Impact of the inhibition of proteins activities and the chemical aspect of polyphenols–proteins interactions

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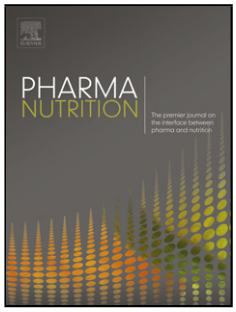

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Full title:

Impact of the inhibition of proteins activities and the chemical aspect of polyphenols-proteins interactions

Running title:

Protein-polyphenol interaction and protein activity inhibition

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Abbreviations: Keap1, Kelch-like ECH-associated protein 1; Nrf2, nuclear factor erythroid 2-related factor 2; PLA_2, phospholipase A_2; PRPs, proline-rich proteins; EGCG, epigallocatechin gallate; NF-κB, nuclear Factor kappa-light-chain-enhancer of activated B cells; LDL, low density lipoproteins; HMG-CoA reductase, 3-hydroxy-3-methylglutaryl coenzyme A reductase; MMP-2 and MMP-9, metalloproteinases; 67LR, 67-kDa laminin receptor; MAO, monoamine oxidase; HCV, hepatitis C virus; CYP3A4, cytochrome P450 family 3 subfamily A polypeptide 4

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Graphical abstract

Highlights

1) Polyphenol-protein interaction depends on the types of protein and polyphenol.
2) Chemical bindings are primarily hydrophobic interactions and hydrogen bonds.
3) Astringency may be caused by the polyphenol-protein interactions.
4) Polyphenols have several very interesting biological activities.
5) Various protein are the targets of differents polyphenols.

Abstract

The good nutritional value and the interesting biological activities of the plant-based nutraceuticals are primarily due to the polyphenols. These latter are among the most important and extensively studied plant secondary metabolites and their interaction with proteins is the subject of considerable researches. This interaction is fundamental to the rational design of functional foods as well as to improve the bioavailability and the biofunctionality of the polyphenols. In this work, we emphasized that the types of proteins and polyphenols influence this interaction and chemical bindings are primarily hydrophobic interactions and hydrogen bonds. We highlighted further the anti-atherosclerosis, anti-inflammatory, anti-diabetic, neuro-protective, antioxidant, anti-proliferative, antimicrobial and the hepatoprotective activities of the polyphenols. We also mentioned that astringency and these health benefits may be caused by the interaction with proteins, and that the proteins targeted by polyphenols are: Kelch-like ECH-associated protein 1, extracellular microbial enzymes, phospholipase A_2, monoamine oxidase, 3-hydroxy-3-methylglutaryl coenzyme A reductase,

laminin receptor, hepatitis C virus NS3 protease, virus-encoded integrase, retroviral reverse transcriptase, leukotoxin, enterotoxin, cholera toxin, α-glucosidase, α-amylase, pro-oxidant enzymes, nuclear factor kappa B, cytochrome P450, metalloproteinases, β- and γ-secretases.

A healthy, balanced diet and rich in polyphenols can prevent and even control the major public health problems worldwide.

Keywords: Polyphenol; protein; chemical aspect; chemical binding; inhibition; impact

1. Introduction

Several techniques were used to study the interactions between proteins and tannins: nuclear magnetic resonance, circular dichroism, mass spectrometry, ultraviolet-visible and fluorescence spectroscopy, microcalorimetry, and flow nephelometric analysis [1]. In addition, scientists in many fields are interested in interaction of tannins with proteins, because such interaction is closely related to leather making, physiological activity of herbal medicines, taste of foodstuffs and beverages, and nutritional value of feeds [2]. Furthermore, the phenolic compounds can lead to changes in the physicochemical and functional properties of proteins, including solubility, thermal stability, and digestibility [3]. Moreover, the nutritional value of proteins may be affected due to the modification of essential amino acids and through the inhibition of proteases [4]. In fact, it was shown that if polyphenols bind to hydrophobic sites of proteins, the protein structure may change because only weak hydrophobic sites could remain on the surface of the protein leading to a possible change in the protein folding and in the protein functionality [5]. On the other hand, nowadays, several healthy effects have been attributed to the intake of tannins due to their antioxidant, radical scavenging, antimicrobial, antiviral and antimutagenic activities thus providing a significant protection against the development of several chronic diseases [6]. Indeed, polyphenols are the effective bioactive components in many natural plant products and they have a variety of health benefits [7]. In addition, the mechanism of action of the polyphenols corresponding to those effects has been, at least in part, ascribable to polyphenols interaction with biomolecules, especially proteins [8]. In effect, it is probable that the interaction of tannins with proteins is fundamental to their observed biological activities [9].

Thermally modified β-lactoglobulin combined with (−)-epigallocatechin-3-gallate (EGCG) form stable co-assembled nanoparticles (Eβ-NPs). The Eβ-NPs inhibited the proliferation of human malignant melanoma cells A375 and human eosophageal carcinoma cells TE-1 with 69.0% and 63.7% greater activity than EGCG, respectively. The Eβ-NPs showed the potential to improve the bioactivity of EGCG in functional foods, since they possessed better bioactivity than native EGCG with respect to the proliferative inhibition of cancer cells [10]. Besides, the antioxidant activity of the human serum albumin–phenolic acid interaction compounds was higher than that of the phenolic acids alone [11]. While, the loading with hordein nanoparticles enhanced the antioxidant capability of resveratrol compared with the free one [12]. On the other hand, the curcumin and egg ovalbumin could form a stable complex which could improve the solubility and photostability of curcumin, indicating that it is an efficient way to improve the bioactivity of curcumin [13]. The complex exhibited a better antioxidant activity compared to the pure curcumin [14]. Moreover, the antioxidant activity of curcumin loaded with β-casein micelle was higher than that of both free β-casein and curcumin. In addition, the curcumin encapsulated in casein nanoparticles showed significantly improved antiproliferation activity against human colorectal and pancreatic cancer cells [12].

The complexation of natural and active functional compounds such as proteins, polyphenols and polysaccharides has been considered an efficient, safe, and convenient strategy for improving the

functional attributes of many polymers to expand their application areas [15]. So, the complexation of proteins and polyphenols may be efficient to improve the biofunctionality of the polyphenols. Besides, the interactions of phenolic compounds and proteins are known to affect the structure of proteins, content of free polyphenols, antioxidant capacity and bioavailability of phenolic compounds in foods. A better understanding of phenolic compound–protein interactions would help to control the functional properties of proteins in food products during processing, transportation and storage [16]. Furthermore, it is necessary to understand the binding mechanism between curcumin and proteins, which is useful for the development of proteins as delivery systems for insoluble polyphenols in the functional foods formulation [13]. Thus, the understanding of the binding mechanism between polyphenols and proteins would be essential to evaluate the bioavailability of polyphenols. Moreover, a rational design of polyphenol-protein particles would ensure a positive contribution to food quality, protein nutrition, and delivery of a health-relevant dose of polyphenols to the gastrointestinal tract [17]. Hence, the polyphenols-proteins interactions and the impact of the inhibition of proteins activities by polyphenols are two key themes which are fundamental to draw attention to the importance of polyphenols. For all the reasons cited above, an insight into the chemical aspect of the polyphenols-proteins interactions and about an interesting impact of the inhibition of proteins activities by polyphenols is the purpose of this work.

2. Chemical aspect of polyphenols-proteins interactions

2.1 Effect of the type of proteins

Proline-rich proteins (PRPs) are one of the dominant classes of salivary proteins and, as their name suggests, they are characterized by a high content in proline residues [18]. They tend to have either an open random-coil or collagen-like helical structural conformations, which provide the molecular flexibility and readily available binding sites for tannins [19]. In fact, they formed particularly strong hydrogen bonds and were conformationally flexible, leading to accessibility of hydrogen bonds sites [20]. They are classified in three groups depending on their isoelectric point and their degree of glycosylation: acidic, basic and glycosylated PRPs [21]. Basic PRPs bind more effectively to condensed tannins than acidic and glycosylated PRPs [22].

Polyphenols–proteins interactions depend on the size, conformation and charge of protein molecules and on the number and the stereospecificity of binding sites on both the polyphenol and protein molecules [23]. Larger PRPs have a greater affinity for tannins than smaller PRPs or peptide fragments [24]. In addition, a specific requirement for polyphenols and proteins interactions appears to be the need for the protein/peptide to have extended conformation and a significant proportion of proline content in order to create a loose helical structure and hydrophobic sticky patches that can associate with phenolic ring structures [25]. The pyrrolidine rings of the prolyl residues act as binding sites and form hydrophobic stacks with the galloyl rings of polyphenols [26]. Furthermore, the proteins that contain high proportions of proline residues in their sequences (casein, gelatine and saliva proteins in humans) have a higher precipitation potential [1]. Indeed, using different physico-chemical methods

to study the tannins-proteins aggregation process, it is now well established that tannins-proteins binding may occur in a specific and selective manner and that proline residues are the preferred binding sites for which tannins exhibit a higher affinity [6]. Moreover, PRPs react better and more strongly with tannins than proteins poor in this amino acid [27]. However, among the salivary proteins, histatins (histidine-rich proteins) have been shown to possess potent tannins-binding ability under slightly alkaline environment [28].

The affinities of salivary proteins to complex tannins depend mainly on their chemical structures [29]. Relatively open proteins, such as nonstructured and PRPs, seem to have a higher affinity for proanthocyanidins than the more closed, globular proteins [30]. In other words, proteins with flexible, random coil structures, bind tannins more strongly and easily than globular ones [27]. Nevertheless, α-amylase seems to be more specific and selective than PRPs in the aggregation with samples containing different amounts of proanthocyanidins [29]. The aromatic groups of polyphenols are supposed to be involved in a face-to-face stacking with amino acid residues of linear proteins, whereas the interaction with globular proteins probably involves only surface exposed residues [31].

2.2 Effect of the type of polyphenols

Tannins are present in a wide variety of foodstuffs of plant origin such as fruits, grains and tea [6]. They are classified on the basis of their structure into two groups: the hydrolysable and the condensed tannins [27]. EGCG is the lowest-molecular-weight polyphenolic to be functionally classified as a tannin [32]. Proanthocyanidins are oligomers and polymers of flavan-3-ol monomer units and the linkage between the different units may be an A-type linkage (containing an ether bond in addition to the C–C bond) or a B-type linkage (C–C bond between monomers) [33].

Hydrogenation of C2=C3 double bond (naringenin), hydroxylation of C3 (kaempferol) and position isomerism of benzene ring B (genistein) weakened the affinities for apigenin binding to β-lactoglobulin [34]. In addition, condensed tannins appear to be more effective than hydrolysable tannins at binding proteins [35]. Simple phenols, such as EGCG, bind proteins weakly, a higher degree of polymerisation and a greater molecular weight of an astringent compound (tannin) are generally agreed to correspond to a greater ability to precipitate proteins [36]. Furthermore, the binding affinity of flavan-3-ols has been reported to be enhanced by the increasing the degree of polymerization, such as in procyanidins [37]. In effect, because polyphenols can act as polydentate ligands on protein surface through their hydroxyl groups and aromatic rings, higher degree of polymerization achieves higher binding efficiency [19]. Moreover, procyanidins constitute a class with great structural diversity which could demonstrate stereospecific interactions with proteins. This can be approached from a variety of structural considerations including the shape, projection of phenolic hydroxyls, addition of galloyl groups, and position of peripheral groups imposed by the stereochemistry of the pyranic ring [38]. However, the proteins-precipitating effectiveness of mixtures of proanthocyanidins and proanthocyanidin gallates seems to increase with increasing degrees of polymerization until an optimal degree of polymerization of 12 units of catechin [30].

The galloylation of polyphenols was previously shown to affect the physico-chemical properties of polyphenols, which is crucial for the mechanism of their antioxidant activities. More precisely, the presence of galloyl groups affects the ability to donate electrons, chelate iron, regenerate tocoferol and also affects the lipophilicity [39]. On the other hand, it has been found that an increase in galloyl moiety increases binding of the catechins with proteins [40]. In fact, the binding affinity of flavan-3-ols has been reported to be enhanced by the addition of a gallate moiety at the 3-OH position of the molecule [37]. In addition, the galloyl ring has a key role for the binding affinity with salivary proteins. EGCG, which contains a galloyl ring in the molecule, promotes the formation of a strong intermolecular network between salivary proteins, in contrast with epicatechin, which lacks the galloyl ring [41]. Nevertheless, the effect of galloylation on binding affinity reaches a plateau with the pentagalloylated molecules, as the affinity of hepta- and octagalloylglucose for PRPs is of the same order as tetra- and pentagalloylglucose [24].

Another feature of polyphenol nature that influences polyphenols–proteins interactions is the flexibility. Gallotannins are flexible and can easily change their molecular conformation, for example: by intramolecular rotations that enable them to adapt better to the binding pocket structure of the protein. More rigid ellagitannins with limited capacity for conformational change interact more weakly with proteins [27]. Furthermore, because of the great diversity in their structure, phenolic compounds have different properties, such as solubility and polarity which enable them to have different interactions with other molecules [5]. Moreover, a lower affinity of a polyphenol for water favors strong association between proteins and the polyphenol [42].

2.3 Chemical bindings

The physicochemical mechanism of tannins-proteins interactions is not simple and depends on many factors. These interactions can be non-covalent (hydrophobic or hydrogen bonds) or covalent (after transition of the tannin into the quinone or phenolic radical form) [27]. The apple polyphenol oxidase oxidises specific substrates (mainly caffeoylquinic acid, catechins and dihydrochalcones) into highly reactive o-quinones through two mechanisms, namely cresolase (monophenolase) and catecholase activities [43]. In addition, phenols may be oxidized in an alkaline solution to its corresponding quinone. The quinone, being a reactive electrophilic intermediate, can readily undergo attack by nucleophiles such as lysine, methionine, cysteine and tryptophan moieties in a protein chain [44]. In other words, polyphenols are able to be oxidized to their corresponding quinones and semiquinones, which can further undergo covalent reactions with an enormous number of nucleophiles such cysteine or lysine on the protein [45]. On the other hand, the Michael reaction typically refers to the base-catalyzed addition of a nucleophile such as an enolate anion (Michael donor) to an activated α,β-unsaturated carbonyl-containing compound (Michael acceptor) [46]. In its reduced form, the selenocystine residue of type Ia thioredoxin reductase (TrxR) is susceptible to alkylation with electrophiles. Numerous inhibitors of type Ia TrxR act by reacting with and inactivating the C-terminal redox center. Some are α, β-unsaturated carbonyls such as quinones, curcumin and 4-hydroxy-2-

nonenal all of which can function as electrophiles in a 1,4 conjugate addition or Michael reaction, forming a covalent adduct, which results in the irreversible inhibition of type Ia TrxR [47]. Indeed, the α,β-unsaturated β-diketo moiety of curcumin participates in nucleophilic addition reactions. This reaction, known as the Michael addition, occurs between the unsaturated ketone as an acceptor and anions of –OH, –SH, –SeH as donors [48]. However, there is at present little evidence for covalent binding of tannin to protein. Indeed, it is generally accepted that there is a reversible interaction between polyphenol and protein in solution, leading to an equilibrium between the soluble tannins-proteins complexes and the reactants. These soluble complexes may reach a size where they are no longer solubles, or they may aggregate or undergo changes resulting in precipitation. The formation of these insoluble complexes is usually reversible, and they may redissolve, for example, by further addition of one of the reactants [49].

Non-covalent interactions can be studied by several techniques such as calorimetry, circular dichroism, dynamic light scattering and small-angle X-ray scattering, electrospray ionisation mass spectrometry, frontal capillary electrophoresis, pulsed ultrafiltration mass spectrometry, size-exclusion chromatography or ultrafiltration combined with other techniques [50]. Polyphenols-proteins complexes are formed by multiple weak interactions (mainly hydrophobic) between amino acid side chains and the polyphenol aromatic rings, indicating that the association of polyphenols with proteins is mainly a surface phenomenon [51]. In effect, proanthocyanidins have phenolic hydroxyl groups and hydrophobic regions that complex the carbonyl groups and hydrophobic amino acids, respectively, of proteins [52]. In addition, hydrophobic interaction played major roles in the process of genistein and kaempferol binding to β-lactoglobulin [34]. Furthermore, according to ultrafiltration measurements, dimers and trimers of catechins were reported to interact mainly with bovine serum albumin via hydrophobic interactions [30]. Moreover, polyphenols preferentially bind to basic PRPs through the hydrophobic interaction of exposed galloyl rings with the pyrrolidine ring of the proline residues [41]. The flat hydrophobic surfaces of proline residues provide sites for interaction with the similarly flat hydrophobic ring regions of the galloyl groups [53]. These interactions could be complemented by hydrogen bonds, which would play an important role in reinforcing and stabilizing the complexes [51]. Due to proline, the proteins are hydrogen bond acceptors as the nitrogen lies near the carbonyl group. This causes strong hydrogen bonds in tannins-proteins complexes [54]. For instance, the polyphenolic structure of the tea polyphenols was found to form strong hydrogen bonds, enabling them to bind strongly with proteins [55]. In fact, hydrogen bonds between the H-acceptor sites of the proteins and the hydroxyl groups carried by polyphenols is also reported to strengthen these interactions [56]. Succinctly, hydrophobic associations occur between the planar surfaces of the tannin aromatic rings and hydrophobic sites of proteins such as pyrrolidine rings of prolyl residues. Whereas, hydrogen bonds effect assists to stabilize the complexes, occurring between the hydroxyl group of tannins and H-acceptor sites (carbonyl and $-NH_2$ groups) of proteins [57]. In other words, polyphenols-proteins interactions are mainly non-covalent hydrophobic interactions which may subsequently be stabilized by hydrogen bonds [5].

2.4 Astringency

It has been suggested that secretion of PRPs is the first line of defense of herbivores against dietary tannins. Indeed, tannins inhibit digestive enzymes and impede assimilation of dietary proteins and other nutrients. Their binding by PRPs is believed to prevent these processes and could also reduce tannins consumption by triggering astringency [58]. In effect, astringency is thought to be due to the interaction and precipitation of salivary proteins, in particular PRPs, by tannins [18]. In addition, in mammals, the presence of PRPs in saliva appears to be linked to the consumption of tannins [21]. Furthermore, the parotid saliva of herbivorous and omnivorous mammals, including humans, contains PRPs, whereas these proteins are absent from the saliva of carnivores [26].

Astringency is usually defined as the array of tactile sensations felt in the mouth including shrinking, puckering and tightening of the oral surface [59]. The intensity of perceived astringency plays a key role in determining the acceptability of various food products [60]. An unpleasant astringent taste, as well as precipitates in products may be unappealing for consumers [54]. A better understanding of the physiological processes involved in the astringent response may enable specific products to be formulated for consumers who wish to benefit from the positive health benefits of consuming tannin-rich foods and beverages, but who are averse to the astringent response that they elicit [61].

Chemical structure characteristics of proanthocyanidins, involving degree of polymerization, galloylation, B-ring trihydroxylation and stereochemistry of the subunits, may result in the intensity of astringency sensation [57]. Astringency can be reduced by the presence of some polysaccharides, especially rhamnogalacturonan II and mannoproteins which also impact aggregation properties of tannins (particle size of tannin aggregates) and of tannins-proteins complexes [62]. In fact, there is considerable evidence that polysaccharides influence the interaction between proanthocyanidins and proteins and astringency perception. Proanthocyanidins are perceived less astringent in the presence of polysaccharides [63]. Thereby, polysaccharides would limit the concentration of available proanthocyanidins, and thus astringency would be reduced [64]. Two main mechanisms have been proposed to explain the reduction of astringency provoked by the addition of polysaccharides. One of them has been proposed to be the formation of polyphenol-protein-polysaccharide ternary soluble complex. The other one implies the preferential interaction between the polyphenol and the polysaccharide, competing with protein aggregation. Similarly, it has also been suggested that polysaccharides could develop a secondary structure in solution creating hydrophobic pockets capable of encapsulating and complex polyphenols [65]. In addition to some polysaccharides, astringency is also perceived as more intense at lower pH values [62]. From a molecular perspective, the increased intensity of perceived astringency at lower pH has been tentatively related to an increase in undissociated phenol groups, which may form hydrogen bonds with salivary proteins [66].

3. Impact of the inhibition of proteins activities by polyphenols

3.1 Antioxidant activity

Oxidative stress induces a variety of organ dysfunction as a result of imbalance between the pro-oxidant and anti-oxidant levels in cells and tissues [67]. The unregulated oxidative modification of lipids, proteins, and nucleic acids induced by multiple oxidants has been implicated in the pathogenesis of many diseases [68]. Dietary polyphenols represent the main source of antioxidants for human use [69]. Polyphenolic antioxidants operate by inhibiting the enzymes involved in the overproduction of reactive species [70]. Moreover, the antioxidant activity of polyphenols has been attributed to the capacity of inhibiting pro-oxidant enzymes including cyclooxygenase, and lipoxygenase [71]. Indeed, dietary flavonoids may act as antioxidants *in vivo* by inhibition of pro-oxidant enzymes such as NADPH oxidase of the NOX family, which is considered the major source of superoxide anion ($O_2^{\bullet-}$) in the vascular wall [72]. $O_2^{\bullet-}$ is highly reactive and can dismute to hydrogen peroxide (H_2O_2), both spontaneously and enzymatically via any of the three isoforms of the superoxide dismutase (SOD). In the presence of Fe^{2+}, H_2O_2 can be converted to the highly reactive hydroxyl radicals ($^{\bullet}OH$) that can damage different macromolecules including lipids, proteins and DNA [73]. Hence, the polyphenols, that inhibit the pro-oxidant enzymes, may play a certain role as antioxidant agents (Figure 1).

3.2 Anti-inflammatory effect

As the upstream regulators of the eicosanoid pathway, phospholipase A_2 (PLA_2) enzymes can be targeted to diminish inflammation at an earlier stage in the process [74]. In addition, PLA_2, which is a main constituent of snake venom, exerts various toxicities including cardiotoxicity, myotoxicity, neurotoxicity, and edema [75]. Intense local inflammation is a characteristic associated with envenomation due to the presence of PLA_2 in the snake venom [76]. Persimmon tannin could bind with the key active residues of PLA_2, such as lysine, histidine, tryptophan and tyrosine, restraining their activity and disturbing the structure of PLA_2, thus showing detoxifying effects on snake venom [75]. Da Silva et al. (2009) [76], by relying on of their results, defend the idea that the polyphenolic compounds present a significant capacity of inhibiting the enzymatic activity of PLA_2. They have supposed that the phenolic hydroxyls are bound to the amino acid Asp 49 and influence the capacity of this amino acid to participate in the coordination of the calcium atom that is essential to the catalytic enzyme [76]. Furthermore, EGCG and (−)-epicatechin gallate, containing the gallate moiety, are potent inhibitors of pancreatic PLA_2 activity in vitro. Among the green tea catechins, EGCG was most effective in inhibiting PLA_2 activity. EGCG may bind to the active site of pancreatic PLA_2 or may change the protein conformation by nonspecific binding [77]. Moreover, quercetin was first demonstrated to be an inhibitor of PLA_2 and later it was reported that quercetagetin, kaempferol-3-O-galactoside, and scutellarein also possessed this activity [78].

In mammals, the NF-E2-related factor 2 (Nrf2)-Kelch-like ECH-associated protein 1 (Keap1) system, inherited from ancestors as anti-stress mechanism, is a defense system aimed to preserve cellular homeostasis [79]. Nrf2 is retained in the cytosol until Keap1 is modified by electrophiles.

Keap1 is also called INrf2, for inhibitor of Nrf2, a less common but more descriptive name. While activation of Nrf2 requires modification of Keap1, it was later found that Keap1 does not just simply retain Nrf2. Rather, Keap1 causes the rapid turnover of the Nrf2 transcription factor by assisting in Nrf2 ubiquitinylation (resulting in rapid degradation by the 26S proteasome). When critical cysteine residues in Keap1 are oxidized or covalently modified, Keap1 is inactivated and the Nrf2 transcription factor half-life is extended (phosphorylation is also required for Nrf2 translocation to the nucleus) [80]. Upon modification of specific thiols, Keap1 allows Nrf2 to translocate into nucleus and activate the expression of a wide array of antioxidative metabolizing/detoxifying and many other genes by binding to the antioxidant response element (ARE) in their regulatory regions [81]. Nrf2 target genes include antioxidant enzymes (such as: heme oxygenase-1), drug metabolizing and detoxification enzymes (such as: glutathione-S-transferase) or metabolic enzymes and regulators (such as: glucose-6-phosphate dehydrogenase) [82]. Polyphenols can react with Keap1. In fact, curcumin is one of the most used polyphenolic Nrf2 inducers for the treatment of Alzheimer's disease. At molecular level, curcumin contains electrophilic α,β-unsaturated carbonyl groups which could selectively react with nucleophiles such as cysteine-thiols present at Keap1, thus releasing Nrf2. The interest of curcumin for the treatment of Alzheimer's disease is based not only on its anti-amyloid-β properties but also on its antioxidant and anti-inflammatory properties and its safety profile [83]. Bisdemethoxycurcumin was more active than either curcumin or demethoxycurcumin in inducing Nrf2-mediated induction of heme oxygenase-1 [84]. In addition, EGCG can inhibit aryl hydrocarbon receptor regulated genes and induce Nrf2-regulated antioxidant enzymes, thus providing protection against polychlorinated biphenyls-induced inflammatory responses in endothelial cells [85]. Furthermore, EGCG attenuates the pathological symptoms of fluoride treated rats by up-regulating Nrf2 expression, and in turn suppresses pulmonary inflammatory cytokines evoked responses. Besides, these findings recommended a potential application of EGCG in pulmonary inflammatory disease therapy. Since, activating this pathway (Nrf2/Keap1) leads to decrease the chances of lung cancer progression, and this will be very useful for the reduction of free radicals induced organs damage by phytochemical therapy [86]. While, nutraceuticals oleuropein and quercetin exhibited hepatoprotective effects against cyclophosphamide induced hepatotoxicity through their anti-inflammatory and antioxidant activities via activation of the Nrf2/heme oxygenase-1 pathway [87]. On the other hand, gallic acid exerted a broad spectrum of potential and beneficial effects including anti-inflammation properties and disturbs protein-protein interaction between Keap1 and Nrf2 which might also contribute to nuclear translocation of Nrf2 [88].

The Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB), a dimeric protein which, in response to stimuli, translocates from the cytoplasm to the nucleus to initiate the expression of several genes which collectively promote multiple inflammation-associated pathologic processes [89]. Most of the main classes of extra virgin olive oil phenols have shown anti-inflammatory effects [90]. NF-κB is likely the major molecular target for the anti-inflammatory effects of polyphenols in the vasculature [91]. In effect, EGCG modulates gene expression by inhibiting various transcription factors including NF-κB [92]. Moreover, rottlerin displayed an inhibitory effect on NF-κB [93]. In addition, many polyphenols including curcumin, resveratrol, pterostilbene, punicalagin, macranthoin

G, salidroside, 4-O-methylhonokiol, lycopene, genistein, obovatol and gallic acid were reported as potent NF-κB inhibitors [94]. From the paragraphs quoted above, we can conclude that the polyphenols, that inhibit PLA_2 and the activities of Keap1 and NF-κB, may play a certain role as anti-inflammatory agents (Figure 2).

3.3 Anti-atherosclerosis potential

Atherosclerosis remains one of the major medical and social problems in the developed countries [95]. It is characterized by the progressive thickening and hardening of medium-sized and large artery walls resulting from fat deposits on their inner lining [96]. Emerging data suggest that polyphenols can regulate cellular lipid metabolism; vascular and endothelial function; haemostasis; as well as platelet function; which represent primary conditions for atherosclerotic plaque formation and development [97].

Atherosclerosis is initiated by endothelial dysfunction predominantly due to the accumulation of apolipoprotein B containing low density lipoproteins (LDL) [98]. Furthermore, LDL accumulation within inner layers, especially intima, results in wall stiffness and thickening. In the next stages of progression, plaque formation inside the wall and the eventual stenosed artery reduces the blood flow [99]. Cholesterol, cholesterol esters and triglycerides are transported within LDL particles from their sites of absorption or synthesis to sites of bioactivity [100]. In fact, it is well known that LDL is the major carrier of cholesterol [101]. Green tea catechins are rapidly incorporated into LDL particles and play a role in reducing LDL oxidation in humans, which suggests that taking green tea catechins is effective in reducing atherosclerosis risk associated with oxidative stress [102]. So, catechins, when incorporated into LDL particles, may play a certain role as anti-atherosclerosis agents.

On the other hand, the regulation of cholesterol production by the body is important in combating cardiovascular disease. The enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase) plays a key role in cholesterol production in the human hepatic system. Drugs that are used for treatment of hypercholesterolemia function based on modulation of the activity of the enzyme [103]. The inhibiting of HMG-CoA reductase leads to a decrease in circulating total cholesterol and LDL-cholesterol concentrations [104]. Bergamot polyphenols can act as HMG-CoA reductase inhibitors, thus mimicking statins action. This has been first suggested for naringin and more recently for melitidin and brutieridin. Structural characteristics of latter compounds allow them to mimic the natural substrates of HMG-CoA reductase and block the rate-limiting step in cholesterol synthesis [105]. Indeed, bergamot juice is rich in melitidin and brutieridin. These flavonoids possess 3-hydroxy-3-methylglutaryl moiety with a structural similarity to the natural substrate of HMG-CoA reductase [106]. From the paragraph quoted above, we can conclude that, HMG-CoA reductase inhibition by polyphenols would reduce the cholesterol level in the blood. From where there would be a reduction in the atherosclerotic plaque formation and development. Thus, the polyphenols, that inhibit HMG-CoA reductase, may play a certain role as anti-atherosclerosis agents (Figure 3).

3.4 Anti-diabetic effect

Nowadays, the number of diabetics is increasing at an alarming rate worldwide [107]. Hydrolysis of starch is one of the main sources of postprandial glucose in the blood, with the enzymes α-amylase and α-glucosidase being involved in starch breakdown [108]. Thereby, inhibition of these starch digestive enzymes can suppress postprandial hyperglycemia by reducing the rate of glucose release and absorption in the small intestine [109].

Hydrophobic interactions, hydrogen bonds and Van der Waals interactions are the predominant forces involved in the complexation of the phenolic compounds with α-glucosidase. For instance, the α-glucosidase inhibition mechanism was recently reported for kaempferol [110]. In addition, punicalagin, ellagic acid and urolithin A showed a very similar dose-dependent inhibition, and much greater than the reference inhibitor for α-glucosidase, acarbose [111]. Furthermore, non-extractable polyphenols also exhibited α-glucosidase inhibitory effect [112]. On the other hand, tea polyphenols can inhibit the activity of α-amylase through binding with the active sites of the enzyme causing competitive inhibition. The binding of inhibitors with α-amylase results in changes in the structure of the enzyme, which may affect its binding properties with starch [113]. Moreover, longan pericarp proanthocyanidins inhibited α-amylase in a dose dependent manner [114]. In addition, B-type oligomeric proanthocyanidins have exhibited excellent inhibition of α-amylase [33]. Furthermore, the inhibition of α-amylase by polyphenols arises as a result of hydrogen bonds between the hydroxyl groups of the phenolic compounds and the catalytic sites of amylase and hydrophobic interactions between the aromatic moieties of polyphenols and the enzyme [115]. From the paragraph quoted above, we can conclude that the polyphenols, that inhibit the α-glucosidase and/or the α-amylase, may play a certain role as anti-diabetic agents (Figure 4).

3.5 Anti-proliferative activity

Quercetin can inhibit tyrosine kinases involved in the change from non-malignant fibroblasts to sarcoma cells and tumor cell proliferation [116]. Gallic acid is able to inhibit the proliferation, migration and invasiveness of cancer cells and induce their apoptosis by affecting, among others, various kinases. EGCG inhibits metalloproteinases MMP-2 and MMP-9, which affect tumor invasion and metastasis [39]. Moreover, other reports suggest that polyphenol-rich extracts have the potential to down-regulate MMP-2 and MMP-9 and suppress migration in human prostate carcinoma DU145 cells [117]. The 67-kDa laminin receptor (67LR) is a cell membrane protein that binds laminin. 67LR expression is higher on tumor cells than on normal cells, and it has been reported that 67LR is overexpressed, among others, in breast cancer, bile duct carcinoma, colorectal cancer, and melanoma cells [118]. EGCG can bind with high affinity to 67LR and through which it can induce some anticancer effects [119]. Hence, the polyphenols, that inhibit some proteins activities involved in specific development of tumor cells, may play a certain role as anticancer agents (Figure 5).

3.6 Neuro-protective effect

Natural polyphenols may exert their neuroprotective effects by targeting multiple proteins and mechanisms [120], through modulation of α-, β- and γ-secretases, inhibition of amyloid-β protein (Aβ) oligomer formation, inhibition of Aβ-induced neurotoxicity and inhibition of Aβ-induced neuroinflammation [121]. In fact, several lines of evidence suggest that accumulation of Aβ by increased production or decreased degradation induces the tau-mediated neuronal toxicity and symptomatic manifestations of Alzheimer's disease. Aβ is produced from its precursor called amyloid precursor protein (APP) through sequential cleavage by β- and γ-secretases. Therefore, with regard to the development of Alzheimer's disease therapeutics, lowering Aβ production by inhibition of β- or γ-secretase activity has been a prime strategy [122]. Polyphenols may inhibit β- and γ-secretases. Indeed, myricetin showed significantly decreased $A\beta_{40}$ and $A\beta_{42}$ levels in the cultured rat primary cortical neuron cells through direct binding and inhibition of β-secretase. Whereas, curcumin inhibits $A\beta_{40}$ and $A\beta_{42}$ formation by inhibiting glycogen synthase kinase 3-mediated phosphorylation of presenilin-1 and γ-secretase activity [123]. Furthermore, EGCG has been reported to down-regulate the activation of extracellular signal-regulated kinase (ERK) and NF-κB in the Aβ-injected mouse brains and subsequently suppress β- and γ-secretase activities inhibiting the β-site amyloid precursor protein leading to amelioration of cognitive dysfunction [120]. Moreover, quercetin, kaempherol, morin, and apigenin directly inhibit β-secretase activity in a concentration dependent manner [121].

Monoamine oxidases A and B (MAOs) are outer mitochondrial membrane enzymes catalyzing the oxidative deamination of a variety of neurotransmitters. MAO-A preferentially deaminates serotonin and norepinephrine, whereas MAO-B deaminates phenylethylamine and benzylamine [124]. The MAO-A isoform is a pharmacological target for the treatment of depression, anxiety, and major depressive disorders, while the MAO-B isoform is a target for the therapy of neurodegenerative disorders such as Parkinson's and Alzheimer's diseases [125]. In effect, since the MAOs metabolise neurotransmitter amines, they have become targets for the treatment of neuropsychiatric and neurodegenerative disorders [126]. Quercetin, apigenin and luteolin had a more potent inhibitory effect on MAO-A than MAO-B [127]. While, homoisoflavonoids have been reported as potent and selective MAO-B inhibitors [128]. In addition, quercetin and myricetin isolated from *Hypericum afrum* together with genistein and chrysin isolated from *Cytisus villosus* have been identified as potent MAO-A and MAO-B inhibitors [124]. Given that, the polyphenols have the ability to cross the blood brain barrier due to their lipophilic nature [129]. From the paragraphs quoted above, we can conclude that the polyphenols, that inhibit the MAO, β- and γ-secretases, may play a certain role as neuro-protective agents (Figure 6).

3.7 Antimicrobial activity

3.7.1 Antiviral activity

Quercetin, a natural nontoxic agent anti-hepatitis C virus (HCV), reduce viral production by inhibiting both the HCV NS3 protease and heat shock proteins essential for HCV replication [130]. Furthermore, several polyphenols, such as caffeic acid phenyl ester, dicaffeoyl quinic acid and dicaffeoyl tartaric acid inhibit the virus-encoded integrase enzyme and show antiviral activity [131]. Moreover, gallic acid showed an activity anti-human immunodeficiency virus through inhibition of retroviral reverse transcriptase [132]. From the paragraph quoted above, we can conclude that the polyphenols, that inhibit viral proteins activities, may play a certain role as antiviral agents.

3.7.2 Antibacterial activity

Polyphenols may inhibit bacterial toxins. In fact, catechins except (−)-catechin inhibited the activity of leukotoxin, with the galloylated catechins having the strongest effect. Pre-incubation of the toxin with the catechins increased the inhibitory action, indicating that the catechins act on the protein, rather than the cell. The secondary structure of leukotoxin was dramatically altered in the presence of catechin, which resulted in an inhibition of toxin binding to cholesterol, an important initial step in the cytotoxic mechanism of the toxin [133]. In addition, pentagalloylglucose, EGCG and gallocatechingallate inhibit binding of *Escherichia coli* heat labile enterotoxin (LT) to its intestinal receptor GM1. The inhibitory activities of these three polyphenols may coincide with the formation of large LT–polyphenol aggregates. Gallocatechingallate and its epimer EGCG are active and contain two galloyl groups. The most active is pentagalloylglucose, the pentahydroxy gallic acid ester of glucose. This suggests that at least two galloyl moieties are required for aggregating activity [134]. Furthermore, resveratrol may inhibit cholera toxin-induced activity directly by associating with cholera toxin and suppressing its enzymatic activity, and indirectly by inhibiting cholera toxin endocytosis into cells [135]. On the other hand, the antimicrobial activity of the sugar beet molasses polyphenols may be due to impaired cellular proteins [136] and that of flavonoids is due to their combination with extracellular and soluble proteins as well as bacterial cell walls [137]. Indeed, the antimicrobial activity of tea polyphenols has been linked to their chemical structure and their ability to form complexes with bacterial membranes and proteins [138]. Moreover, tannins seem to affect bacterial growth in several mechanisms, such as inhibition of extracellular microbial enzymes [139]. Thus, the polyphenols, that inhibit bacterial proteins activities, may play a certain role as antibacterial agents.

3.8 Hepatoprotective activity

Many cytochrome P450s (CYPs) are crucial detoxication enzymes that metabolize drugs [140]. The liver is the richest source of drug metabolism, which is regulated by the expression of drug-metabolism enzymes [141]. Cytochrome P450 family 3 subfamily A polypeptide 4 (CYP3A4) [142]

accounts for approximately 30–40% of total CYPs proteins in the human liver and is responsible for the metabolism of more than 60% of the drugs on the market [140].

In spite of the necessity of oxygen to maintain life, sometimes it can become toxic through the generation of reactive oxygen species, which play an important role in the liver pathology because of lipid peroxidation and DNA damage [143]. Furthermore, CYPs of endoplasmic reticulum start their metabolism within the body by generating the highly reactive trichloromethyl radical ($CCl_3^{\bullet}$) which rapidly reacts with oxygen to form the highly reactive trichloromethylperoxyl radical ($CCl_3OO^{\bullet}$). The later molecule rapidly reacts with lipids to form lipid peroxidation products [144]. On the other hand, the intake of a high-dose green tea polyphenols results in a liver-specific decrease in the CYP3A expression level [145]. In fact, some flavonoids exhibited the selective inhibition toward CYP3A4 rather than other major human CYPs [146]. Moreover, resveratrol seems to inhibit CYP3A4 [147]. Indeed, resveratrol was reported to be an inhibitor of CYP3A4 with an IC_{50} of 20 µM in rat liver microsomes and an IC_{50} of 4 µM in human liver microsomes [148]. Given that, lipid peroxidation was considered the main mechanism by which oxidant stress causes cell death during hepatic ischemia-reperfusion and other liver disease processes [149]. Thereby, the CYP3A4 inhibition by polyphenols would reduce $CCl_3OO^{\bullet}$ generation. From where, there would be a reduction in lipid peroxidation. Hence, the polyphenols, that inhibit the CYP3A4, may play a certain role as hepatoprotective agents (Figure 7).

4. Polyhenols-proteins interactions impact

4.1 Antioxidant activity preservation

Dietary matrix, pH changes, enzymatic activity, interactions with dietary compounds, as well as the nature of each compound, are the factors that have the greatest impact on the stability and release of antioxidant compounds after gastrointestinal digestion [150]. In effect, a number of studies reported that polyphenols-proteins interactions had a masking effect on the free radical scavenging activity of polyphenols [151]. On the other hand, anthocyanins bound to a high protein matrix are protected during transit through the upper gastrointestinal tract allowing greater amounts to be available for delivery to the colon [152]. In addition, a comparative study of several food proteins, which bind to flavan-3-ols showed the prevalence of β-casein as a carrier for EGCG over other common food proteins [37]. In fact, due to polyphenols-proteins interactions, proteins could be carriers of polyphenols through the gastrointestinal tract [5]. These interactions might influence polyphenols antioxidant activity and bioavailability. They could function as carriers of polyphenols through the gastrointestinal tract and protect them from oxidation reactions [51]. So, the polyphenols-proteins interactions may play a certain role in the preservation of the pro-oxidant enzymes inhibition by the polyphenols through the gastrointestinal tract.

4.2 Anti-proliferative activity preservation

Much of the recent work summarized in over 400 review articles has focused on curcumin's efficacy as an anticancer agent in a wide variety of cancers including gastrointestinal, colon, and glioblastoma as examples [153]. Moreover, several plant foods, such as fruits, vegetables, herbal tea and mushroom, have shown inhibitory effects on colon cancer cells [154]. EGCG, a major extractable polyphenol in green tea, when is added to milk remains bioactive and reduces colon cancer cell proliferation at high polyphenol content [155]. On the other hand, β-lactoglobulin is the major whey protein in bovine milk. It has a hydrophobic core, containing eight antiparallel β-strands, which is called the calyx, and is the main binding site in the protein. β-lactoglobulin is resistant to acidity, and digestion by gastric proteases. Therefore, it is an attractive candidate for delivering bioactive compounds and improving their bioavailability [156]. Due to the enhanced intrinsic resistance of β-lactoglobulin to proteolytic degradation, this protein can be a good carrier of various polyphenols in the gastrointestinal tract [157]. Furthermore, different reports confirmed that due to interactions with proteins, polyphenols could be delivered to the lower parts of the gastrointestinal tract. This is a way to increase the bioavailability and bioaccessibility, but also to preserve the anti-proliferative activity of polyphenols [158]. Indeed, when bound to proteins, polyphenols could preserve their anti-proliferative activity which was found for green tea polyphenols [5]. Thus, the polyphenols-proteins interactions may play a certain role in the preservation of the inhibition by polyphenols of some proteins activities involved in cancer development in the colon (See: *3.5 Anti-proliferative activity*).

5. Conclusion

Polyphenols-proteins interactions are mainly non-covalent hydrophobic interactions which may subsequently be stabilized by hydrogen bonds [5]. Moreover, the precipitation of polyphenols-proteins complex is due to formation of sufficient hydrophobic surface on the complex and affected by types of proteins (size, conformation, and charge of the protein), types of polyphenols (size, length, and flexibility), and the number and stereospecificity of binding sites on both polyphenol and protein molecules [151]. The proteins activities inhibition by polyphenols may play a certain role in some of the biological activities of polyphenols, which are: anti-atherosclerosis, anti-inflammatory, anti-diabetic, neuro-protective, antioxidant, anti-proliferative, antimicrobial and hepatoprotective activities. Seeing that, polyphenols may inhibit: pro-oxidant enzymes, PLA_2, HMG-CoA reductase, α-glucosidase, α-amylase, MAO, β- and γ-secretases, extracellular microbial enzymes, CYP3A4, some proteins activities involved in specific development of tumor cells, some proteins activities essential for viral replication, Keap1 and NF-κB activities. On the other hand, polyphenols-proteins interactions may preserve the inhibitory activities of polyphenols on the pro-oxidant enzymes, through the gastrointestinal tract, and on some proteins activities involved in cancer development in the colon. Hence, polyphenols-proteins interactions would ensure the release of a health-relevant dose of polyphenols to the gastrointestinal tract. Finally, both polyphenols-proteins interactions and the proteins activities inhibition by polyphenols may influence the physiological aspect of the polyphenols.

Conflicts of interest

The authors declare no conflict of interest.

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Figure captions

Figure 1. A schema approximated and simplified in order to highlight that the polyphenols that inhibit the pro-oxidant enzymes, such as the NADPH oxidase of the NOX family, may play a certain role as antioxidant agents.

Figure 2. A schema approximated and simplified in order to highlight that the polyphenols, that inhibit the NF-κB activity, may play a certain role as anti-inflammatory agents.

Figure 3. A schema approximated and simplified in order to highlight that the polyphenols, that inhibit HMG-CoA reductase, may play a certain role as anti-atherosclerosis agents and catechins may reduce atherosclerosis risk.

Figure 4. A schema approximated and simplified in order to highlight that the polyphenols, that inhibit the α-glucosidase and/or the α-amylase, may play a certain role as anti-diabetic agents.

Figure 5. A schema approximated and simplified in order to highlight that the polyphenols, that inhibit some proteins activities involved in specific development of tumor cells, may play a certain role as anticancer agents.

Figure 6. A schema approximated and simplified in order to highlight that the polyphenols, that inhibit the MAO deaminating activity, may play a certain role as neuro-protective agents.

Figure 7. A schema approximated and simplified in order to highlight that the polyphenols, that inhibit the cytochrome P450, may play a certain role as hepatoprotective agents.