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).

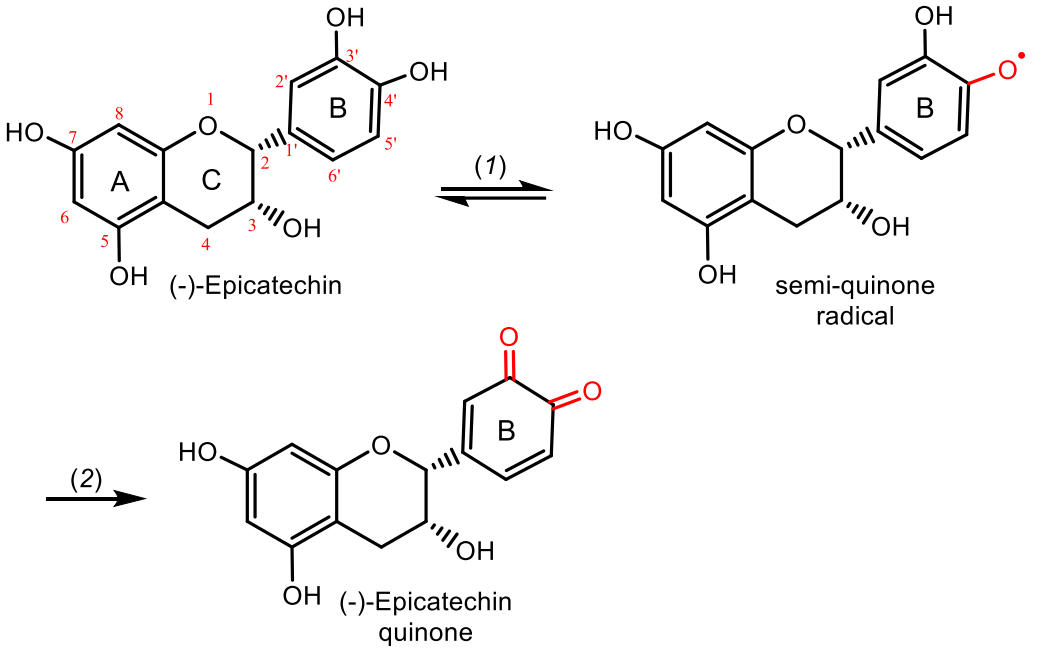

Fig. 1. Reactions of polyphenols with different food components, illustrated by the flavan-3-ol, (-)-epicatechin, which is present in *e.g.*, green tea, grapes, wine, and beer. Reactions 1 and 2 show the oxidation of epicatechin to a semiquinone radical followed by a quinone compound (Singleton 1985;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

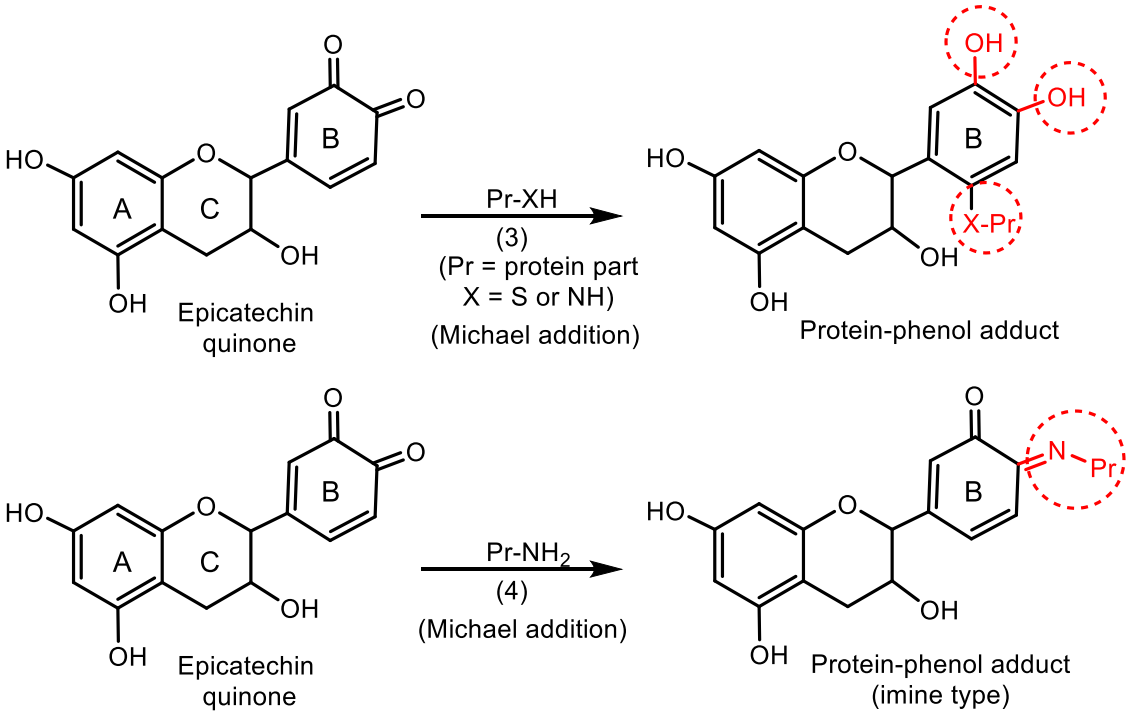

Fig. 2. Reactions of polyphenols with different food components, illustrated by the flavan-3-ol, epicatechin, which is present in, *e.g.*, green tea, grapes, wine, and beer. Reaction 3 shows the Michael addition occurring between a quinone and a nucleophilic group on amino acids, peptides and proteins, 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).

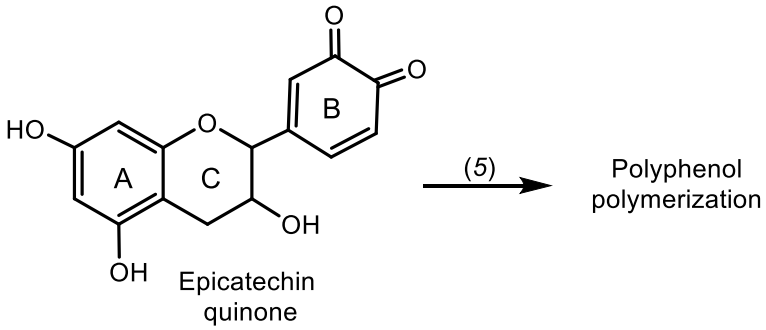

Fig. 3. Reactions of polyphenols with different food components are illustrated by the flavan-3-ol (epicatechin), which are present in green tea, grapes, wine, and beer. Reaction 5 shows polyphenol polymerization (Prigent *et al.* 2008; Jongberg *et al.* 2011; Li *et al.* 2016; Tang *et al.* 2017).

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).

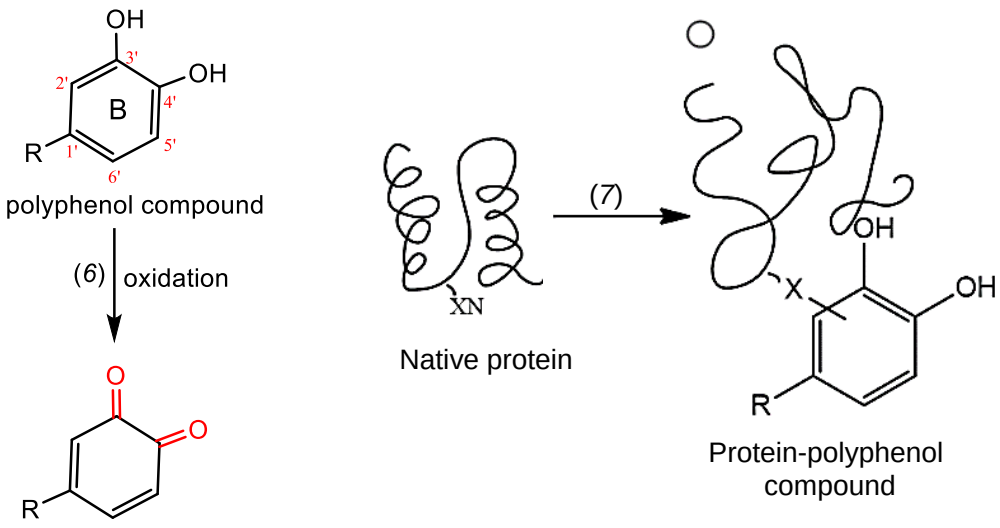

Fig. 4. Effect of polyphenol reactions on protein structure. -XH denotes a nucleophilic group on a protein. Reaction 6 shows the oxidation of polyphenol to *o*-quinone. Reaction 7 shows Michael addition of *o*-quinone to a native protein to form a protein-polyphenol compound, which is likely to change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

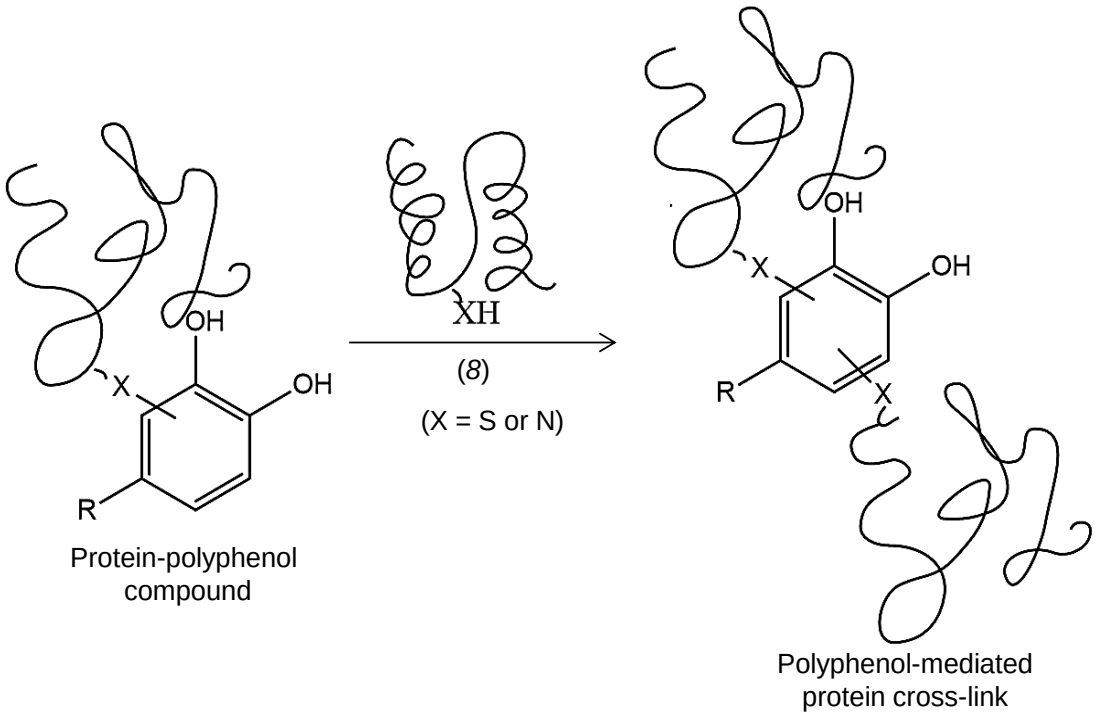

Fig. 5. Effect of polyphenol reactions on protein structure. -XH denotes a nucleophilic group on a protein. Reaction 8 shows a second Michael addition with another protein to form a phenol-mediated protein cross-linked compound.

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).

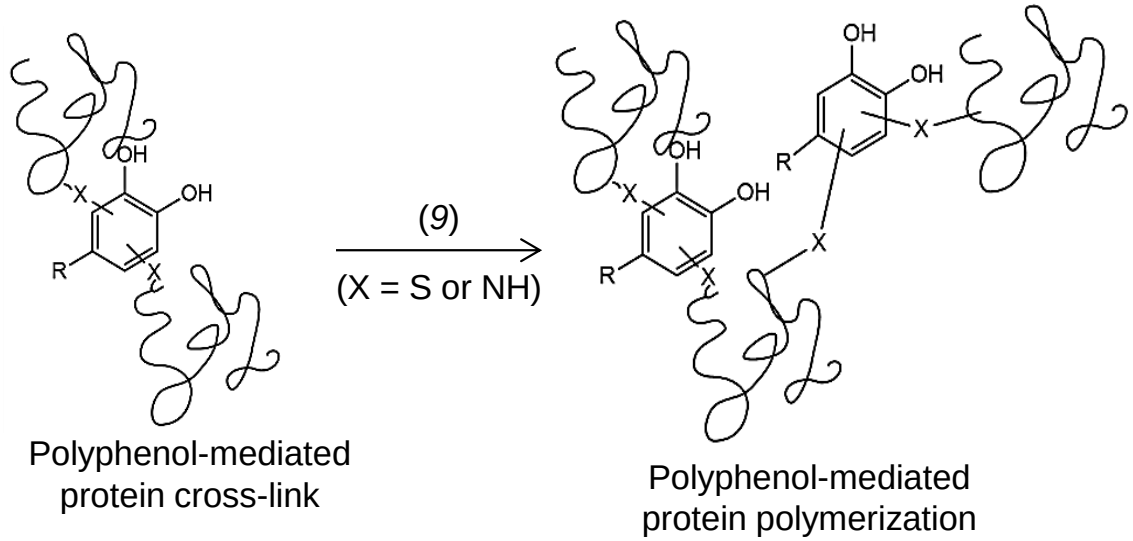

Fig. 6. Effect of polyphenol reactions on protein structure. -X denotes a nucleophilic group on a protein. Reaction 4 shows phenol-mediated protein polymerization occurring after multiple Michael addition reactions, which is likely to change protein functionality and digestibility (Tang *et al.* 2017;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

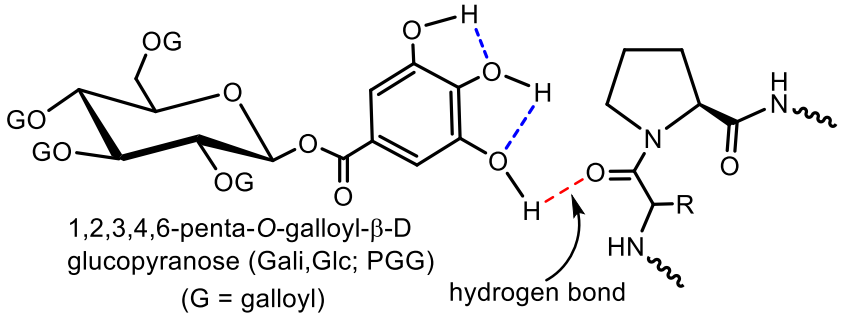

Fig. 7. Interaction between the galloyl group and prolyl via hydrogen bond formation with amide group (Murray *et al.* 1994; Baxter *et al.* 1997)

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.

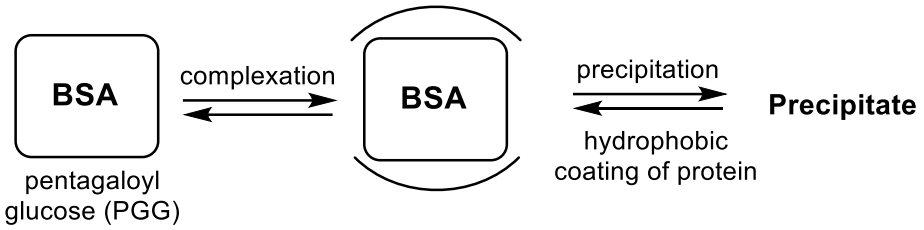

Fig. 8. Precipitation complexation of BSA by gallotannin-like hydrophobic galloylglucopyranoses (Dufour and Dangles 2005).

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).

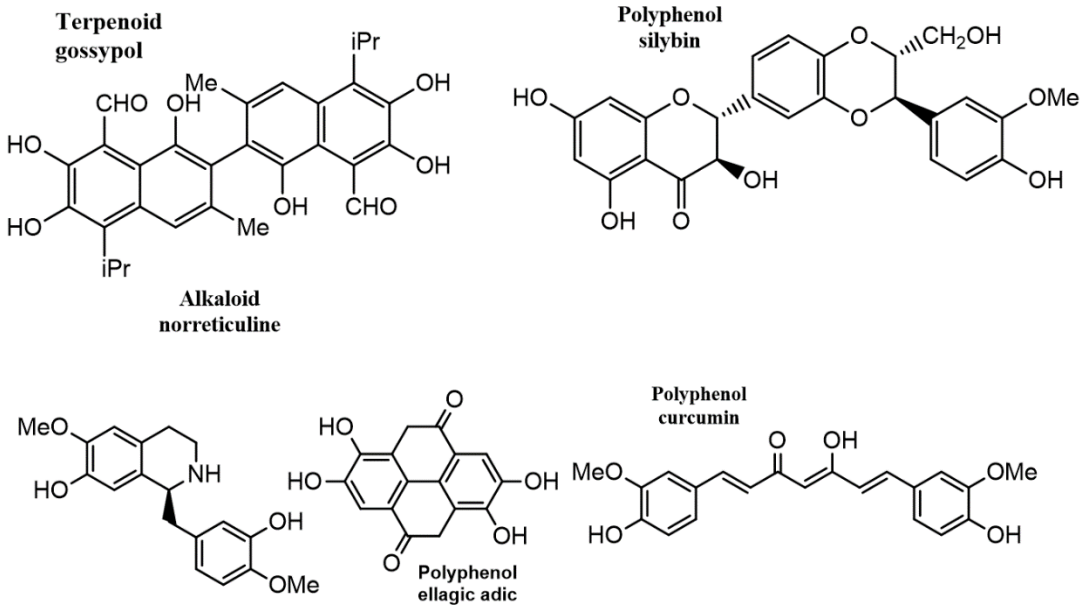

Fig. 9. Polyphenols (Plants) (Cozza *et al.* 2006; Skrzypczak-Jankun *et al.* 2006)

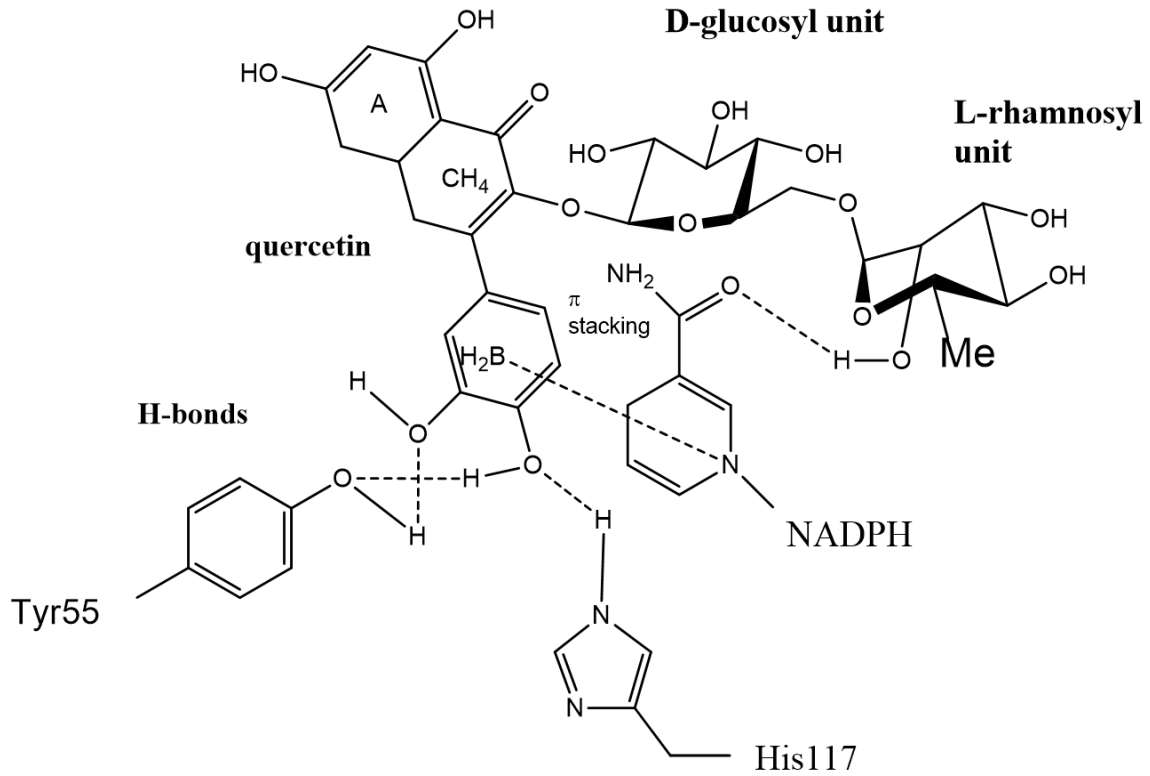

Fig. 10. Interactions between π-stacking and hydrogen bonding within bovine prostaglandin F synthase in the presence of enzyme cofactor NADPH (Komoto *et al.* 2004)

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).

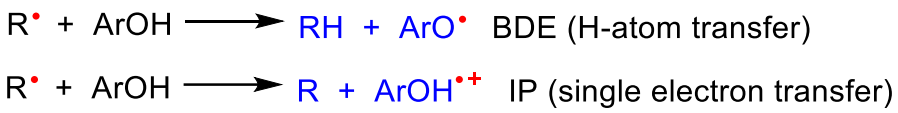

Fig. 11. H-atom transfer (HAT) and single electron transfer through which polyphenols express their anti-oxidant action (Wu *et al.* 1996; Leopoldini *et al.* 2004).

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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REFERENCES CITED

Ali, M., Homann, T., Khalil, M., Kruse, H.-P., and Rawel, H. (2013). "Milk whey protein modification by coffee-specific phenolics: Effect on structural and functional properties," *Journal of Agricultural and Food Chemistry* 61(28), 6911-6920. DOI: 10.1021/jf402221m

Andjelkovic, M., Van Camp, J., De Meulenaer, B., Depaemelaere, G., Socaciu, C., Verloo, M., and Verhe, R. (2006). "Iron-chelation properties of phenolic acids bearing catechol and galloyl groups," *Food Chemistry* 98(1), 23-31. DOI: 10.1016/j.foodchem.2005.05.044

Arsad, S. S., Zainudin, M. A. M., de Gobba, C., Jongberg, S., Larsen, F. H., Lametsch, R., Andersen, M. L., and Lund, M. N. (2020). "Quantitation of protein cysteine-phenol adducts in minced beef containing 4-methyl catechol," *Journal of Agricultural and Food Chemistry* 68(8), 2506-2515. DOI: 10.1021/acs.jafc.9b07752

Baxter, N. J. Lilley, T. H., Haslam, E., and Williamson, M. P. (1997). "Multiple interactions between polyphenols and a salivary proline-rich protein repeat result in complexation and precipitation," *Biochemistry* 36(18), 5566-5577. DOI: 10.1021/bi9700328

Beart, J. E., Lilley, T. H., and Haslam, E. (1985). "Plant polyphenols—Secondary metabolism and chemical defence: Some observations," *Phytochemistry* 24(1), 33-38. DOI: 10.1016/S0031-9422(00)80802-X

Bongartz, V., Brandt, L., Gehrmann, M. L., Zimmermann, B. F., Schulze-Kaysers, N., and Schieber, A. (2016). "Evidence for the formation of benzacridine derivatives in alkaline-treated sunflower meal and model solutions," *Molecules* 21(1), article no. 91. 10.3390/molecules21010091

Buryanovskyy, L., Fu, Y., Boyd, M., Ma, Y., Hsieh, T.-c., Wu, J. M., and Zhang, Z. (2004). "Crystal structure of quinone reductase 2 in complex with resveratrol," *Biochemistry* 43(36), 11417-11426. DOI: 10.1021/bi049162o

Canuti, V., Cecchi, L., Khatib, M., Guerrini, L., Mulinacci, N., and Zanoni, B. A. (2020). "New extract from pomegranate (*Punica granatum* L.) by-products as a potential oenological tannin: Preliminary characterization and comparison with existing commercial products," *Molecules* 25, article no. 4460. DOI: 10.3390/molecules25194460

Cao, Y., and Xiong, Y. L. (2015). "Chlorogenic acid-mediated gel formation of oxidatively stressed myofibrillar protein," *Food Chemistry* 180(1), 235-243. DOI: 10.1016/j.foodchem.2015.02.036

Charlton, A. J., Baxter, N. J., Lilley, T. H., Haslam, E., McDonald, C. J., and Williamson, M. P. (1996). "Tannin interactions with a full-length human salivary proline-rich protein display a stronger affinity than with single proline-rich repeats," *FEBS Letters* 382(3), 289-292. DOI: 10.1016/0014-5793(96)00186-X

Charlton, A. J., Haslam, E., and Williamson, M. P. (2002). "Multiple conformations of the proline-rich protein/epigallocatechin gallate complex determined by time-averaged nuclear Overhauser effects," *Journal of the American Chemical Society* 124(33), 9899-9905. DOI: 10.1021/ja0126374

Chen, Y., and Hagerman, A. E. (2005). "Reaction pH and protein affect the oxidation products of β-pentagalloyl glucose," *Free Radical Research* 39(2), 117-124. DOI: 10.1080/10715760400013789

Cilliers, J. J. L., and Singleton, V. L. (1990). "Caffeic acid autoxidation and the effects of thiols," *Journal of Agricultural and Food Chemistry* 38(9), 1789-1796. DOI: 10.1021/jf00099a002

Colahan-Sederstrom, P. M., and Peterson, D. G. (2005). "Inhibition of key aroma compound generated during ultrahigh-temperature processing of bovine milk via epicatechin addition," *Journal of Agricultural and Food Chemistry* 53(2), 398-402. DOI: 10.1021/jf0487248

Comert, E. D., Akillioglu, H. G., and Gokmen, V. (2017). "Mitigation of ovalbumin glycation in vitro by its treatment with green tea polyphenols," *European Food Research and Technology* 243(1), 11-19. DOI: 10.1007/s00217-016-2717-x

Cooper-Driver, G. A., and Bhattacharya M. (1998). "Role of phenolics in plant evolution," *Phytochemistry* 49(5), 1165-1174.

Cozza, G., Bonvini, P., Zorzi, E., Poletto, G., Pagnano, M. A., Sarno, S., Donella-Deana, A., Zagotto, G., Rosolen, A., Pinna, L. A., Meggio, F., and Moro, S. (2006). "Identification of ellagic acid as potent inhibitor of protein kinase CK2: A successful example of a virtual screening application," *Journal of Medicinal Chemistry* 49(8), 2363-2366. DOI: 10.1021/jm060112m

Dangles, O. and Dufour, C. (2008). "Flavonoid-protein binding processes and their potential impact on human health," in: *Recent Advances on Polyphenol Research*, F. Daayf, and V. Lattanzio (eds.), Wiley-Blackwell, Oxford, pp. 67-87. DOI: 10.1002/9781444302400.CH3.

Douat-Casassus, C., Chassaing, S., Di Primo, C., and Quideau, S. (2009). "Specific or nonspecific protein-polyphenol interactions? Discrimination in real time by surface plasmon resonance," *ChemBioChem* 10(14), 2321-2324. DOI: 10.1002/cbic.200900287

Dufour, C., and Dangles, O. (2005). "Flavonoid-serum albumin complexation:

Determination of binding constants and binding sites by fluorescence spectroscopy," *Biochimica et Biophysica Acta* 1721(1-3), 164-173. DOI: 10.1016/j.bbagen.2004.10.013

Dufour, C., Loonis, M., and Dangles, O. (2007). "Inhibition of the peroxidation of linoleic acid by the flavonoid quercetin within their complex with human serum albumin," *Free Radical Biology and Medicine* 43(2), 241-252. DOI: 10.1016/j.freeradbiomed.2007.04.009

Edelmann, A., and Lendl, B. (2002). "Toward the optical tongue: Flow-through sensing of tannin− protein interactions based on FTIR spectroscopy," *Journal of the American Chemical Society* 124(1), 14741-14747. DOI: 10.1021/ja026309v

Ehrnhoefer, D. E., Bieschke, J., Boeddrich, A., Herbst, M., Masino, L., Lurz, R., Engemann, S.., Pastore, A., and Wanker, E. E. (2008). "EGCG redirects amyloidogenic polypeptides into unstructured, off-pathway oligomers," *Natural Structure & Molecular Biology* 15(1), 558-566. DOI: 10.1038/nsmb.1437

Fang, J.-G., and Zhou, B. (2008). "Structure-activity relationship and mechanism of the tocopherol-regenerating activity of resveratrol and its analogues," *Journal of Agricultural and Food Chemistry* 56(23), 11458-11463. DOI: 10.1021/jf802665s

Fang, J.-G., Lu, M., Chen, Z.-H., Zhu, H.-H., Li, Y., Yang, L., Wu, L.-M., and Liu, Z.-L. (2002). "Antioxidant effects of resveratrol and its analogues against the free-radical-induced peroxidation of linoleic acid in micelles," *Chemistry* 8(18), 4191-4198. DOI: 10.1002/1521-3765(20020916)8:18<4191::AID-CHEM4191>3.0.CO;2-S

Feldman, K. S., Sambandam, A., Lemon, S. T., Nicewonger, R. B., Long, G. S., Battaglia, D. F., Ensel, S. M., and Laci, M. A. (1999). "Binding affinities of gallotannin analogs with bovine serum albumin: ramifications for polyphenol-protein molecular recognition," *Phytochemistry* 51(57), 867-872. DOI: 10.1016/s0031-9422(99)00144-2

Ferguson, L. R. (2001). "Role of plant polyphenols in genomic stability," *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenisis* 475(1-2), 89-111. DOI: 10.1016/s0027-5107(01)00073-2

Gledhill, J. R., Montgomery, M. G., Leslie, A. G. W., and Walker, J. E. (2009). "Mechanism of inhibition of bovine F1-ATPase by resveratrol and related polyphenols," *Proceedings of the National Academy Sciences of the United States of America* 104(34), 13632-13637. DOI: 10.1073/pnas.0706290104

Glombitza, K.-W., and Schmidt, A. (1999). "Nonhalogenated and halogenated phlorotannins from the brown alga *Carpophyllum angustifolium*," *Journal of Natural Products* 62(9), 1238-1240. DOI: 10.1021/np990076c

Hagerman, A. E., and Butler, L. G. (1981). "The specificity of proanthocyanidin-protein interactions," *Journal of Biological Chemistry* 256(9), 4494-4497.

Hagerman, A. E., and Butler, L. G. (1991). "Tannins and lignins," in: *Herbivores: Their Interaction with Secondary Plant Metabolites*, Vol. 1, G. A. Rosenthal, and M. R. Berenbaum (eds.), Academic Press, San Diego, pp. 355-388. DOI: 10.1016/B978-0-12-597183-6.50015-2

Hagerman, A. E., Rice, M. E., and Ritchard, N. T. (1998). "Mechanisms of protein precipitation for two tannins, pentagalloyl glucose and epicatechin16 (4→8) catechin (procyanidin)," *Journal of Agricultural and Food Chemistry* 46(7), 2590-2595. DOI: 10.1021/jf971097k

Hagerman, A. E., Dean, R. T., and Davies, M. J. (2003). "Radical chemistry of epigallocatechin gallate and its relevance to protein damage," *Archives of*

Biochemistry and Biophysics 414(1), 115-120. DOI: 10.1016/s0003-9861(03)00158-9

Harborne, J. B., and Williams, C. A. (2000), "Advances in flavonoid research since 1992," *Phytochemistry* 55(6), 481-504. DOI: 10.1016/S0031-9422(00)00235-1

Hasni, I., Bourassa, P., Hamdani, S., Samson, G., Carpentier, R., and Tajmir-Riahi, H. A. (2011). "Interaction of milk alpha- and beta-caseins with tea polyphenols," *Food Chemistry* 126(2), 630-639. DOI: 10.1016/j.foodchem.2010.11.087

Haslam, E. (1974). "Polyphenol-protein interactions," *Biochemical Journal* 139(1), 285-288. DOI: 10.1042/bj1390285

Haslam, E. (1996). "Natural polyphenols (vegetable tannins) as drugs: Possible modes of action," *Journal of Natural Products* 59(2), 205-215. DOI: 10.1021/np960040+

Haslam, E. (1998) *Practical Polyphenolics: From Structure to Molecular Recognition and Physiological Action*, Cambridge University Press, Cambridge.

Haslam, E., and Cai, Y. (1994). "Plant polyphenols (vegetable tannins): Gallic acid metabolism," *Natural Product Report* 11, 41-66. DOI: 10.1039/NP9941100041

Haslam, E., Lilley, T. H., Cai, Y., Martin, R., and Magnolato, D. (1989). "Traditional herbal medicines-the role of polyphenols," *Planta Medica* 55(1), 1-8. DOI: 10.1055/s-2006-961764

Hatier, J.-H. B., and Gould, K. S. (2008). "Anthocyanins function in vegetative organs," In: *Biosynthesis, Functions, and Applications*, K. Gould, K. Davies, and C. Winefield (eds.), Springer, New York, pp. 1-20. DOI: 10.1007/978-0-387-77335-3_1

Hattenschwiler, S., and Vitousek, P. M. (2000). "The role of polyphenols in terrestrial ecosystem nutrient cycling," *Trends in Ecology & Evolution* 15(6), 238-243. DOI: 10.1016/S0169-5347(00)01861-9

Hauber, I., Hohenberg, H., Holstermann, B., Hunstein, W., and Haube, J. (2009). "The main green tea polyphenol epigallocatechin-3-gallate counteracts semen-mediated enhancement of HIV infection," *Proceeding of National Academy of Sciences of the United States of America* 106(22), 9033-9038. DOI:10.1073/pnas.0811827106

He, Q., Lv, Y., and Yao, K. (2007). "Effects of tea polyphenols on the activities of alphaamylase, pepsin, trypsin and lipase," *Food Chemistry* 101(3), 1178-1182. DOI: 10.1016/j.foodchem.2006.03.020

He, Z., Chen, J., and Moser, E. (2015). "Interaction of β-lactoglobulin with (−)-epigallocatechin-3-gallate under different processing conditions of pH and temperature by the fluorescence quenching method," *European Food Research & Technology* 241(3), 357-366. DOI: 10.1007/s00217-015-2466-2

Heer, M. I. de., Korth, H.-G., and Mulder, P. (1999). "Poly methoxy phenols in solution: O− H bond dissociation enthalpies, structures, and hydrogen bonding," *Journal of Organic Chemistry* 64(19), 6969-6975. DOI: 10.1021/jo9901485

Hofmann, T., Glabasnia, A., Schwarz, B., Wisman, K. N., Gangwer, K. A., and Hagerman, A. E. (2006). "Protein binding and astringent taste of a polymeric procyanidin, 1,2,3,4,6-penta-O-galloyl-β-d-glucopyranose, castalagin, and grandinin," *Journal of Agricultural and Food Chemistry* 54(25), 9503-9509. DOI: 10.1021/jf062272c

Holder, S., Zemskova, M., Zhang, C., Tabrizizad, M., Bremer, R., Neidigh, J.W., and Lilly, M. B. (2007). "Characterization of a potent and selective small-molecule inhibitor of the PIM1 kinase," *Molecular Cancer Therapeutics* 6(1), 163-172. DOI: 10.1158/1535-7163.MCT-06-0397

Jaldappagari, S., Balakrishnan, S., Hegde, A. H., Teradal, N. L., and Narayan, P. S. (2013). "Interactions of polyphenols with plasma proteins: Insights from analytical

techniques," *Current Drug Metabolism* 14(4), 456-473. DOI: 10.2174/1389200211314040009

Jansson, T., Rauh, V., Danielsen, B. P., Poojary, M. M., Waehrens, S. S., Bredie, W. L. P., Sorensen, J., Petersen, M. A., Ray, C. A., and Lund, M. N. (2017). "Green tea polyphenols decrease Strecker aldehydes and bind to proteins in lactose-hydrolyzed UHT milk," *Journal of Agricultural and Food Chemistry* 65(48), 10550-10561. DOI: 10.1021/acs.jafc.7b04137

Jansson, T., Wæhrens, S. S., Rauh, V., Danielsen, B. P., Sørensen, J., Bredie, W. L. P., Petersen, M. A., Ray, C. A., and Lund, M. N. (2019). "Effect of green tea catechins on physical stability and sensory quality of lactose-reduced UHT milk during storage for one year," *International Dairy Journal* 95(1), 25-34. DOI: 10.1016/j.idairyj.2019.03.007

Jia, J., Gao, X., Hao, M., and Tang, L. (2017). "Comparison of binding interaction between β-lactoglobulin and three common polyphenols using multi-spectroscopy and modelling methods," *Food Chemistry* 228(1), 143-151. DOI: 10.1016/j.foodchem.2017.01.131

Jöbstl, E., O'Connell, J., Fairclough, J. P. A., and Williamson, M. P. (2004). "Molecular model for astringency produced by polyphenol/protein interactions," *Biomacromolecules* 5, 942- 949. DOI: 10.1021/bm0345110

Jongberg, S., Gislason, N. E., Lund, M N., Skibsted, L. H., and Waterhouse, A. L. (2011). "Thiol-quinone adduct formation in myofibrillar proteins detected by LC-MS," *Journal of Agricultural and Food Chemistry* 59(13), 6900-6905. DOI: 10.1021/jf200965s

Jongberg, S., Terkelsen, L. S., Miklos, R., and Lund, M. N. (2015). "Green tea extract impair emulsion properties by disturbing protein disulfide cross-linking," *Meat Science* 100(1), 2-9. DOI: 10.1016/j.meatsci.2014.09.003

Jongberg, S., Andersen, M.L., and Lund, M. N. (2020). "Covalent protein-polyphenol bonding as initial steps of haze formation in beer," *Journal of the American Society of Brewing Chemists* 78(2), 153-164. DOI: 10.1080/03610470.2019.1705045

Kanakis, C. D., Hasni, I., Bourassa, P., Tarantilis, P. A., Polissiou, M. G., and TajmirRiahi, H. A. (2011). "Milk beta-lactoglobulin complexes with tea polyphenols," *Food Chemistry* 127(3), 1046-1055. DOI: 10.1016/j.foodchem.2011.01.079

Kashiwada, Y., Nonaka, G.-I., Nishioka, I., Lee, K.J.-H., Bori, I., Fukushima, Y., Bastow, K. F., and Lee, K.-H. (1993). "Tannins as potent inhibitors of DNA topoisomerase II in vitro," *Journal of Pharmaceutical Science* 82(5), 487-492. DOI: 10.1002/jps.2600820511

Kawamoto, H., Nakatsubo, F., and Murakami, K. (1996), "Stoichiometric studies of tannin-protein co-precipitation," *Phytochemistry* 41(5), 1427-1431. DOI: 10.1016/0031-9422(95)00728-8

Keppler, J. K., Schwarz, K., and van der Goot, A. (2020). "Covalent modification of food proteins by plant-based ingredients (polyphenols and organosulphur compounds): A common place reaction with novel utilization potential," *Trends in Food Science & Technology* 101(1), 38-49. DOI: 10.1016/j.tifs.2020.04.023

Khalifa, I., Xia, D., Dutta, K., Peng, J., Jia, Y., and Li, C. (2020). "Mulberry anthocyanins exert anti-AGEs effects by selectively trapping glyoxal and structural-dependently blocking the lysyl residues of β-lactoglobulins," *Bioorganic Chemistry* 96(1), article no. 103615. DOI: 0.1016/j.bioorg.2020.103615

Klabunde, T., Petrassi, H. M., Oza, V. B., Raman, P., Kelly, J. W., and Sacchettini, J. C. (2000). "Rational design of potent human transthyretin amyloid disease inhibitors," *National Structural Biology* 7(1), 312-321. DOI: 10.1038/74082

Komoto, J., Yamada, T., Watanabe, K., and Takusagawa, K. (2004). "Crystal structure of human prostaglandin F synthase (AKR1C3)," *Biochemistry* 43(8), 2188-2198. DOI: 10.1021/bi036046x

Kroll, N. G., Rawel, H. M., and Rohn, S. (2003). "Reactions of plant phenolics with food proteins and enzymes under special consideration of covalent bonds," *Food Science and Technology Research* 9(3), 205-218. DOI: 10.3136/fstr.9.205

Kumamoto, T., Fujii, M., and Hou, D.-X. (2009). "Akt is a direct target for myricetin to inhibit cell transformation," *Molecular and Cellular Biochemistry* 332(1), 33-41. DOI: 10.1007/s11010-009-0171-9

Lakowicz, J. R. (2006). *Principles of Fluorescence Spectroscopy*, Springer, New York.

Lambrinidis, G., Halabalaki, M., Katsanou, E. S., Skaltsounis, A.-L., Alexis, M. N., and Mikros E. (2006). "The estrogen receptor and polyphenols: Molecular simulation studies of their interactions, A review," *Environmental Chemistry Letters* 4(1), 159-174. DOI: 10.1007/s10311-006-0065-y

Lattanzio, V., Cardinali, A., Ruta, C., Fortunato, I. M., Lattanzio, V. M. T., Linsalata, V., and Cicco, N. (2009). "Relationship of secondary metabolism to growth in oregano (*Origanum vulgare* L.) shoot cultures under nutritional stress," *Environmental and Experimental Botany* 65(1), 54-62. DOI: 10.1016/j.envexpbot.2008.09.002

Lattanzio, V., Kroon, P., Quideau, S., and Treutter D. (2008). "Plant phenolics - Secondary metabolites with diverse functions," in: *Recent Advances in Polyphenol Research*, Vol. 1, F. Daayf and V. Lattanzio (eds.), Wiley-Blackwell, Oxford, pp. 1-35. DOI: 10.1002/9781444302400.ch1

Le Bourvellec, C., and Renard, C. M. G. C. (2012). "Interactions between polyphenols and macromolecules: Quantification methods and mechanisms," *Critical Reviews in Food Science and Nutrition* 52(3), 213-248. DOI: 10.1080/10408398.2010.499808

Leake, D. S. (1997). "The possible role of antioxidants in fruit and vegetables in protecting against coronary heart disease," in: *Phytochemistry of Fruit and Vegetables*, F. A. Tomas-Barberan and R. J. Robins (eds.), Clarendon Press, Oxford, UK, pp. 287-311.

Lesschaeve, I., and Noble, A. C. (2005). "Polyphenols: Factors influencing their sensory properties and their effects on food and beverage preferences," *American Journal of Clinical Nutrition* 81(1), 330S-335S. DOI: 10.1093/ajcn/81.1.330S

Leopoldini, M., Marino, T., Russo, N., and Toscano, M. (2004). "Antioxidant properties of phenolic compounds: H-atom versus electron transfer mechanism," *Journal of Physical Chemistry A* 108(22), 4916-4922. DOI: 10.1021/jp037247d

Li, A.S.-H., Bandy, B., Tsang, S.-S., and Davison, A. J. (2000). "DNA-breaking versus DNA-protecting activity of four phenolic compounds in vitro," *Free Radical Research* 33(5), 551-566. DOI: 10.1080/10715760000301091

Li, Y., Jongberg, S., Andersen, M. L., Davies, M. J., and Lund, M. N. (2016). "Quinone induced protein modifications: Kinetic preference for reaction of 1,2-benzoquinones with thiol groups in proteins," *Free Radical Biology & Medicine* 97(1), 148-157. DOI: 10.1016/j.freeradbiomed.2016.05.019

Li, Y., Li, L., Lund, M. N., Li, B., Hu, Y., and Zhang, X. (2018). "Kinetic investigation of the trapping of Nε-(carboxymethyl) lysine by 4-methylbenzoquinone: A new mechanism to control Nε-(carboxymethyl)lysine levels in foods," *Food Chemistry*

244(1), 25-28. DOI: 10.1016/j.foodchem.2017.09.144

Liang, Y., and Were, L. (2020). "Cysteine's effect on chlorogenic acid quinone induced greening and browning: Mechanisms and effect on antioxidant reducing capacity," *Food Chemistry* 309(1), article no. 125697. DOI: 10.1016/j.foodchem.2019.125697

Lopes, G. K. B., Schulman, H. M., and Hermes-Lima, M. (1999). "Polyphenol tannic acid inhibits hydroxyl radical formation from Fenton reaction by complexing ferrous ions," *Biochimica et Biophysica Acta* 1472(1-2), 142-152. DOI: 10.1016/S0304-4165(99)00117-8

Ma, L., Bueschl, C., Schuhmacher, R., and Waterhouse, A. L. (2019). "Tracing oxidation reaction pathways in wine using 13C isotopolog patterns and a putative compound database," *Analytica Chimica Acta* 1054(1), 74-83. DOI: 10.1016/j.aca.2018.12.019

McManus, J. P., Davis K. G., Beart, J. E., Gaffney, S. H., Lilley, T. H., and Haslam, E. (1985). "Polyphenol interactions. Part 1. Introduction; some observations on the reversible complexation of polyphenols with proteins and polysaccharides," *Journal of Chemical Society* 1985(9), 1429-1438. DOI: 10.1039/P29850001429

Middleton, E. J., Kandaswami, C., and Theoharides, T. C. (2000). "The effects of plant flavonoids on mammalian cells: Implications for inflammation, heart disease, and cancer," *Pharmacological Reviews* 52(4), 673-751.

Mira, L., Fernandez, M. T., Santos, M., Rocha, R., FlorÞncio, M. H., and Jennings, K. R. (2002). "Interactions of flavonoids with iron and copper ions: a mechanism for their antioxidant activity," *Free Radical Research* 36(11), 1199-1208. DOI: 10.1080/1071576021000016463

Mnch, J., Rcker, E., Stndker, L., Adermann, K., Goffinet, C., Schindler, M., Wildum, S., Chinnadurai, R., Rajan, D., Specht, A., Gimnez-Gallego, G., Sanchez, P. C., Fowler, D. M., Koulov, A., Kelly, J. W., Mothes, W., Grivel, J.-C., Margolis, L., Keppler, O. T., Forssmann, W.-G., and Kirchhoff, F. (2007). "Semen-derived amyloid fibrils drastically enhance HIV infection," *Cell* 131(6), 1059-1071. DOI: 10.1016/j.cell.2007.10.014

Murray, N. J., Williamson, M. P., Lilley, T. H., and Haslam, E. (1994). "Study of the interaction between salivary proline-rich proteins and a polyphenol by 1H-NMR spectroscopy," *European Journal of Biochemistry* 219(3), 923-935. DOI: 10.1111/j.1432-1033.1994.tb18574.x

Nikolantonaki, M., and Waterhouse, A. L. (2012). "A method to quantify quinone reaction rates with wine relevant nucleophiles: A key to the understanding of oxidative loss of varietal thiols," *Journal of Agricultural and Food Chemistry* 60(34), 8484-8491. DOI: 10.1021/jf302017j

Northup, R. R., Yu, Z., Dahlgren, R. A., and Vogt, K. A. (1995). "Polyphenol control of nitrogen release from pine litter," *Nature* 377(1), 227-229. DOI: 10.1038/377227a0

Okuda, T., Yoshida, T., and Hatano, T. (1991). "Chemistry and biological activity of tannins in medicinal plants," in: *Economic and Medicinal Plant Research*: *Plants and Traditional Medicine*, H. S. Wagner and N. R. Farnsworth (eds.), Academic Press, London, pp. 129-164.

Okuda, T., Yoshida, T., Hatano, T., and Ito, H. (2009). "Ellagitannins renewed the concept of tannins," in: *Chemistry and Biology of Ellagitannins: An Underestimated Class of Bioactive Plant Polyphenols*, S. Quideau (ed.), World Scientific, Singapore, pp. 1-54.

Quideau, S. and Feldman K. S. (1996). "Ellagitannin chemistry," *Chemical Reviews* 96(1), 475-503. DOI: 10.1021/cr940716a

Packer, L., Rimbach, G., and Virgili, F. (1999). "Antioxidant activity and biologic properties of a procyanidin-rich extract from pine (*Pinus maritima*) bark, pycnogenol," *Free Radical Biology and Medicine* 27(5-6), 704-724. DOI: 10.1016/s0891-5849(99)00090-8

Pascal, C., Poncet-Legrand, C., Imberty, A., Gautier, C., Sarni-Manchado, P., Cheynier, V., and Vernhet, A. (2007). "Interactions between a non glycosylated human proline-rich protein and flavan-3-ols are affected by protein concentration and polyphenol/ protein ratio," *Journal of Agricultural and Food Chemistry* 55(12), 4895-4901. DOI: 10.1021/jf0704108

Pascal, C., Poncet-Legrand, C., Cabane, B., and Vernhet, A. (2008). "Aggregation of a proline-rich protein induced by epigallocatechin gallate and condensed tannins: Effect of protein glycosylation," *Journal of Agricultural and Food Chemistry* 56(15), 6724-6732. DOI: 10.1021/jf800790d

Pascal, C., Pat, F., Cheynier, V., and Delsuc, M. A. (2009). "Study of the interactions between a proline-rich protein and a flavan-3-ol by NMR: Residual structures in the natively unfolded protein provides anchorage points for the ligands," *Biopolymers* 91(9), 745-755. DOI: 10.1002/bip.21221

Pierpoint, W. S. (1969). "o-Quinones formed in plant extracts," *Biochemical Journal* 112(5), 609-616. DOI: 10.1042/bj1120609

Pietta, P.-G. (2000). "Flavonoids as antioxidants," *Journal of Natural Products* 63, 1035-1042. DOI: 10.1021/np9904509

Prigent, S. V. E., Voragen, A. G. J., Li, F., Visser, A. J. W. G., van Koningsveld, G. A., and Gruppen, H. (2008). "Covalent interactions between amino acid side chains and oxidation products of caffeoylquinic acid (chlorogenic acid)," *Journal of the Science of Food and Agriculture* 88(10), 1748-1754. DOI: 10.1002/jsfa.3275

Porat, Y., Abramowitz, A., and Gazit, E. (2006). "Inhibition of amyloid fibril formation by polyphenols: Structural similarity and aromatic interactions as a common inhibition mechanism," *Chemical and Biology & Drug Design* 67(1), 27-37. DOI: 10.1111/j.1747-0285.2005.00318.x

Quideau, S., Jourdes, M., Lefeuvre, D., Montaudon, D., Saucier, C., Glories, Y., Pardon, P., and Pourquier, P. (2005). "The chemistry of wine polyphenolic c-glycosidic ellagitannins targeting human topoisomerase II," *Chemistry - A European Journal* 11(22), 6503-6513. DOI: 10.1002/chem.200500428

Ragan, M. A., and Glombitza, K. (1986). "Phlorotannins, brown algal polyphenols," *Progress in Phycological Research* 4(1), 177-241.

Rawel, H. M., Kroll, J., and Rohn, S. (2001). "Reactions of phenolic substances with lysozyme - physicochemical characterization and proteolytic digestion of the derivates," *Food Chemistry* 72(1), 59-71. DOI: 10.1016/S0308-8146(00)00206-5

Richard, T., Vitrac, X., Merillon, J. M., and Monti, J. P. (2005). "Role of peptide primary sequence in polyphenol-protein recognition: An example with neurotensin," *Biochimica et Biophysica Acta - General Subjects* 1726(3), 238-243. DOI: 10.1016/j.bbagen.2005.07.017

Richard, T., Lefeuvre, D., Descendit, A., Quideau, S., and Monti, J.-P. (2006). "Recognition characters in peptide-polyphenol complex formation," *Biochimica et Biophysica Acta (BBA) - General Subjects* 1760(6), 951-958. DOI: 10.1016/j.bbagen.2006.01.005

Rield, K. M., and Hagerman, A. E. (2001). "Tannin-protein complexes as radical scavengers and radical sinks," *Agricultural and Food Chemistry* 49(10), 4917-4923.

DOI: 10.1021/jf010683h

Rohn, A., Rawel, H. M., and Kroll, J. (2002). "Inhibitory effects of plant phenols on the activity of selected enzymes," *Journal of Agricultural and Food Chemistry* 50(12), 3566-3571. DOI: 10.1021/jf011714b

Romanet, R., Bahut, F., Nikolantonaki, M., and Gougeon, R. D. (2020). "Molecular characterization of white wines antioxidant metabolome by ultra-high performance liquid chromatography high-resolution mass spectrometry," *Antioxidants* 9(2), 115. DOI: 10.3390/antiox9020115

Sailler, B., and Glombitza, K.-W. (1999). "Phlorethols and fucophlorethols from the brown alga *Cystophora retroflexa*," *Phytochemistry* 50(5), 869-881.

Sang, S., Hou, Z., Lambert, J. D., and Yang, C. S. (2005). "Redox properties of tea polyphenols and related biological activities," *Antioxidants & Redox Signaling* 7(11-12), 1704-1714. DOI: 10.1089/ars.2005.7.1704

Sarni-Manchado, P., Cheynier, V., and Moutounet, M. (1999). "Interactions of grape seed tannins with salivary proteins," *Journal of Agricultural and Food Chemistry* 47(1), 42-47. DOI: 10.1021/jf9805146

Scalbert, A., and Haslam, E. (1987). "Polyphenols and chemical defense of the leaves of *Quercus robur*," *Phytochemistry* 26(12), 3191-3195. DOI: 10.1016/S0031-9422(00)82468-1

Shi, X., Ye, J., Leonard, S. S., Ding, M., Vallyathan, V., Castranova, V., Rojanasakul, Y., and Dong, Z. (2000). "Antioxidant properties of (-)-epicatechin-3-gallate and its inhibition of Cr (VI)-induced DNA damage and Cr (IV)-or TPA-stimulated NF-κB activation," *Molecular and cellular biochemistry* 206(8), 125-132. DOI: 10.1023/a:1007012403691

Shim, J.-H., Choi, H.S., Pugliese, A., Lee, S.-Y., Chae, J.-I., Choi, B.Y., Bode, A.M., Dong, Z. (2009). "(-)-Epigallocatechin gallate regulates CD3-mediated T cell receptor signaling in leukemia through the inhibition of ZAP-70 kinase," *Journal of Biological Chemistry* 283(42), 28370-28379. DOI: 10.1074/jbc.M802200200

Simon, C., Barathieu, K., Laguerre, M., Schmitter, K.-M., Fouquet, E., Pianet, I., and Dufourc, E. J. (2003). "Three-dimensional structure and dynamics of wine tannin− saliva protein complexes. A multitechnique approach," *Biochemistry* 42(35), 10385-10395. DOI: 10.1021/bi034354p

Singleton, V.L. (1985). "Oxygen with phenols and related reactions in musts, wines, and model systems: Observations and practical implications," *American Journal of Enology and Viticulture* 38(1), 69-77.

Skrzypczak-Jankun, E., McCabe, N. P., Selman, S. H., and Jankun, J. (2006). "Curcumin inhibits lipoxygenase by binding to its central cavity: Theoretical and X-ray evidence," *International Journal of Molecular Medicine* 6(5), 521-526. DOI: 10.3892/ijmm.6.5.521

Spencer, C. M., Cai, Y., Martin, R., Lilley, T. H., and Haslam, E. (1990). "The metabolism of gallic acid and hexahydroxydiophenic acid in higher plants part 4; polyphenol interactions part 3. Spectroscopic and physical properties of esters of gallic acid and (S)-hexahydroxydiphenic acid with D-glucopyranose (4C1)," *Journal of the Chemical Society* 1990(4), 651-660. DOI: 10.1039/P29900000651

Spencer, J. P. E. (2009). "The impact of flavonoids on memory: Physiological and molecular considerations," *Chemical Society Reviews* 38(1), 1152-1161. DOI: 10.1039/B800422F

Sugihara, N., Ohnishi, M., Imamura, M., and Furuno, K. (2001). "Differences in

antioxidative efficiency of catechins in various metal-induced lipid peroxidations in cultured hepatocytes," *Journal of Health Science* 47(2), 99-106. DOI: 10.1248/jhs.47.99

Tachibana, H., Koga, K., Fujimara, Y., and Yamada, K. (2004). "A receptor for green tea polyphenol EGCG," *Nature Structural Molecular Biology* 11(1), 380-381. DOI: 10.1038/nsmb743

Tang, H. R., Covington, A. D., and Hancock, R. A. (2003). "Structure-activity relationships in the hydrophobic interactions of polyphenols with cellulose and collagen," *Biopolymers* 70, 403-413. DOI: 10.1002/bip.10499

Tazeddinov, D., Toshev, A. D., Abylgazinova, A., Rahman, M. R., and Bin Bakri, M. K. (2022). "A review of polyphenol and whey protein-based conjugates," *BioResources* 17(4), page numbers pending; DOI: 10.15376/biores.17.4 Tazeddinova

Treutter, D. (2006). "Significance of flavonoids in plant resistance: A review," *Environmental Chemistry Letters* 4(1), 147-157. DOI: 10.1007/s10311-006-0068-8

Umeda, D., Yano, S., Yamada, K., and Tachibana, H. (2008). "Green tea polyphenol epigallocatechin-3-gallate signaling pathway through 67-kDa laminin receptor," *Journal of Biological Chemistry* 283(6), 3050-3058. DOI: 10.1074/jbc.M707892200

Velickovic, T. D. C., and Stanic-Vucinic, D. J. (2018). "The role of dietary phenolic compounds in protein digestion and processing technologies to improve their antinutritive properties," *Comprehensive Reviews in Food Science and Food Safety* 17(1), 82-103. DOI: 10.1111/1541-4337.12320

Verg, S., Richard, T., Moreau, S., Nurich, A., Merillon, J.-M., Vercauteren, J., and Monti, J.-P. (2002). "First observation of solution structures of bradykinin-penta-O-galloyl-d-glucopyranose complexes as determined by NMR and simulated annealing," *Biochimica et Biophysica Acta (BBA) - General Subjects* 1571, 89-101. DOI: 10.1016/s0304-4165(02)00183-6

Verg, S., Richard, T., Moreau, S., Richelme-David, S., Vercauteren, J., Prom, J. C., and Monti, J.-P. (2002). "First observation of non-covalent complexes for a tannin-protein interaction model investigated by electrospray ionisation mass spectroscopy," *Tetrahedron Letters* 43(13), 2363-2366. 10.1016/S0040-4039(02)00255-1

Walker, E. H., Pacold, M. E., Peristic, O., Stephens, L., Hawkins, P. T., Wymann, M. P., and Williams, R. L. (2000). "Structural determinants of phosphoinositide 3-kinase inhibition by wortmannin," *Molecular Cell* 6(4), 909-919. DOI: 10.1016/s1097-2765(05)00089-4

Waterhouse, A. L., and Laurie, V. F. (2006). "Oxidation of wine phenolics: A critical evaluation and hypotheses," *American Journal of Enology and Viticulture* 57(3), 306-313.

Wu, Y.-D., and Lai, D. K. W. (1996). "A density functional study of substituent effects on the O−H and O−CH3 bond dissociation energies in phenol and anisole," *Journal of Organic Chemistry* 61(22) 7904-7910. DOI: 10.1021/jo960069i

Yan, Y., Hu, J., and Yao, P. (2009). "Effects of casein, ovalbumin, and dextran on the astringency of tea polyphenols determined by quartz crystal microbalance with dissipation," *Langmuir* 25(1), 397-402. DOI: 10.1021/la8030123

Yang C. S., Wang, X., Lu, G., and Picinich, S. C. (2009). "Cancer prevention by tea: Animal studies, molecular mechanisms and human relevance," *Nature Reviews Cancer* 9(1), 429-439 DOI: 10.1038/nrc2641

Yearley, E. J., Zhurova, E. A., Zhurov, V. V., and Pinkerton, A. A. (2007). "Binding of genistein to the estrogen receptor based on an experimental electron density study,"

Journal of American Chemical Society 129(48), 15013-15021. DOI: 10.1021/ja075211j

Yin, J., Hedegaard, R. V., Skibsted, L. H., and Andersen, M. L. (2014). "Epicatechin and epigallocatechin gallate inhibit formation of intermediary radicals during heating of lysine and glucose," *Food Chemistry* 146(1), 48-55. DOI: 10.1016/j.foodchem.2013.09.032

Zhang, M., Vervoort, L., Moalin, M., Mommers, A., Douny, C., den Hartog, G. J. M., and Haenen, G. R. M. M. (2018). "The chemical reactivity of (-)-epicatechin quinone mainly resides in its B-ring," *Free Radical Biology and Medicine* 124, 31-39. DOI: 10.1016/j.freeradbiomed.2018.05.087

Zheng, J., and Ramirez, V. D. (2009). "Inhibition of mitochondrial proton F0F1-ATPase/ATP synthase by polyphenolic phytochemicals," *British Journal of Pharmacology* 130(5), 1115-1130. DOI: 10.1038/sj.bjp.0703397

Zhou, B., Miao, Q., Yang, L., and Liu, Z.-L. (2005). "Antioxidative effects of flavonols and their glycosides against the free-radical-induced peroxidation of linoleic acid in solution and in micelles," *Chemistry* 11(2), 680-691. DOI: 10.1002/chem.200400391

Zucker, W. V. (1983). "Tannins: Does structure determine function? An ecological perspective," *The American Naturalist* 121(3), 335-365. DOI: 10.1086/284065

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