al.* Inhibition by red wine extract, resveratrol, of cytokine release by alveolar macrophages in COPD. Thorax 2003; 58(11): 942-46.
[193] Hernández JAM, Solomon A. Participación del sistema nervioso y del tracto gastrointestinal en la homeostasis energética. Rev Med 2006; 50(1): 27-37.
[194] Schwartz MW, Woods SC, Porte D, Seeley RJ, Baskin DG. Central nervous system control of food intake. Nature 2000; 404(6778): 661-71.
[195] Cummings DE, Overduin J. Gastrointestinal regulation of food intake. J Clin Invest 2007; 117(1): 13-23.
[196] Solomon A, De Fanti BA, Martínez Hernández JA. Control del apetito y peso corporal: la ghrelina y la señalización orexigénica. Nutr Clin 2004; 24(3): 13-27.
[197] Havel PJ, Larsen PL, Cameron JL, Conn PM, Freeman ME. Control of food intake Neuroendocrinology in physiology and medicine, 1st ed. New York: Humana Press 2000.
[198] Kishi T, Elmquist JK. Body weight is regulated by the brain: a link between feeding and emotion. Mol Psychiatry 2005; 10: 132-46.
[199] Broberger C. Brain regulation of food intake and appetite: molecules and networks. J Intern Med 2005; 258: 301-27.
[200] Hernández-Jiménez S. Fisiopatología de la obesidad. Gac Méd Méx 2004; 140(2):2.
[201] Palou A, Bonet ML, Picó C, Rodríguez AM. Nutrigenómica y obesidad. Rev Med Univ Navarra 2004, 48(2): 36-48.

[202] Konturek SJ, Konturek PC, Pawlik T, Brzozowski T. Brain-gut axis and its role in the control of food intake. J Physiol Pharmacol 2004; 55(2): 137-54.
[203] Rashid K, Wachira FN, Ngure RM, *et al.* Kenyan purple tea anthocyanins ability to cross the blood brain barrier reinforcing brain antioxidant capacity in mice. Afr Crop Sci J 2014; 22: 819-28.
[204] Janle EM, Lila MA, Grannan M, *et al*. Pharmacokinetics and tissue distribution of 14C-labeled grape polyphenols in the periphery and the central nervous system following oral administration. J Med Food 2010; 13(4): 926-33.
[205] Youdim KA, Qaiser MZ, Begley DJ, Rice-Evans C A, Abbott NJ. Flavonoid permeability across an *in situ* model of the blood–brain barrier. Free Radic Biol Med 2004; 36(5): 592-604.
[206] Schaffer S, Halliwell B. Do polyphenols enter the brain and does it matter? Some theoretical and practical considerations. Genes Nutr 2012; 7(2): 99-109.
[207] Ishisaka A, Ichikawa S, Sakakibara H, *et al.* Accumulation of orally administered quercetin in brain tissue and its antioxidative effects in rats. Free Radic Biol Med 2011; 51(7): 1329-36.
[208] Nakagawa K, Miyazawa T. Absorption and distribution of tea catechin, (-)-epigallocatechin-3-gallate, in the rat. J Nutr Sci Vitaminol (Tokyo) 1997; 43: 679-84.
[209] Ferruzzi MG, Lobo JK, Janle EM, *et al.* Bioavailability of gallic acid and catechins from grape seed polyphenol extract is improved by repeated dosing in rats: implications for treatment in Alzheimer's disease. J Alzheimers Dis 2009; 18: 113-24.
[210] Carvalho FB, Gutierres JM, Bueno A. Anthocyanins control neuroinflammation and consequent memory dysfunction in mice exposed to lipopolysaccharide. Mol Neurobiol 2016: 1-19.
[211] Galho AR1, Cordeiro MF, Ribeiro SA, *et al.* Protective role of free and quercetin-loaded nanoemulsion against damage induced by intracerebral haemorrhage in rats. Nanotechnology 2016; 27(17): 175101.
[212] Baldissarelli J, Santi A, Schmatz R, *et al.* Hypothyroidism Enhanced Ectonucleotidases and Acetylcholinesterase Activities in Rat Synaptosomes can be Prevented by the Naturally Occurring Polyphenol Quercetin Cell Mol Neurobiol 2016 1-11.
[213] Javed H, Vaibhav K, Ahmed ME, *et al.* Effect of hesperidin on neurobehavioral, neuroinflammation, oxidative stress and lipid alteration in intracerebroventricular streptozotocin induced cognitive impairment in mice. J Neurol Sci 2015 Jan 15; 348(1-2): 51-9.
[214] Seely KA, Levi MS, Prather PL. Retraction: The dietary polyphenols trans-resveratrol and curcumin selectively bind human CB1 cannabinoid receptors with nanomolar affinities and function as antagonists/inverse agonists. J Pharmacol Exp Ther 2009; 330(1): 31-39.
[215] Ali SH, Madhana RM, Athira KV, *et al.* Resveratrol ameliorates depressive-like behavior in repeated corticosterone-induced depression in mice. Steroids 2015; 101: 37-42.
[216] Wang T, Yang YJ, Wu PF, *et al.* Tetrahydroxystilbene glucoside, a plant-derived cognitive enhancer, promotes hippocampal synaptic plasticity. Eur J Pharmacol 2011, 650(1): 206-14.
[217] Sulakhiya K, Kumar P, Gurjar SS, Barua CC, Hazarika NK. Beneficial effect of honokiol on lipopolysaccharide induced anxiety-like behavior and liver damage in mice. Pharmacol Biochem Behav 2015; 132: 79-87.
[218] Cittadini MC, Canalis AM, Albrecht C, Soria EA. Effects of oral phytoextract intake on phenolic concentration and redox homeostasis in murine encephalic regions. Nutr Neurosci 2015; 18(7): 316-22.
[219] Miranda AR, Canalis AM, Serra SV, Soria EA. In: Análisis multidimensional de los efectos deseados y colaterales del ácido clorogénico en neurotoxicidad aguda inducida por arsénico en ratones, Proceedings of the XLVII Reunión anual de la Sociedad Argentina de Farmacologia Experimental, Córdoba, Argentina, November 4-6, 2015, SAFE 2015, pp 129.

PMID: 28000547