Plant Based Polyphenol Associations with Protein: A Prospective Review

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This review discusses the classes of plant polyphenols along with their binding mechanisms with protein molecules. Generally, polyphenols bind in covalent and non-covalent orientations with protein molecules. Their addition to the protein usually results in undesirable flavors and tastes inside the proteins. They also affect the color of the food. Plant polyphenols are found to act in a protective way against cardiovascular disease, neurodegenerative diseases, diabetes, and cancer. In addition to redox activity, their modes of action include the inhibition of key enzymes, modulation of transcription factors or cell receptors, and finally, perturbation of protein aggregates. Dietary polyphenols usually play a key role in protein digestion by forming covalent and non-covalent bonds with proteins. In addition, polyphenols and plant phenolics possess the scavenging ability of reactive oxygen species (ROS), including radical/non-radical oxygen species including HOC•, H_2O_2, HOCl, $^1O_2$ (singlet oxygen), and oxidatively generated radicals derived from LDL biomolecules such as ROOC• and oligonucleic acids.

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INTRODUCTION

Polyphenols have been defined as compounds having a large number of di/trihydroxy phenyls units, either in an oligomeric manner or multiple phenolic motifs displayed in a monomeric way. Based on this definition, lignin polymers generally would not be included in the category of polyphenols. The reasons for investigating polyphenols could be the range of basic structure to chemically elaborated complex and transformed oligo/polymeric substances and their biological/physicochemical properties, making them interesting and unique. The question arises as to why plants select heavy metabolite production with different phenolic components; the answer to this question is still debatable and may differ with different polyphenols (Treutter 2006; Hatier and Gould 2008; Lattanzio *et al.* 2008, 2009). Plant polyphenols have various functions, such as plant resistance to pathogens and animals from insects, solar radiation protection, reproduction,

growth, and nutrition ground organisms' interaction (Hagerman and Buttler 1991; Northup *et al.* 1995; Cooper-Driver and Bhattacharya 1998; Harborne and Williams 2000; Hattenschwiler and Vitousek 2000). Seasonal changes and time of evolution allow plants to learn how to cope with environmental changes and pressure by deploying an arsenal of unique metabolisms and endless structural diversity sources (Scalbert and Haslam 1987; Zucker 1983). Various benefits that plant phenolics provide to plants and other organisms could be the result of biochemical properties linked to the phenyl group. This study explains the types and classes of polyphenols, their mechanisms with which they interact with proteins, their binding modes, food structure/functional properties changes, the role through which they extract oxygen from compounds, their future outlook, and the future challenges for research and development of plant polyphenols.

Plant Polyphenols and Their Classes

Haslam (1998) described three classes of polyhydroxphenyl products. Polyphenols represent the plant secondary products, derived from the polyketide pathway or shikimate-derived phenylpropanoid, containing more than a single phenolic ring, and lacking any nitrogen-based functional group in their basic structure. These three classes of "true" polyphenols are as follows: (1) the proanthocyanidins, condensed tannins, including prodelphinidins, profisetinidins, and procyanidins derived by oligomerization of the unit flavan-3-ol like fisetinidal, (epicatechin), EGC (Quideau and Feldman 1996; Okuda *et al.* 2009); (2) the gallo/ellagitannins, hydrolyzable tannins, derived from the shikimate-derived gallic acid metabolism, leading to multiple mono/oligomeric polyphenolic galloyl ester compounds, through phenolic oxidative reaction or esterification and produces sugar type products, mainly D-glucose (Haslam and Cai 1994; Quideau and Feldman 1996; Okuda *et al.* 2009); and (3) phlorotannins, present in red-brown algae (Fig. 4) and derived from oligomerization of phloroglucinol dehydrogenative coupling (Fig. 5) (Ragan and Glombitza 1986; Okuda *et al.* 1991; Glombitza and Schmidt 1999; Sailler and Glombitza 1999). All of these three polyphenol classes are termed tannins.

Binding Between Polyphenols and Proteins

Many polyphenols (especially having high molecular weight) characteristically interact strongly with protein by covalent bonds (irreversible and form new compounds) or non-covalent bonds (reversible and can alter protein structure but not polyphenol structure) (Jia *et al.* 2017). Non-covalent bonding includes hydrogen bonding, hydrophobic links, and ionic binding and depends on the protein/polyphenol nature and food product conditions (pH and salts). In different studies, the bonding type of protein-polyphenol is not specified and can be a mixture of both bonding types, depending on different conditions (Le Bourvellec and Renard 2012; He *et al.* 2015).

Covalent Bonding between Polyphenols and Proteins

Protein-polyphenol covalent bonding requires an oxidative environment. Polyphenol must be oxidized to quinone before reacting with nucleophilic protein groups, and food *o*-quinones can be formed enzymatically (phenol oxidases and peroxidases) or non-enzymatically (by autoxidation) catalyzed by Cu and Fe trace levels (Singleton 1985; Waterhouse and Laurie 2006; Zhang *et al*. 2018). The intermediate formation of the semiquinone radical is a consequence of the oxidation (Fig. 1; Reactions 1 and 2).

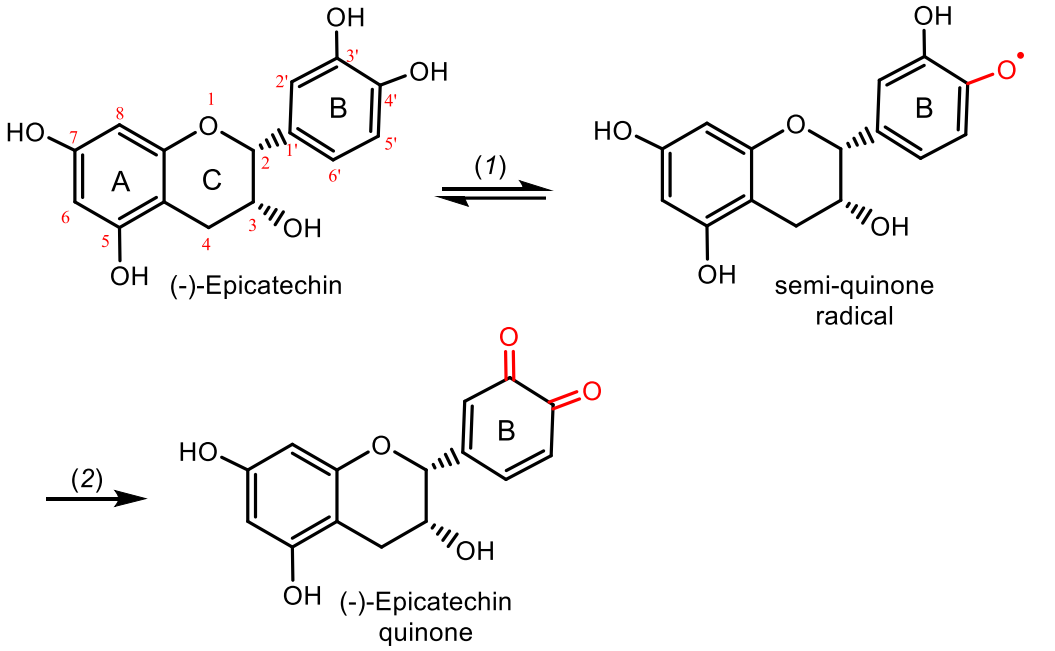

Fig. 1. Reactions of polyphenols with different food components, illustrated by the flavan-3-ol, (-)-epicatechin, which is present in *e.g.*, green tea, grapes, wine, and beer. Reactions 1 and 2 show the oxidation of epicatechin to a semiquinone radical followed by a quinone compound (Singleton 1985; Waterhouse and Laurie 2006).

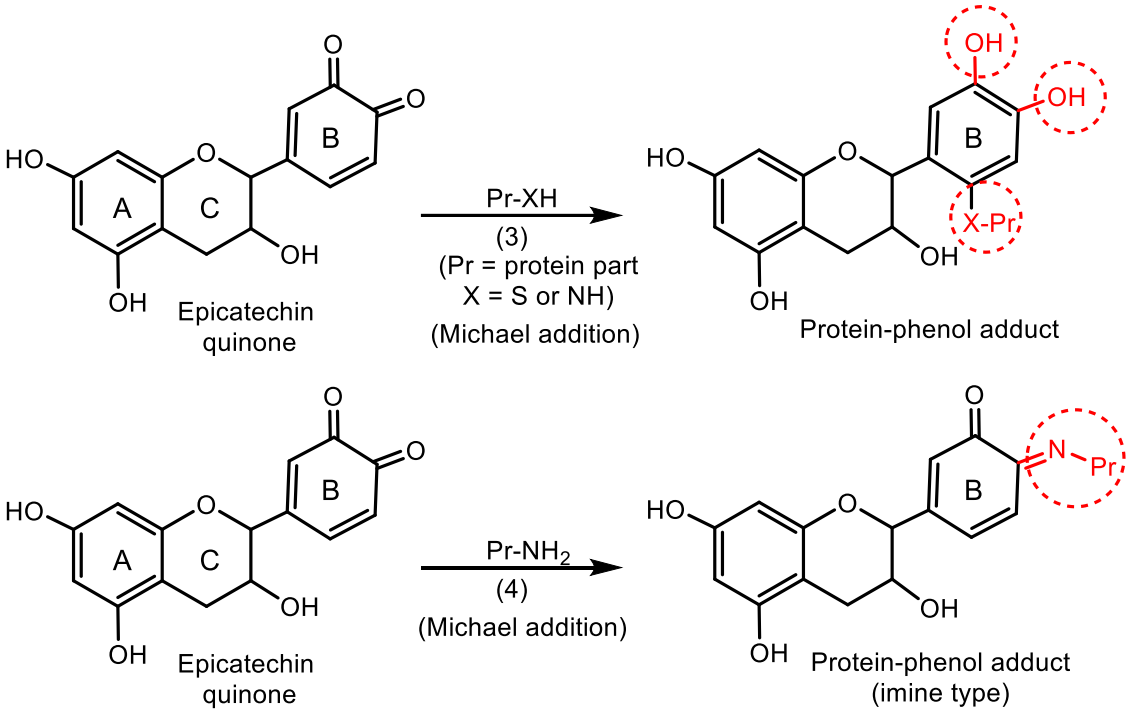

Fig. 2. Reactions of polyphenols with different food components, illustrated by the flavan-3-ol, epicatechin, which is present in, *e.g.*, green tea, grapes, wine, and beer. Reaction 3 shows the Michael addition occurring between a quinone and a nucleophilic group on amino acids, peptides and proteins, illustrated by Pr-XH. Reaction 4 shows the reaction between a quinone and an amine group to form a benzoquinone imine (Pierpoint 1969; Prigent *et al.* 2008; Yin *et al.* 2014).

The oxidation involves semiquinone radical formation, and autoxidation is stimulated at high pH, because of the acid-base equilibrium of readily oxidized phenol and phenolate (Cilliers and Singleton 1990). *o*-Quinones, strong electrophiles, may react through Michael addition reactions (Reaction-03) with protein, amino acids, and peptides nucleophilic groups or form benzoquinone imines (Reaction-04) by reacting with amines at the quinone carbonyl group (Pierpoint 1969; Prigent *et al.* 2008; Yin *et al.* 2014), as shown in Fig. 2.

The *o*-quinone and thiol group in the Michael addition reaction is used in winemaking, as small thiol compounds (glutathione or cysteine) are added to prevent polyphenol polymerization, resulting in colorless adduct, as also formed in milk and meat (Singleton 1985; Waterhouse and Laurie 2006; Jongberg *et al.* 2011). The amine group reaction with *o*-quinones is slower as compared to thiol groups, described by the rate constant between 4-methylbenzoquinone (4-MBQ) and different proteins and amino acids and related to different studies (Pierpoint 1969; Li *et al.* 2012; Li *et al.* 2016).

The proteins with free thiol groups were found to favor Michael's addition reaction with 4-MBQ with a second-order rate constant at an acidic pH (rate increases with increasing pH) [Table 1] (Jongberg *et al.* 2011). Amine groups reacted too slowly at pH less than 6.5 to determine rate constant but increasing pH to 7-8 resulted in a second-order rate constant, but the reaction rate of *N*-α-acetyl-L-Arg with 4-MBQ was too slow to determine rate constant (Li *et al.* 2016).

Table 1. Second Order Rate Constants for Michael Addition Reactions between Different Amino Acids and 4-MBQ, Proteins and Peptides, BSA, CML, NEM, Serum Albumin, *N*-Ethyl-maleimide

Nucleophilic Group	Compound	$K^2(M^{-1}s^{-1})$[b]	pH[a]
Thiol Group	L-Cys	$7.0 \cdot 10^5$	6.0
	Nα-acetyl-L-Cys	$1.8 \cdot 10^5$	6.0
	Nα-acetyl-L-Cys	$5.2 \cdot 10^5$	6.5
	Glutathione	$5.4 \cdot 10^5$	6.0
Guanidine group	Nα-acetyl-L-Arg	9.5 ± 1.4 Too Low	7.0
Amine group	Amine group	0.7 ± 1	6.5
	L-Gly	2.0 ± 0.3	7.0
	Nε-acetyl-L-Cys	4.0 ± 0.4	7.0
	L-Lys	8.4 ± 0.5	7.0
	Nα-acetyl-L-Cys	0.9 ± 0.1	7.0
	CML	0.9 ± 0.1	7.0

Proteins	Compound	[Thiols][c]	$K^2(M^{-1}s^{-1})$[b]	pH[a]
With free thiol Group	Human serum albumin	0.21	$(4.8 \pm 0.2)\ 10^3$	7.0
	BSA	0.38	$(3.1 \pm 0.2)\ 10^4$	7.0
	BSA (NEM treated)[d]	0.16	$(1.0 \pm 0.1)\ 10^4$	7.0
With amine groups	α-Lactalbumin	--	$(4.0 \pm 0.2)\ 10^2$	

[a]The most neutral pH values are included, Reactions with pH > 6.5 were investigated by the stopped flow; [b]Reactions with amines at pH < 7.0, were slow and are obtained from previous work of Yan *et al.* (2009), except for CML which is from the previous works such as Nikolantonaki and Waterhouse (2012); [c]Concentrations of Thiol has been determined from Ellman Assay; [d]NEM is to block thiol group in BSA.

Polyphenols have the potential to react with proteins at pH ≥ 7. However, the quinone reaction with thiol groups in wine takes place at pH 3.2 to 3.5 (aroma compounds), in mode wine at pH 3 to 8 (amino acids and peptides), in Cys-aqueous solution at pH 2.7 to 5.0, and in bovine serum albumin (BSA) at pH 6.5 to 7.0 (Li *et al.* 2016; Ma *et al.* 2019; Romanet *et al*. 2020). The conditions required for amine-phenol adduct formation are unclear, but as a whole, these studies explain the requirement of high temperature for benzoquinone imine formation and low temperature for Michael's addition reaction, which may be due to polyphenol nature, pH, or ferric ions/oxidizing agents.

The Michael addition reaction occurs on functional groups other than thiol or amine groups, but the reaction rate constants are not known. Prigent *et al.* (2008) found a minor reaction rate of Arg with oxidized chlorogenic acid, which was also confirmed by Pierpoint (1969) and Li *et al.* (2016). The LC-MS/MS on Arg residues of meat protein extracts when incubated with rosmarinic acid and H_2O_2/ascorbic acid/ Fe (III), gives Michael additional products, suggesting the importance of polyphenol nature and reaction conditions (Prigent *et al.* 2008; Tang *et al.* 2017). The Trp and Tyr residues produce chlorogenic acid adducts, showing the reaction of pyrrole and phenol moieties of amino acids with quinones. The most reactive amino groups are Tyr and Lys, then His and Trp, while serine, Arg, methionine, asparagine, threonine, and glutamine are not reactive, excluding Cys (Prigent *et al.* 2008). Numerous studies explain the reactivity of Trp pyrrole groups by quinones. Their reaction degree can be evaluated by intrinsic Trp fluorescence loss, which shows their non-covalent bonding; their covalent bonding can be observed by other methods such as NMR/MS spectroscopy (Rawel *et al.* 2001; Kroll *et al*. 2003; Dufour and Dangles 2005; Tang *et al.* 2017).

Covalent bonding of food polyphenols with proteins can be studied in the systems incubated from 1 to 24 h from 50 °C to room temperature at pH 9. With these conditions and their high reactivity, the Lys and quinones have been modified with each other (Rawel *et al.* 2001; Kroll *et al.* 2003; Comert *et al.* 2017).

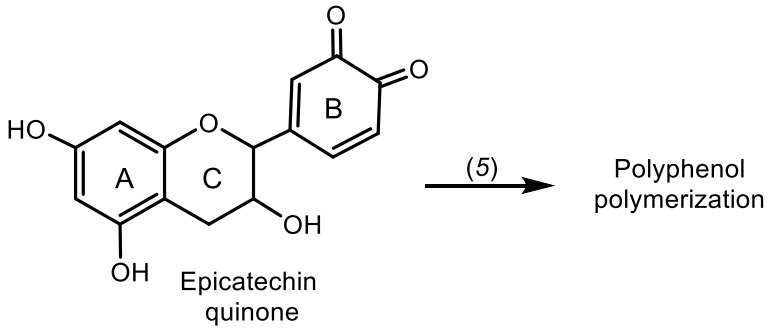

Fig. 3. Reactions of polyphenols with different food components are illustrated by the flavan-3-ol (epicatechin), which are present in green tea, grapes, wine, and beer. Reaction 5 shows polyphenol polymerization (Prigent *et al.* 2008; Jongberg *et al.* 2011; Li *et al.* 2016; Tang *et al.* 2017).

Other methods of covalent bonding between protein/polyphenols include the one-step reaction of mixing the oxidizing agent with protein/polyphenol or a two-step reaction in which polyphenol is oxidized to o-quinone first and then reacts with amino acids or peptides (Prigent *et al.* 2008; Jongberg *et al.* 2011; Li *et al*. 2016; Tang *et al.* 2017). The one-step method gives more protein-polyphenol production but causes undesired protein oxidation by oxidizing radical formation or protein structural changes at basic pH. The

two-step reaction includes *o*-quinone oxidation by periodate resin, which can be eliminated by filtration or electrolysis (Jongberg *et al.* 2016; Li *et al.* 2016). The two-step process of polymerization is a standard of L-Cys and 4-MBQ, which is made to measure the formation of the 4-MBQ-thiol in realistic conditions (Fig. 3).

Milk contains 4MC-Cys and imitates UHT-treatment when subjected to heat, whereas unheated milk also has 4MC to 4-MBQ, showing the presence of Michael's addition reaction. Epigallocatechin gallate binding to proteins in UHT treated milk, protein binding to 4MC in stored meat, and polyphenol binding to protein in beer can be shown by protein blot staining with redox agent (nitroblue tetrazolium) (Jansson *et al.* 2017, 2019; Arsad *et al.* 2020; Jongberg *et al.* 2020). NBT with polyphenols addition can also stain milk proteins with blocked thiols, indicating quinone-amino acid reaction, while NBT blot assay can include non-covalent interactions of protein-polyphenols, which can be suppressed by the SDS-PAGE technique (Chen and Hagerman 2005; Jansson *et al.* 2017; 2019).

Non-Covalent Binding

Protein-polyphenol non-covalent binding is due to hydrogen bonding and hydrophobic interaction. Polyphenol hydroxyl group deprotonation, which takes place at an alkaline pH, is required for electrostatic connections to be undetectable in foods. (Le Bourvellec and Renard 2012; Jaldappagari *et al.* 2013). The protein-polyphenol chemical structure determines the binding nature, so strong binding is visible with proline-rich proteins and hydrophobic polyphenols (Hagerman *et al.* 2003; Le Bourvellec and Renard 2012). Tannins are large plant polyphenol polymers. Their protein interactions are widely studied; many studies reveal the structure-affinity link for non-covalent binding (Hagerman *et al.* 2003; Le Bourvellec and Renard 2012; Jaldappagari *et al.* 2013). Milk proteins (β-lactoglobulin) interact non-covalently with polyphenols, causing enzyme activity inhibition and altered protein structure, while at pH ≥ 6.4 and temperature ≥ 80 °C, (Hasni *et al.* 2011; Kanakis *et al.* 2011; Le Bourvellec and Renard 2012; Jia *et al.* 2017; Khalifa *et al.* 2020). This can be done due to the oxidation of epigallocatechin gallate and covalent bonds at high temperatures with β-lactoglobulin (He *et al.* 2015). Non-covalent binding can be observed by fluorescence quenching, occurring due to the molecular contact between quencher (polyphenol) and fluorophore (protein), mainly due to the static quenching by forming a non-fluorescent complex of protein-polyphenol (Dufour and Dangles 2005; Lakowicz 2006; Le Bourvellec and Renard 2012; Jaldappagari *et al.* 2013; He *et al.* 2015; Jia *et al*. 2017). According to the literature, the Michael addition reaction can be studied using intrinsic fluorescence spectroscopy on Trp residues or polyphenol antioxidative capacity on Trp oxidative loss. Still, it should be reconsidered as the Trp fluorescence signal loss is due to Trp fluorescence quenching by polyphenols or other interferences caused by polyphenols.

Effects of Polyphenol Reaction on Food Quality

Some polyphenols create undesirable flavor and taste caused by the Maillard reaction and lipid oxidation, which is due to the antioxidative function of carbonyl trapping. (Colahan-Sederstrom and Peterson 2005; Jansson *et al.* 2017). Polymeric polyphenols such as tannins and proanthocyanidins cause astringency, but they can also be caused by phenolics and monomeric polyphenols. The astringency sensation is caused by the interacting ability of polyphenols with salivary proteins (Chen and Hagerman 2005).

Bitterness can be lessened by polymerization, but little flavonoid configuration differences can significantly reduce sensory properties and some other values such as ionic strength, viscosity, pH, and sweetness. Ethanol content also affects astringency and bitterness (Lesschaeve and Noble 2005). Thus, polyphenols must be carefully used with an active and appropriate dose of solubility.

Polyphenol-induced Changes of Color in Food Products

The polyphenol type and amino acid site determine the color change caused by Michael's addition reaction, as the thiol group makes products of red/green color, depending on the polyphenol used (Colahan-Sederstrom and Peterson 2005; Pierpoint 1969; Li *et al.* 2016; Waterhouse and Laurie 2006). Epigallocatechin gallate tea extract addition to UHT milk makes a product of red color, while the reaction of amine groups with chlorogenic acid makes the green color product, which is particularly important during alkaline protein extraction (Prigent *et al.* 2008; Bongartz *et al.* 2016). Free Cys addition reduces green color formation, as it competes with Lys at pH 8 to 9 for chlorogenic acid quinones (Liang and Were 2020).

Changes in Protein Structure and Functionality by Polyphenol Bonding

The denaturing temperature and surface activity (charge, hydrophobicity) can be affected by polyphenol-protein conjugation, which can be re-oxidized to undergo second Michael addition with other proteins to make large protein polymers when occurring at different sites (Jongberg *et al.* 2011; Kroll *et al.* 2013; Cao and Xiong 2015; Jongberg *et al.* 2015; Tang *et al*. 2017). These reactions are shown in Fig. 4 (Reactions 6 and 7). The re-oxidization of the conjugated polyphenol undergoes a second Michael addition, resulting in a polyphenol-mediated protein cross-link as shown in Fig. 5 (Reaction 8).

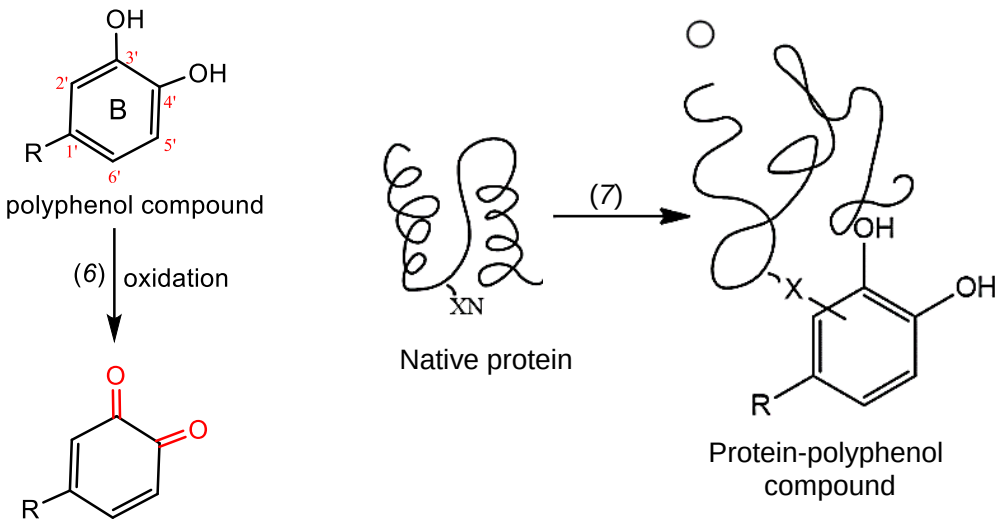

Fig. 4. Effect of polyphenol reactions on protein structure. -XH denotes a nucleophilic group on a protein. Reaction 6 shows the oxidation of polyphenol to *o*-quinone. Reaction 7 shows Michael addition of *o*-quinone to a native protein to form a protein-polyphenol compound, which is likely to change protein folding and structure (Jongberg *et al.* 2011; Kroll *et al.* 2013; Cao and Xiong 2015; Jongberg *et al.* 2015; Tang *et al*. 2017).

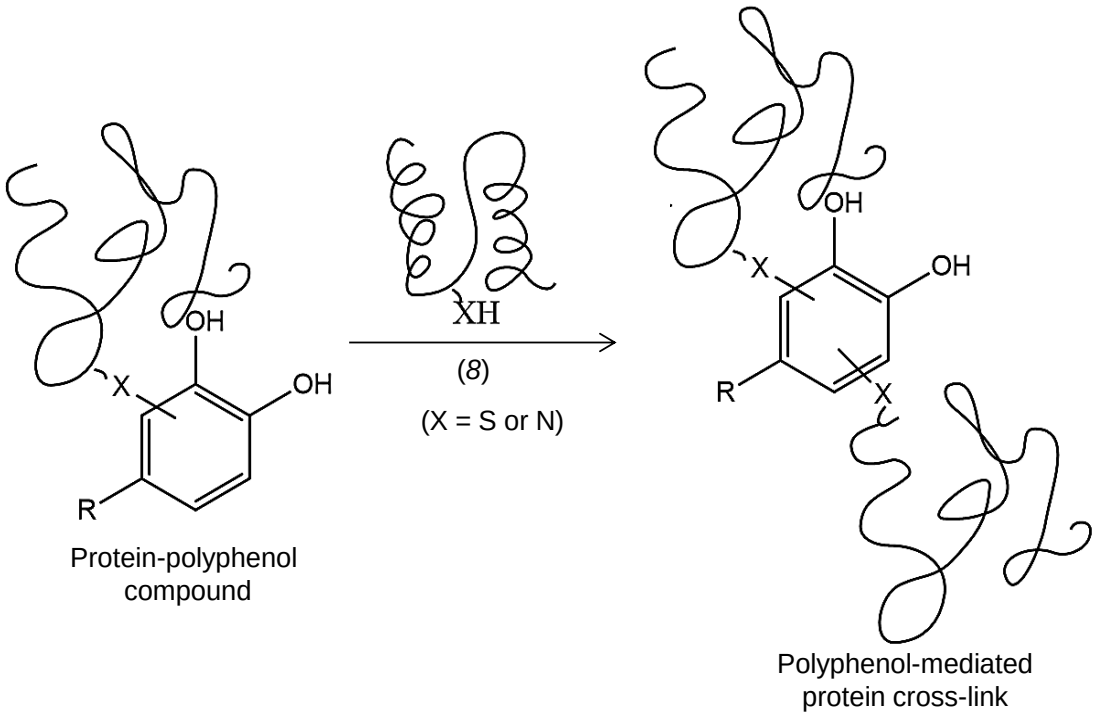

Fig. 5. Effect of polyphenol reactions on protein structure. -XH denotes a nucleophilic group on a protein. Reaction 8 shows a second Michael addition with another protein to form a phenol-mediated protein cross-linked compound.

The occurrence of this reaction at the same protein leads to large protein polymers (Tang *et al.* 2017; Jongberg *et al.* 2020), as shown in Fig. 6 (Reaction 9).

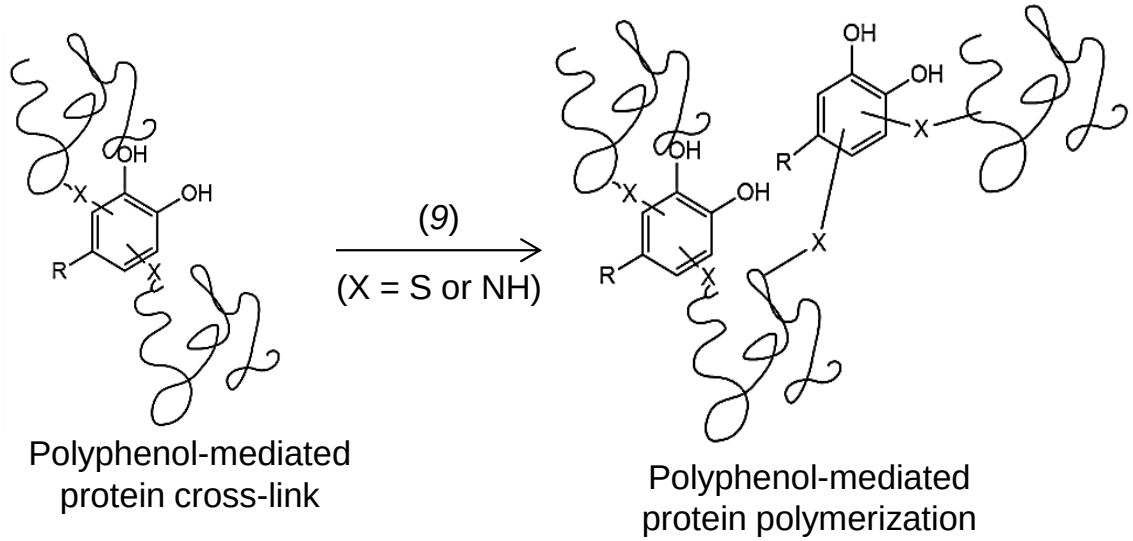

Fig. 6. Effect of polyphenol reactions on protein structure. -X denotes a nucleophilic group on a protein. Reaction 4 shows phenol-mediated protein polymerization occurring after multiple Michael addition reactions, which is likely to change protein functionality and digestibility (Tang *et al.* 2017; Jongberg *et al.* 2020).

Two binding sites are required for polyphenol-mediated protein polymerization, while others such as epicatechin require three sites and rosmarinic acid requires six sites and rosemary extract requires only one site, allowing only one Michael addition reaction and no obvious protein polymerization.

Protein functionality can be changed by polyphenol bonding degree to protein and polyphenol concentration, which improves myofibrillar protein gelation and *vice versa* (Cao and Xiong 2015). Polyphenol-protein binding can also affect other functional qualities including water-binding capacity, textural properties, protein solubility, thermal stability, and emulsification (Ali *et al.* 2013; Cao and Xiong 2015; Jongberg *et al.* 2015). The UHT milk stability during storage can be improved by adding green tea extract (Kroll *et al.* 2003; Jansson *et al.* 2019; Keppler *et al.* 2020).

Polyphenols and Proteins

Few plant polyphenols act on plants and humans by their capacity to exert antioxidant activity and ability to form precipitating protein compounds in a non-specific way (Beart *et al.* 1985; Haslam *et al.* 1989; Haslam 1996). Nevertheless, plant polyphenols can act in a protective way against cardiovascular disease (CVD), neurodegenerative diseases, diabetes, and cancer. In addition to redox activity, their modes of action include inhibiting key enzymes, modulation of transcription factors or cell receptors, and finally, perturbation of protein aggregates. Furthermore, they regulate cell function in the areas of proliferation and growth, apoptosis, inflammation, metastasis, angiogenesis, and various immune responses by affecting signal processing (Packer *et al.* 1999; Sang *et al.* 2005; Spencer 2009; Yang *et al.* 2009).

Polyphenol Protein Association

The research on protein-polyphenol interactions includes molecular mechanistic protein precipitation by polyphenol defense methods, action mode of herbal medicines, and astringency (Haslam 1974). The presence of catecholic and pyrogallic units is essential for enzyme precipitation, resulting in hydrogen-bond formation with ketoimide groups of enzyme part of b-pleated sheets. Regarding the structure of gallotannic b-PGG (Fig. 6), it was found that molecules have an optimum binding configuration to the enzyme and polyphenol in a ratio of 1:20 (Haslam 1974). The polyphenol's ability to bind with proteins with proline-rich content was understood, and their molecular interaction with saliva PRPs (proline-rich proteins) was thoroughly examined, especially related to astringency. NMR spectroscopic analyses of polyphenol complexes with peptides mimic the PRP's polyprotein helices and explain the link between mouse salivary PRPs and b- PGG (Murray *et al.* 1994; Charlton *et al.* 1996; Baxter *et al.* 1997). The hydrogen bond deployment between peptide carboxyl group residues, preceding proline molecules, and b-PGG galloyl meta hydroxy group is shown in Fig. 7 (Murray *et al.* 1994; Baxter *et al.* 1997).

The proline residue selection was observed in the complex formation between procyanidin B3 catechin and Gly-Pro-Gly-Gly, but no proline interaction residue was observed. Therefore, several studies on peptides or proteins with polyphenolic compounds have been done to get the details of physicochemical properties governing protein polyphenol complex formation, and the aim was not only the information about astringency but also their binding method to protein affecting their bioavailability and antioxidant activity (Dangles and Dufour 2008; Dufour *et al.* 2007; Rield and Hagerman 2001). The research methods include the techniques of NMR spectroscopy, circular dichroism, FTIS, mass spectrometry, dynamic light, and small-angle X-ray scattering, equilibrium dialysis,

electronic transmission microscopy, size-exclusion chromatography, calorimetry, nephelometry, quartz crystal microbalance and fluorescent quenching (Charlton *et al.* 2002; Edelmann and Lendl 2002; Verg *et al.* 2002; Simon *et al.* 2003; Jobstl *et al.* 2004; Richard *et al.* 2005; 2006; Pascal *et al.* 2007; 2008; Pascal *et al.* 2009). Some of the more prominent and conflicting elements are discussed below.

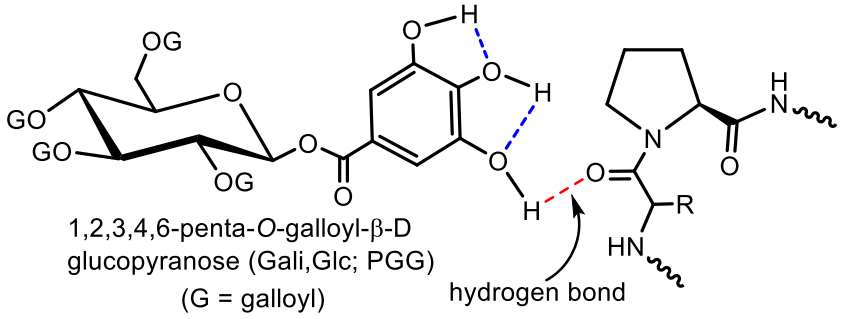

Fig. 7. Interaction between the galloyl group and prolyl via hydrogen bond formation with amide group (Murray *et al.* 1994; Baxter *et al.* 1997)

The dominant cause of the association is the hydrophobic effects, which get more stabilized by hydrogen bonding, and these hydrophobic stacking, in the case of PRPs, produce primary driving forces, which follow hydrogen bond formation between proline carbonyl groups and phenolic hydroxy groups, making the complex (Fig. 7) (Haslam 1974). However, it was also suggested that hydrogen bonding between two groups, instead the large polyphenols bind to many proline sites, in a polydentate way and makes the polyphenol polyphenol-protein complexes (Bazter *et al.* 1997). The nature and quantity of polyphenol-protein interactions depend on the polyphenol physiochemical properties, and one of the causes of protein complexation and precipitation is the galloylation of ECG and RGCG flavonols (Fig. 6) (Pascal *et al.* 2007; Poncet-Legrand *et al.* 2007). These flavan-3-ols galloylated 3.0 are the smallest polyphenols, capable of this activity. Increasing the D-glucopyranose core galloyl group would increase the protein-binding ability until the optimum β-PGG structure is achieved, and further galloylation does not cause any change (Hatano *et al.* 2003). The galloyl group position on the sugar core affects the protein binding ability, as shown by BSA, in which the sugar core affects the α-PGG, having more affinity for BSA than β-diastereomer (Feldman *et al.* 1999; Kawamoto *et al.* 1996). The α-PGG axially oriented O-1 galloyl group has a more open molecular structure, exposing more galloyl units for protein hydrophobic links as compared to β-PGG pentagalloylated species (Feldman *et al.* 1999**)**. This molecule has an optimum binding structure for gallotannins and galloylated glucose. Thus, synthetic β-PGG analog *myo*-inositol has more affinity than β-PGG BSA (Feldman *et al.* 1999).

The polyphenol conformational flexibility encourages interaction with protein. Although α-PGG has the same molecular weight and galloyl group number as tetraarylated/biaryl vescalagin (Canuti *et al.* 2020), BSA has more affinity (Haslam 1974; McManus *et al.* 1985; Spencer *et al.* 1990; Tang *et al.* 2003; Richard *et al.* 2006). Based on these observations, less hydrophilic polyphenol has a better binding affinity with proteins such as collagen, salivary PRPs, bradykinin peptide, casein, or globular protein BSA (Tazeddinov *et al.* 2022). Kawamoto *et al.* (1996) described the BSA two-stage precipitation process from galloylated glucose compounds. The first stage involves the protein polyphenol complexation, having minimum galloyl groups until the formation of a

hydrophobic protein coat, which leads to second stage precipitation until the total galloyl bound unit reaches 30. The precipitated BSA amount increases with an increase in galloyl units up to 85 units, and then BSA completely precipitates without BSA-polyphenolic cross-linking or polyphenol self-aggregation (Dufour and Dangles 2005), as shown in Fig. 8.

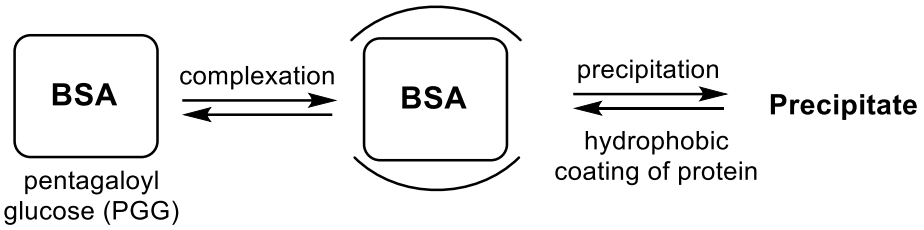

Fig. 8. Precipitation complexation of BSA by gallotannin-like hydrophobic galloylglucopyranoses (Dufour and Dangles 2005).

This relation is due to the polyphenolic hydrophobic character involved, and it could be a reversible and non-specific process. This process could not be applied to all protein/polyphenol like β-PGG and may depend on the experimental conditions, which may not be related to natural systems (McManus *et al.* 1985; Lambrinidis *et al.* 2006). To study the type of polyphenol, Hagerman *et al.* (1998) explained different precipitating complexation modes for proanthocyanidins on the data collected by procyanidin (epicatechin and catechin), which turns out to be more efficient than β-PGG.

EC 16-C is more polar and hydrophilic than β-PGG, so it could precipitate BSA by the action of hydrogen bonds. The other controlling factors are polyphenol hydrophilic character, protein binding site number, and overall size (Hagerman *et al.* 1998; Simon *et al.* 2003; Zucker 1983; Hagerman *et al.* 1998; Sarni-Manchado *et al.* 1999; Hofmann *et al.* 2006; Poncet-Legrand *et al.* 2007). Compact globular proteins have lower proanthocyanidin affinity, due to the protein flexibility (Hagerman and Butler 1981; Hofmann *et al.* 2006).

Although *C*-glucosidic ellagitannins (castalagin and granidins) have strained conformation and are poor BSA protein precipitators, their affinities for proline-rich gelatin are 50% and 30% lower, respectively, than flexible EC 16-C procyanidins (Hofmann *et al.* 2006). The higher flexibility of gelatin could be due to structural rigidity compensation of ellagitannins by protein wrapping around polyphenol. Thus, both physical and chemical properties of polyphenols (flat, hydrophobic, disclike, and flexible like β-PGG and gallotannins), (spherical, hydrophilic, and rigid like ellagitannins) and (threadlike, elongated, flexible, and hydrophilic like condensed tannins) are determining parameters for polyphenol interactions. To study the combination of match and mismatch, affinities could be observed, and protein-polyphenol complexation and precipitation should also be considered. The protein surface dissociation constants exceed the micromolar range and result in stronger interaction, depending upon the involved protein and polyphenol that can bind in 1:1 complex, when having strong affinity. For example, for studying the inhibition mechanism of mitochondrial ATP synthase/ATPase by polyphenols, quercetin and piceatannol were collected by Zheng and Ramirez (2009). These polyphenols inhibit the F1-ATPase rotary mechanism by binding to the annulus inside the surface made from protein subunits (a and b), and this binding site acts as a hydrophobic site between the bTP subunit and g subunit (Gledhill *et al.* 2009).

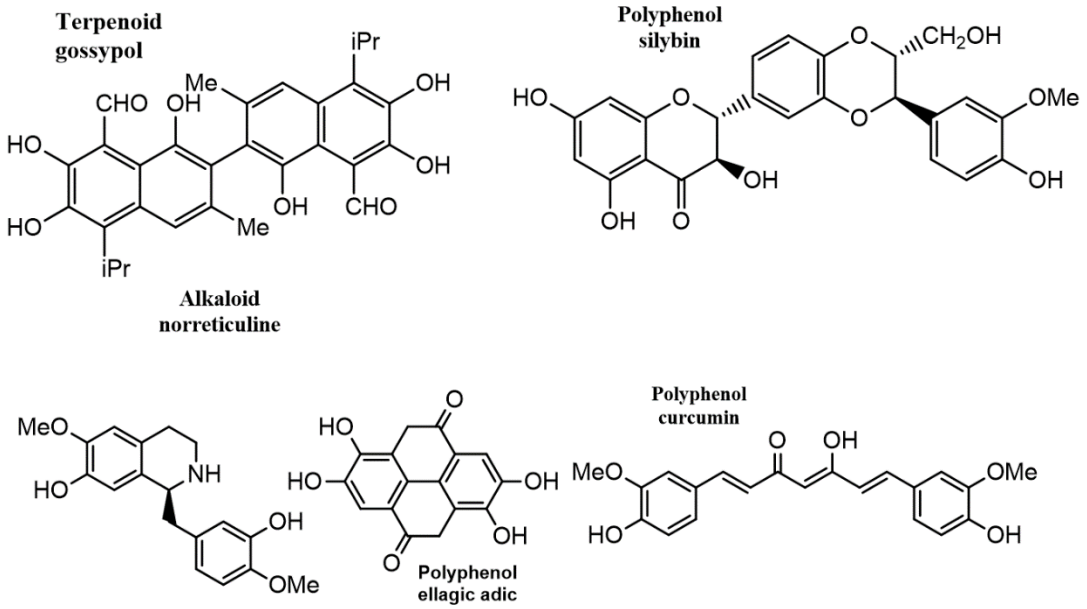

Fig. 9. Polyphenols (Plants) (Cozza *et al.* 2006; Skrzypczak-Jankun *et al.* 2006)

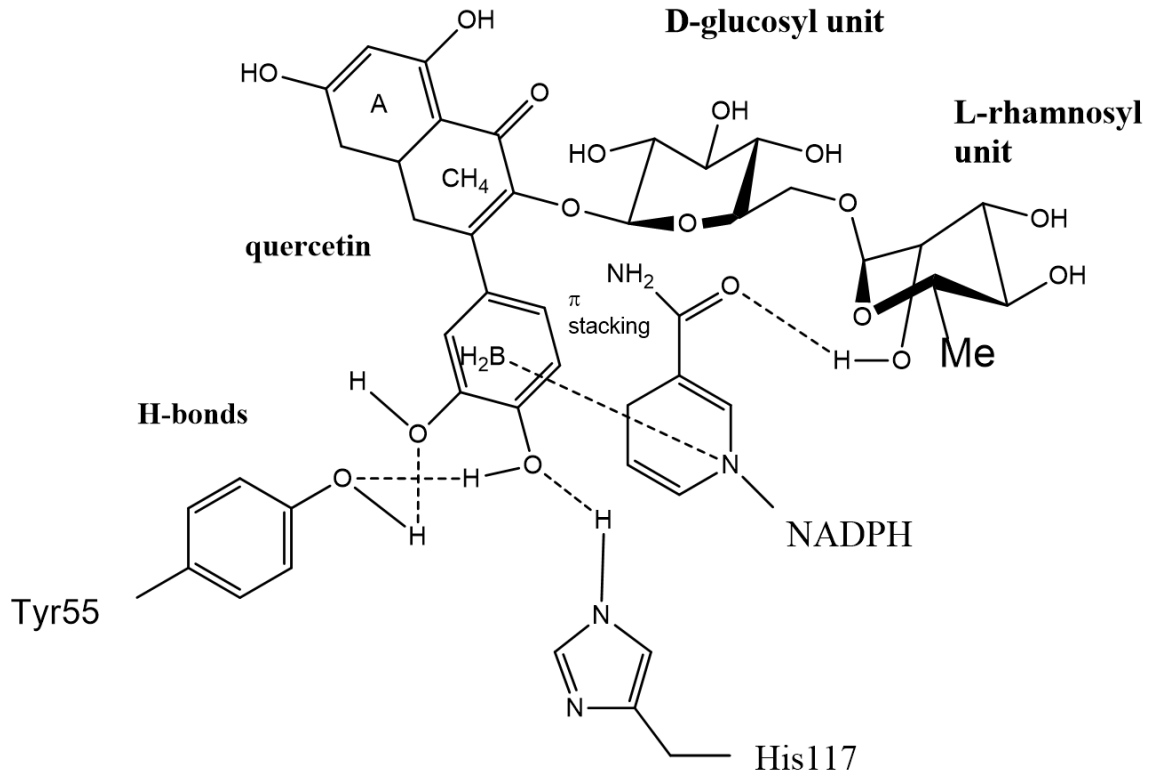

Fig. 10. Interactions between π-stacking and hydrogen bonding within bovine prostaglandin F synthase in the presence of enzyme cofactor NADPH (Komoto *et al.* 2004)

All bound polyphenols adopt planar and distorted conformations and show the same binding mode of molecular features of quercetin and resveratrol, where polyphenols also bind to hydrophobic pockets and make hydrogen bonding between amino acids and phenolic hydroxy groups (Klabunde *et al.* 2000; Walker *et al.* 2000; Buryanovskyy *et al.* 2004; Hofmann *et al.* 2006; Holder *et al.* 2007; Cozza *et al.* 2006; Skrzypczak-Jankun 2006; Kumamoto *et al.* 2009) by arginine residue from ER ligand-binding domain (Yearley *et al.* 2007).

Molecular targets of tea polyphenol EGCG were studied, and it was observed that there was binding of metastasis-laminin tumor cell with nanomolar KD value. The CD3 mediated T-cell leukemia receptor is regulated by EGCG by the enzyme inhibition of tyrosine kinase (Tachibana *et al.* 2004; Imeda *et al*. 2008; Shim *et al.* 2009). Rutin, quercetin 3-*O*-glucosidase (Fig. 8) inhibits prostaglandin F synthase binding to enzyme hydrophobic site. The X-ray crystal structure of the complex formed between the NADPH, rutin, and bovine PGFS shows the hydrogen bond. This inhibitor adopts a 'U-shape' with p-stacking interaction in the active site between NADPH ring and the B ring (Fig. 10) (Komoto *et al.* 2004). Phytoestrogens contain isoflavone genistein and bind with estrogen receptors, which have many health benefits (Komoto *et al.* 2004; Lambrinidis *et al.* 2005). Hydrogen bonds are formed between negatively charged OH groups and positively charged NH/OH water hydrogen atoms, and genistein is locked

Polyphenols such as ellagitannins have been studied for their binding evaluation to proteins. Kashiwada *et al.* (1993**)** explained the inhibition mechanism of human DNA topoisomerase 11a (Top 2a) by molecules of ellagitannins (Quideau *et al.* 2005). Vescalin (*C*-glucosidic ellagitannins), shows more inhibition ability towards Top 2a than etoposide (standard Top 2a Inhibitor), with DNA decantation and inhibition at 10 mm (Quideau *et al.* 2005). These studies explain the real-time interaction of Top 2a and polyphenol, and analytical methods are developed based on surface plasmon resonance (SPR) spectroscopy, allowing the discrimination between specific and non-specific interaction. This SPR-based system causes vescalin attachment to SPR sensor chip by sulfhydryl thioether spaces, installed by *C*-glucosidic ellagitannin chemoselective reactivity. There was no BSA-streptavidin interaction observed from vescalin interaction (Douat-Casassus 2009).

Resveratrol and tea 3-*O*-galloylated flavonol EGCG has anti-fibrillogenic ability, fighting against neurodegenerative pathology misfolding disorders in the human protein. The EGCG directly binds to polypeptides (amyloid-β and α-synuclein), preventing their aggregation into toxic fibrillar Aβ and αS compounds involved in Alzheimer's or Parkinson's disease (Ehrnhoefer *et al.* 2008). Highly stable oligomers were found in the peptide region by self-assembling monomers (Ehrnhoefer *et al.* 2008).

Hauber *et al.* studied the potential evaluation of EGCG. The peptide segment (extracted from prostatic acidic phosphatase) was targeted. It is secreted in large quantities in human semen, and increases HIV-1 infection, which is due to b-sheet-rich amyloid fibrils (Mnch *et al.* 2007; Hauber *et al.* 2009). It was also observed that EGCG is a strong antagonist against fibrillar structure activities by degrading them and enhancing HIV-1 infection property. Its bonding with DAPH-12 (compound inhibiting prionogenesis) improve eradicating capacity of prions. It was found that DAPH-12 directly stimulates the EGCG-resistant prions and links with EGCG to inhibit the prion strain structure formation. EGCG anti-fibrillogenic activity comparison with other polyphenols reveals the pyrogallol groups on compact polyphenols enabling aromatic, hydrogen-bonded, polypeptide interactions, undergoing fibril production, determines their potency (Porat *et al.* 2006).

These observations of polyphenols with prionogenic/amyloidogenic polypeptides show therapeutic action of polyphenol fibrillogenesis for neurodegenerative treatment.

HEALTH ASPECTS OF POLYPHENOL REACTIONS

Changes in Protein Digestibility

Studies on the polyphenol role in protein digestibility suggest that protein digestibility is decreased by the polyphenol presence both by covalent and non-covalent binding (Rohn *et al.* 2002; He *et al.* 2007; Velickovic and Stanic-Vucinic 2018). The protein may be less digestible due to cleavage site modification of digestive enzyme or by protein polymerization. In addition, polyphenol protein binding may cause protein unfolding, increasing cleavage site exposure, and causing protein digestibility to improve (Velickovic and Stanic-Vucinic 2018). Digestive enzymes can be potentially inactivated *in vitro* by non-covalent polyphenol (Simon *et al.* 2003; Velickovic and Stanic-Vucinic 2018).

Polyphenols as Scavengers for Reactive Oxygen Species (ROS)

The other important feature of polyphenols and plant phenolic is their scavenging ability of reactive oxygen species (ROS), including radical/non-radical oxygen species such as HOC, H_2O_2, O_2-C, HOCl,10_2, and oxidatively generated radicals, derived from LDL biomolecules such as ROOC and ROC, oligonucleic acids, and proteins, having harmful effects (Leake 1997; Harborne and Williams 2000; Li *et al*. 2000; Shi *et al.* 2000; Middleton *et al.* 2000; Ferguson 2001). This antioxidation property is related to the prevention of chronic diseases and other diseases such as CVD, neurodegeneration, carcinogenesis, and skin damage by polyphenolic plants. Plant polyphenol can be used as antioxidants by metal ions chelation including copper (I), copper (II), iron (II), and iron (III) (Lopes *et al.* 1999; Pietta 2000; Sugihara *et al.* 2001; Mira *et al.* 2002; Andjelkovic *et al.* 2006). It showed a protective role and synergistic antioxidant regeneration (Wu *et al.* 1996; Pietta 2000; Fang *et al.* 2002; Zhou *et al.* 2005; Leopoldini *et al.* 2004; Fang and Zhou 2008).

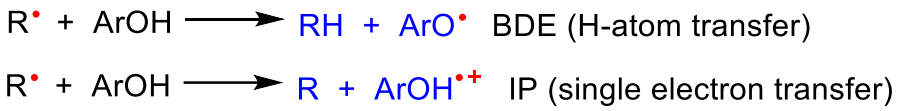

Fig. 11. H-atom transfer (HAT) and single electron transfer through which polyphenols express their anti-oxidant action (Wu *et al.* 1996; Leopoldini *et al.* 2004).

The antioxidant efficiency depends on the H-atom transfer to LOOC and the resulting phenoxy atom stability. The ArOC formation and stability depend upon the parent ArOH. The structure of the compound is determined by the hydroxyl group position, and their implementation in the intramolecular hydrogen bond formation (Heer *et al.* 1999). The single electron transfer to RC radical from ArOH to form a stable cation, which is shown in Fig. 11.

FUTURE OUTLOOK AND CHALLENGES

Plant polyphenol studies, on different levels, have challenges, and despite the progress of polyphenols formed, organic chemists have many challenges in producing complex products. Plant polyphenols are antioxidants that are present in food, used as plant metabolites, able to oxidize into quinonoid species, and able to modify pathogenic biomolecules. If the polyphenol chemopreventive action could be attributed to their antioxidant activity, then they can be used in the production of 'prodrugs' against cancer based on generating toxic compounds. If plant polyphenols miss the therapeutic properties due to a lack of adherence and poor bioavailability, chemists can elaborate on possible analogs to produce drugs from natural products, and the polyphenol-based design drugs, targeting specific proteins, give other research directions. Plant polyphenols are inspiring scientists for anticancer agent research, use of natural antioxidants as food safety, and as antifibrillogenic agents fighting against neurodegenerative diseases and functionalized material with unique properties.

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