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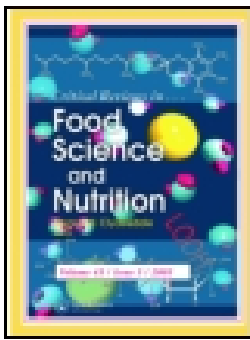
## **Inhibitory mechanisms of polyphenols on heme protein-mediated lipid oxidation in muscle food: New insights and advances**

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# Inhibitory mechanisms of polyphenols on heme protein-mediated lipid oxidation in muscle food: New insights and advances

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## ABSTRACT

Lipid oxidation is a major cause of quality deterioration that decreases the shelf-life of muscle-based foods (red meat, poultry, and fish), in which heme proteins, particularly hemoglobin and myoglobin, are the primary pro-oxidants. Due to increasing consumer concerns over synthetic chemicals, extensive research has been carried out on natural antioxidants, especially plant polyphenols. The conventional opinion suggests that polyphenols inhibit lipid oxidation of muscle foods primarily owing to their strong hydrogen-donating and transition metal-chelating activities. Recent developments in analytical techniques (e.g., protein crystallography, nuclear magnetic resonance spectroscopy, fluorescence anisotropy, and molecular docking simulation) allow deeper understanding of the molecular interaction of polyphenols with heme proteins, phospholipid membrane, reactive oxygen species, and reactive carbonyl species; hence, novel hypotheses regarding their antioxidant mechanisms have been formulated. In this review, we summarize five direct and three indirect pathways by which polyphenols inhibit heme protein-mediated lipid oxidation in muscle foods. We also discuss the relation between chemical structures and functions of polyphenols as antioxidants.

## KEYWORDS

Hemoglobin; myoglobin; antioxidant; covalently bound; structural change; shelf-life


## 1. Introduction

The global production of meat (beef, poultry and pork) and fish have reached around 328 and 156 million tons in 2020, respectively (Fao 2021). However, roughly one thirds of muscle foods (red meat, poultry, and fish) is lost or wasted globally, and the quality deterioration (short shelf-life) due to rancidity or spoilage along the food supply chain is one important cause resulting in muscle food loss (Gustavsson et al. 2011; Tatiyaborworntham et al. 2022). Lipid oxidation is the leading cause of quality deterioration and rancidity (off-flavor) development of muscle foods during processing and storage (Shah, Bosco, and Mir 2014; Wu, Abdollahi, and Undeland 2021), leading to discoloration, changes in texture, and nutritional loss (Wu, Richards, and Undeland 2022). Consequently, lipid oxidation may also result in the formation of compounds that are harmful to health due to the reaction of lipid oxidation products and other components of the muscle (Jiang and Xiong 2016). Heme-proteins (hemoglobin, Hb and myoglobin, Mb) have been identified as the primary pro-oxidants of lipid oxidation in muscle foods (Cai et al. 2013; Richards 2010; Wu, Ghirmai, and Undeland 2020). Use of antioxidants in food is common due to ease of application, and lack of requirements for specific equipment. In addition, antioxidants in powder or liquid extract forms can be applied

directly into the food matrix or in encapsulated or nanostructure-loaded forms for enhanced stability, controlled release, improved solubility, and distribution (Milinčić et al. 2019; Wu, Richards, and Undeland 2022). Alternatively, antioxidants can be incorporated into active food packaging materials (Lai 2021; Wu, Richards, and Undeland 2022). In this regard, antioxidants of natural origins such rosemary and green tea extracts provide alternatives for clean-label muscle foods due to the negative impression of consumers toward synthetic chemicals (Delgado-Pando et al. 2021). Plant extracts consist of several groups of chemical compounds, among which polyphenols are of great interest due to their effectiveness as antioxidants and their diversity in their structures and modes of antioxidant action as shown in Figure 1 (Halake, Birajdar, and Lee 2016; Shah, Bosco, and Mir 2014). Thus, identifying the key compounds that can specifically target heme protein-mediated lipid oxidation may be crucial for meat and meat products.

Polyphenols are a group of secondary plant metabolites with well-known natural antioxidants (Miller and Ruiz-Larrea 2002; Wojtunik-Kulesza et al. 2020). They can be divided into five structural groups, namely, flavonoids, phenolic acids, stilbenes, tannins, and lignans, each with one or more subgroups (Y. Kim, Ahn, et al. 2016; Wojtunik-Kulesza et al.

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2020). Polyphenols can prevent or delay lipid oxidation due to their strong hydrogen-donating potential and ability to chelate transition metal ions (Brewer 2011; Miller and Ruiz-Larrea 2002). In addition, polyphenols might prevent completely brown discoloration of fresh meat by reducing hemin ( $\text{Fe}^{3+}$ ) into heme ( $\text{Fe}^{2+}$ ) from hemoglobin and myoglobin (see Sec. 4.1).

In contrast, heme proteins promote lipid oxidation in raw and cooked meat, much more so than inorganic iron (Johns, Birkinshaw, and Ledward 1989; Richards 2010). Notably, various pathways are involved in heme protein-mediated lipid oxidation, the most prominent pathway being heme protein autoxidation, heme release, iron released by heme destruction, and ferryl radical formation (Tatijaborworntham and Richards 2018; Wu et al. 2017). Hence, prevention or delay of heme protein-mediated lipid oxidation is essential for prolonging the shelf-life of meat, meat products, and other muscle foods. To the best of our knowledge, there are so far no attempts to review or summarize the inhibitory mechanisms of polyphenols on heme proteins-mediated lipid oxidation in muscle food.

This review describes the pathways involved in heme protein-mediated lipid oxidation, followed by a classification of polyphenols according to chemical structure and biological sources. The use of polyphenols as antioxidants to improve the oxidative stability of muscle foods is also reviewed. Furthermore, pathways by which polyphenols inhibit heme-protein mediated lipid oxidation, including free radical and reactive carbonyl scavenging, via their reducing capacity, the binding between polyphenols and heme proteins, partitioning of polyphenols into membranes, as well as other indirect pathways, are described in this review.

## 2. Heme protein-mediated lipid oxidation

Myoglobin (Mb) and hemoglobin (Hb) are the main heme proteins in muscle tissue (Wu, Richards, and Undeland 2022). Mb is located within muscle cells and consists of a single polypeptide chain and a prosthetic heme group, protoporphyrin IX, with a central iron atom (Berg, Tymoczko, and Stryer 2002b). Hb is a tetramer consisting of two  $\alpha$ - and two  $\beta$ -subunits, each containing the prosthetic, iron-containing protoporphyrin IX group, and is located within red blood cells (Berg, Tymoczko, and Stryer 2002c; Richards 2010). Other heme-containing proteins, including cytochrome *c*, catalase, and P450 reductase, are also found in muscle tissue but at much smaller quantities (Berg, Tymoczko, and Stryer 2002a; Richards 2010). The various pathways suggested to be involved in heme protein-mediated lipid oxidation are illustrated in Scheme 2 described by Baron and Andersen (2002). Importantly, antioxidants may prevent or delay lipid oxidation by interfering with these pathways. For example, free radical-scavenging activity of  $\alpha$ -tocopherol prevents the reactive lipid radicals ( $\text{L}^{\bullet}$ ,  $\text{LO}^{\bullet}$ , and  $\text{LOO}^{\bullet}$ ) from attacking other lipid molecules. Haptoglobin and hemopexin are naturally-present scavengers that rid of hemoglobin and hemin, respectively, which are lipid oxidation promoters

released upon hemolysis (Cooper et al. 2013; Grunwald and Richards 2012).

External stimuli e.g. thermal treatment, oxygen, and light can also influence the oxidation of heme proteins and the lipid oxidation induced by heme proteins oxidation. Autoxidation of heme proteins from the ferrous ( $\text{Fe}^{2+}$ ) to the ferric ( $\text{Fe}^{3+}$ ) state results in the formation of the so-called met forms of the heme proteins, which are the reason for the brown discoloration of fresh meat (Ramanathan, Suman, and Faustman 2020). Light and oxygen concentration can cause discoloration of meat by inducing the oxidation of heme proteins. Exposure of exposure meat to UV light may promote surface discoloration due to oxidation of reddish oxymyoglobin to brownish metmyoglobin, especially when headspace oxygen is greater than 20% (Djenane et al. 2001), which is particularly the case for high-oxygen packaging. Vacuum or modified atmosphere packaging with carbon dioxide is one way to alleviate the oxidation of hemoglobin and myoglobin and lipid oxidation (Marcinkowska-Lesiak et al. 2017). Cooking can change folding of heme proteins, resulting in denaturation of the globin protein and release of heme, and thermal degradation of heme liberates free iron, which is also a potent pro-oxidant in cooked meat (Zhang et al. 2022). The discoloration, in other words, oxidation of heme proteins due to light, oxygen, or thermal treatment, is associated with lipid oxidation. The ferric hemoproteins, i.e., metHb and metMb, are more pro-oxidant than their ferrous counterparts (Wu, Park, and Richards 2022; Wu, Richards, and Undeland 2022). The met forms react with  $\text{H}_2\text{O}_2$  to form the perferryl ( $\text{Fe}^{4+}$ ), which is rapidly reduced to the ferryl ( $\text{Fe}^{4+}$ ) form of the heme protein (Baron and Andersen 2002; Carlsen, Møller, and Skibsted 2005; Shikama 1998). The perferryl radical might also be able to abstract  $\text{H}^+$  from an unsaturated fatty acid (LH), resulting in the formation of a lipid alkyl radical ( $\text{L}^{\bullet}$ ), capable of propagating lipid oxidation (Wu, Richards, and Undeland 2022). Likewise, the ferryl form can react with LH to form  $\text{L}^{\bullet}$ , or it might react with lipid hydroperoxides (LOOH) to form other radicals capable of propagating lipid oxidation, namely, the lipid peroxy radical ( $\text{LOO}^{\bullet}$ ) (Wu, Richards, and Undeland 2022).

The protoporphyrin IX moiety, heme, dissociates more readily from the ferric forms of the heme proteins than from the ferrous forms (Wu et al. 2017). Dissociation of heme formed during autoxidation of the heme proteins enables the breakdown of preformed LOOHs (Wu, Richards, and Undeland 2022), leading to the formation of lipid alkoxy ( $\text{LO}^{\bullet}$ ) and  $\text{LOO}^{\bullet}$  radicals, which are known to propagate lipid oxidation (Carlsen, Møller, and Skibsted 2005). Heme also dissociates more readily from Hb than Mb (Cai et al. 2016). Therefore, it has been suggested that the release of heme is a more critical factor in promoting lipid oxidation than autoxidation of the heme proteins in washed cod muscle (Grunwald and Richards 2006b).

Heme proteins can also act as pro-oxidants via the Fenton-like reaction, which is an oxidation process of organic compounds in the presence of a transition metal (e.g., iron) and  $\text{H}_2\text{O}_2$  (Carlsen, Møller, and Skibsted 2005; Dunford 2002). In its simplest form, the Fenton reaction is

the reaction between  $\text{Fe}^{2+}$  and  $\text{H}_2\text{O}_2$  to form  $\text{Fe}^{3+}$ ,  $\cdot\text{OH}$ , and  $\text{OH}^-$ . However, other reactive oxygen species, such as superoxide anion ( $\text{O}_2^{\cdot-}$ ) and its conjugate acid ( $\text{HO}_2^+$ ), may also be involved. Furthermore, the hydroxyl radical ( $\cdot\text{OH}$ ) is highly reactive and can easily initiate lipid oxidation (Carlsen, Møller, and Skibsted 2005). Under certain conditions, iron from the heme proteins may leak and bind to negatively charged phospholipids of the cell membrane and react in a Fenton-like manner with preformed LOOH in the membranes (Carlsen, Møller, and Skibsted 2005). Metals initiating Fenton-like reactions in meat are not necessarily endogenous to the meat but may originate from processing equipment (Richards 2010).

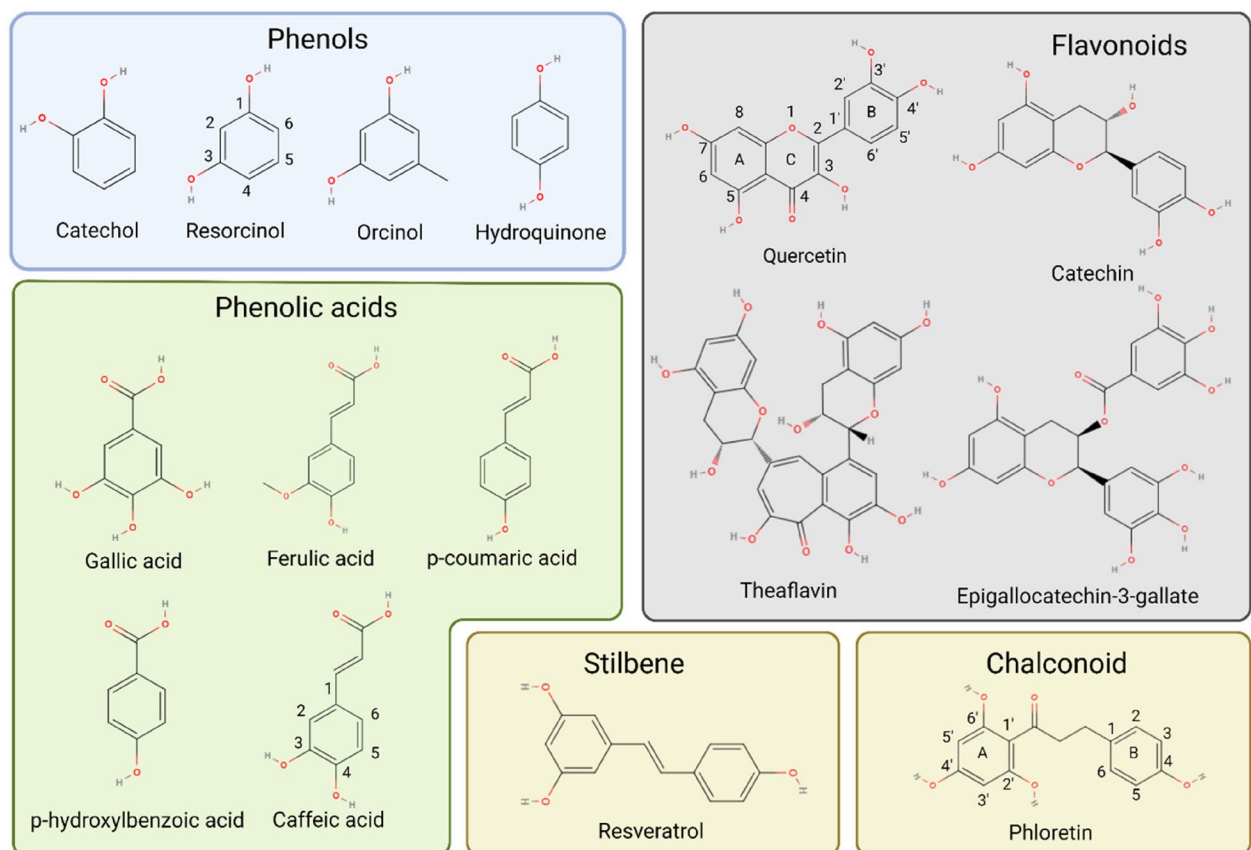
The relative percentages of Mb and Hb, based on total heme proteins isolated from various species, were reviewed by Wu, Richards, and Undeland (2022). Hb dominates in chicken and most fish species, while Mb appears to be the dominating heme protein in turkey, beef, pork, and specific muscles of a select species of fish (Wu, Richards, and Undeland 2022). As mentioned, the relative ability of Hb and Mb to promote lipid oxidation depends mainly on their ability to dissociate heme, which is generally more significant in Hb (Cai et al. 2016), though autoxidation of Mb appears to be faster than that of Hb (Cai et al. 2016). In minced rainbow trout muscle, Hb is a much more effective promoter of lipid oxidation than Mb (Cai et al. 2013). However, it is also the predominant heme protein in this species (Richards and Hultin 2002).

### 3. Polyphenol classifications and being antioxidants in muscle food

#### 3.1. Polyphenol classifications by chemical structure and sources

Polyphenols are secondary organic plant metabolites formed from some phenol units with industrial and therapeutic applications (Prabhu et al. 2021). Classes, subclasses, and dietary sources of the most common polyphenols are presented in [supplementary material Table S1](#). The chemical structures of some polyphenols are illustrated in [Figure 1](#). Dietary polyphenols act as protectants against oxidative stress, and degenerative diseases, most of these biological actions being based on their antioxidant properties (Han, Shen, and Lou 2007). The food industry uses natural and synthetic antioxidants to reduce the oxidative changes in meat and meat products that may cause negative effects on their quality, such as changes in their sensory and nutritional properties (Papuc et al. 2017). Notably, the confirmation of the synthetic antioxidants' toxicological and carcinogenic effects oriented the food industry towards using natural products more frequently (Kumar et al. 2015; Shah, Bosco, and Mir 2014).

As noted earlier, polyphenols is divided into the major classes phenolic acids, flavonoids (flavonols, flavanols, isoflavones, flavanones, anthocyanins, proanthocyanins, etc.), polyphenolic amides, stilbenes, lignans, and volatile oils (e.g., carvacrol, eugenol, menthol thymol) (Baniwal et al. 2021;



**Figure 1.** Chemical structures of different classes of phenolic compounds.

Brewer 2011; Kumar et al. 2014; Papuc et al. 2017; Prabhu et al. 2021; Rasouli, Farzaei, and Khodarahmi 2017; Singla et al. 2019). Notably, caffeic, carnosic, chlorogenic, gallic, and rosmarinic acids are among the most widely studied phenolic acids (Jiang and Xiong 2016; Papuc et al. 2017).

**Phenolic acids** formed of aromatic rings with one carboxylic acid group represent a major class of plant-based phenolics (Prabhu et al. 2021). Plant-based food, including seeds, fruits, skin, and leafy vegetables, is the prime phenolic acid source (Rashmi and Negi 2020). Additionally, hydroxybenzoic and hydroxycinnamic acids represent phenolic acid sub-classes. Hydroxybenzoic acid has as 2<sup>nd</sup> sub-classes the salicylic acid, vanillic acid, protocatechuic acid, gallic acid, benzoic acid, and ellagic acid (Ozcan et al. 2014). Caffeic, cinnamic, coumaric, ferulic, and sinapic acids are known common examples of hydroxycinnamic acids (Singla et al. 2019; Teixeira et al. 2013).

The different classes of **flavonoids** including *anthocyanidins* (delphinidin, peonidin, cyanidin, pelargonidin), *flavan-3-ols* (catechin, epicatechin, galocatechin), *flavanones* (hesperetin, naringenin), *flavones* (apigenin, baicalein, chrysin), *flavonols* (kaempferol, quercetin), *isoflavones* (daidzein, glycitein), and others are major classes of polyphenols (Harborne and Williams 2000; Papuc et al. 2017; Prabhu et al. 2021; Rasouli, Farzaei, and Khodarahmi 2017; Singla et al. 2019).

**Other polyphenols**, including *stilbenes* (piceatannol, resveratrol), *lignans* (enterodiol, pinoselin, sesamol, sinol), *tannins*, *lignins*, etc., also have an extensive range of

industrial and therapeutic applications depending, on their activities (Kumar et al. 2014; Prabhu et al. 2021; Rasouli, Farzaei, and Khodarahmi 2017; Singla et al. 2019).

### 3.2. Polyphenols as antioxidants to improve stability to oxidation and color in muscle food

All meat and fish products are susceptible to oxidation. Due to the higher content of heme proteins and phospholipids, poultry meat is more prone to oxidative rancidity development than red meat (Sen and Mandal 2016). Meat and fish product lipid oxidation also develops many compounds that may promote adverse effects in humans (Berastegi et al. 2014). Therefore, adding antioxidants to muscle food products is necessary to improve their storage stability, sensory quality, and nutritional value. Alongside the antioxidants commonly used in meat and fish, different plants with antioxidative properties are becoming increasingly appreciated as food additives (Kumar et al. 2015; Sen and Mandal 2016). Polyphenols can chelate metals and donate H to oxygen radicals; thus, they are incredibly effective antioxidants that slow oxidation by two primary mechanisms (Table 1). Plant polyphenols and extracts rich in polyphenols added to all types of meat and meat products delay or prevent lipid oxidation, decrease rancidity development, preserve meat color, and increase microbiological quality and shelf-life better than/or as well as synthetic antioxidants without

**Table 1.** Summary of literature references on use of polyphenols in muscle matrices and proposed mechanisms.

Polyphenol source (major compounds)	Muscle matrix	Proposed antioxidant mechanisms	References
Rosemary extract (carnosic acid, carnosol)	Herring by-product mince	Rosemary extract reduced methemoglobin to oxyhemoglobin and suppressed hemin loss.	Wu, Sajib, and Undeland (2021)
Grape seed extract	Beef ( <i>longissimus lumborum</i> ) patties	Patties with grape seed extracts (0.10–0.75 g/kg) restricted oxidation of oxy-myoglobin to metmyoglobin.	Yang et al. (2022)
Caffeic acid	Washed cod mince	Caffeic acid formed a covalent adduct with a thiol group on hemoglobin, making the heme protein less pro-oxidative.	Yin et al. (2016)
Quercetin	Washed cod mince	Quercetin reduced methemoglobin to oxyhemoglobin and bound to methemoglobin covalently and suppressed hemin loss.	Wu et al. (2022b)
Caffeic acid	Washed cod and turkey minces	Caffeic acid accelerated oxidation of hemoglobin and bound to methemoglobin, reducing the heme loss and solubility of the heme protein.	Park et al. (2013)
Quercetin and quercetin- $\beta$ -d-glucoside	Mechanically separated turkey mince	The polyphenols binding with muscle membranes established a molecular trap or physical barrier. The trap or barrier could decrease the access of heme proteins or hemin to membrane phospholipids	Kathirvel and Richards (2009)
Olive mill wastewater (oleacein, hydroxytyrosol, verbascoside, tyrosol)	Beef hamburgers	Phenolic extract preserved oxy-myoglobin and inhibited lipid oxidation by scavenging Reactive oxygen species and free radicals.	Barbieri et al. (2021)
Carnola extracts (sinapic acid, ferulic acid, p-hydroxybenzoic acid)	Cooked beef, chicken, and pork	Free radical scavenging activity of cinnamic acid derivatives worked synergistically in inhibiting lipid oxidation.	Brettonnet et al. (2010)
Willowherb ( <i>Epilobium hirsutum</i> L.) extract (ellagic acid, myricetin, quercetin, gallic acid)	Beef patties	Phenolic compounds scavenge both reactive oxygen species and oxygen resulted in formation of quinones that accelerated oxidation of myoglobin.	Cando et al. (2014)
Green tea extract (catechin, epicatechin)	Bologna type sausage	Phenolic acids formed covalent conjugates on myofibrillar protein help stabilize free radicals.	Jongberg et al. (2013)
Rosemary extract (carnosic acid, carnosol)	Washed cod mince	Caffeic acid was able to regenerate $\alpha$ -tocopherol, reduce oxidation of hemoglobin, quench free radical.	Larsson and Undeland (2010)
Caffeic acid	Washed cod mince	Caffeic acid had the highest lipoxygenase inhibitory activity.	Maqsood and Benjakul (2010)
Catechin, caffeic acid, ferulic acid, tannic acid	Mackerel mince	Tannic acid was the most potent antioxidant which was related to reducing activity against free radicals. Catechin had the highest metal chelating activity.	Maqsood and Benjakul (2010)
Rosemary extract	Pork sausage	A combination between rosemary extract and phospholipase A2 caused depletion of neutral lipid hydroperoxides.	Whalin et al. (2022)

adulteration of the organoleptic or nutritional characteristics (Papuc et al. 2017; Tomović et al. 2017).

Coffee residue extracts rich in polyphenols showed potent antioxidant activity in raw and cooked meat during storage (J. H. Kim, Ahn, et al. 2016). Lipid and oxymyoglobin oxidation also decreased in stored cattle and pig muscles after treatment with ellagic acid and olive leaf extract (Hayes et al. 2009). The efficiency in preserving the redness value of grape seed extract in raw beef patties during refrigeration was increased compared to tea catechins. At the same time, the inhibition rate of lipid oxidation was reduced after using tea catechins (Liu et al. 2015). Additionally, polyphenols from leafy green vegetables improved the color and oxidation resistance in refrigerated minced beef patties (Kim et al. 2013). Likewise, lipid peroxidation was inhibited during cold storage of raw beef sausages treated with *Ziziphus* ethanolic in an aqueous extract, demonstrating a concentration-solvent-dependent manner (Abdulla, Abdel-Samie, and Zaki 2016). Therefore, their higher antioxidant activity suggests they could be used as natural antioxidants in the food industry. The Hooker chives root extract added to pork patties during refrigeration decreased conjugated (CD) dienes and thiobarbituric acid-reactive substances (TBARS) values proportional to the level of polyphenolic extract and also blocked meat discoloration (Cho et al. 2015). Furthermore, rape bee pollen extracts, which are rich in flavonoids, when used to prepare pork salami decreased peroxide and TBARS values during processing (Y. Zhang, Wu, et al. 2016).

The inhibitory activity on lipid dioxygenation of catechin and caffeic, ferulic, and tannic acids in fish mince increased, depending on the concentration of all phenolics tested. However, the highest lipoxygenase inhibitory activity was observed for caffeic acid (Maqsood and Benjakul 2010). Adding young apple polyphenols to grass carp fillets delayed the decrease in fatty acid contents and reduced the

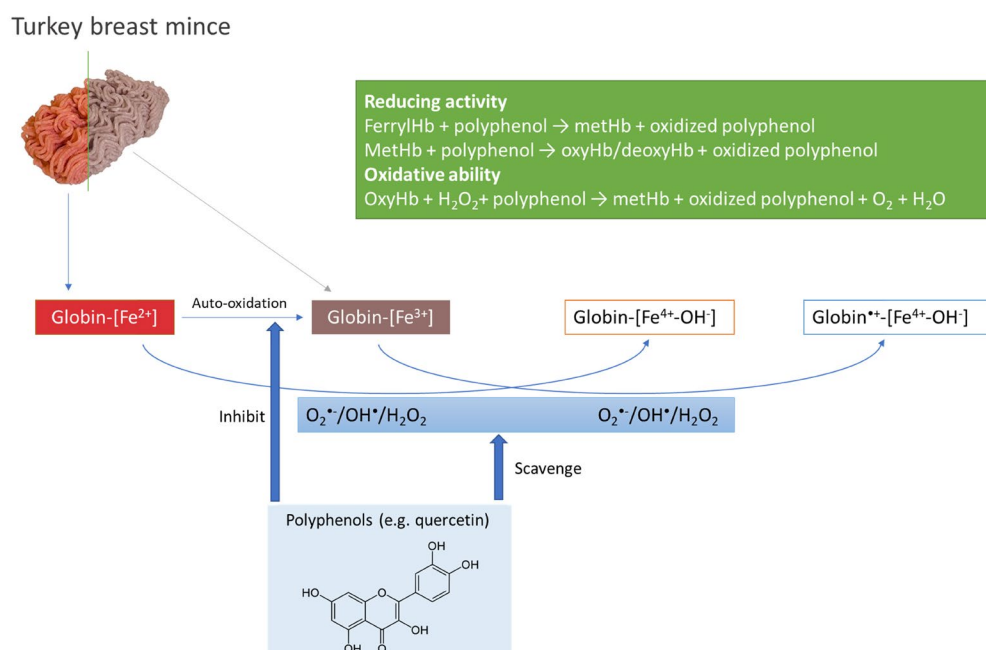
degeneration of myofibrillar protein and thiol groups without affecting their taste (Sun et al. 2017). Sea buckthorn fruit polyphenols also improved the resistance to oxidation of lipids and myoglobin in frozen carp muscle (Papuc et al. 2012). Additionally, tannic acids blocked lipid and protein oxidation, preserved meat color, and decreased off-flavor formation in raw and cooked chicken breast meat during storage (Al-Hijazeen et al. 2016). Furthermore, rosemary and clove ethanolic extracts rich in polyphenols produced a lower TBARS value and discoloration in chicken meat (H. Zhang, Wu, et al. 2016).

Available polyphenols added to meat and fish products can reduce lipid peroxidation, inhibit lipoxygenase activity, increase meat color stability, decrease the degradation of myofibrillar protein and thiol groups, and delay bacterial development, suggesting their use to extend the shelf-life of food. Future studies should clarify the different polyphenols' antagonistic or synergistic actions and find the optimum polyphenol classes, quantities, and uses for preservation (Papuc et al. 2017).

## 4. Pathways of polyphenols to inhibit heme protein-mediated lipid oxidation

### 4.1. The reducing capacity of polyphenols toward oxidized forms of Hb and Mb

Both polyphenols and heme proteins contain active redox groups and can chemically undergo redox reactions (Papuc et al. 2017). In this manner, polyphenols can lessen the pro-oxidative activity of heme proteins by reductively converting the oxidized forms of heme proteins, which are the pro-oxidative forms, to their less pro-oxidative reduced forms (Figure 2). The oxidized forms of Mb are



**Figure 2.** The oxidation of heme proteins in muscle food and the reducing/oxidative capacity of polyphenols toward heme proteins.

metmyoglobin, ferrylmyoglobin, and perferrylmyoglobin. Likewise, Hb oxidizes into methemoglobin, ferrylhemoglobin, and perferrylhemoglobin. These oxidized heme proteins possess the peroxidase-like activity to decompose lipid hydroperoxides into lipid free radicals, which are crucial in the propagation of lipid oxidation (Carlsen, Møller, and Skibsted 2005; Reeder et al. 2004). In addition, the hyper-valent radical forms, perferrylmyoglobin and perferrylhemoglobin, can also initiate the oxidation of lipids by abstracting electrons from oxidizable substrates e.g., unsaturated lipids and amino acid side chains (Jongberg et al. 2011; Jongberg et al. 2014; Tatiyaborworntham and Richards 2018). The ferryl form of hemoglobin was also detected in trout hemoglobin during the onset of lipid oxidation in a washed cod muscle model (Tatiyaborworntham and Richards 2018; Tatiyaborworntham, Yin, and Richards 2021).

#### 4.1.1. Reactions between polyphenols and ferryl heme proteins

The abilities of polyphenols to convert ferrylmyoglobin back to metmyoglobin have been demonstrated (Banasiak and Gebicka 2009; Hu and Skibsted 2002; Jongberg et al. 2014; J. Yin, Andersen, et al; Figure 2). The ferrylhemoglobin-scavenging activity was proposed as an additional mechanism of alleviating the pro-oxidative effect of hemoglobin by flavonoids (Banasiak and Gebicka 2009). In this sense, flavonoids retard hydrogen-peroxide-mediated oxidation of oxyhemoglobin to methemoglobin, in which ferrylhemoglobin is formed as an intermediate. Additionally, Kassa et al. (2021) found that pre-exposure to sickle cell methemoglobin and its reduced form with 5-fold molar excess of caffeic acid for 48 h reduced the formation of ferryl species in the presence of hydrogen peroxide. Therefore, these findings suggest that caffeic acid may bind to the protein, either covalently or non-covalently, and interfere with the reaction with hydrogen peroxide.

An outer-sphere electron transfer mechanism was suggested for epigallocatechin gallate-mediated reduction of ferrylmyoglobin due to large positive activation entropy (Hu and Skibsted 2002). In contrast, J. Yin, Andersen, et al. emphasized that the ferrylmyoglobin-reducing activity of polyphenols is related to the pKa of the most acidic phenol groups rather than the oxidation potentials or the dissociation energy of the O-H bond of the substituted hydroxyl groups. Furthermore, an inner-sphere electron transfer mechanism was proposed for epigallocatechin gallate, where the binding of phenolic compounds and protein precedes the proton and electron transfers.

#### 4.1.2. Reactions between polyphenols and met-heme proteins

Conversion of metmyoglobin to its reduced form, deoxymyoglobin, not only reduces the pro-oxidative form of myoglobin but also improves the color stability of non-cooked meat. The heme iron of myoglobin and hemoglobin can be reduced by several polyphenols, each with different efficacies (Inai et al. 2014; Wu et al. 2022b; Figure 2). Inai et al.

(2014) reported that keampferol, myricetin, and quercetin could effectively reduce metmyoglobin at 5:1 molar ratio between the phenolic compound and Mb. Meanwhile, sinapic acid, catechin, nordihydroguaiaretic acid, taxifolin, morin, and ferulic acid required a higher dose of a 10:1 molar ratio. Similarly, quercetin reduced turkey methemoglobin at a 5:1 molar ratio, with a pH of 8.0 at 4°C (Wu et al. 2022b).

#### 4.1.3. Reactions between polyphenols and oxy-heme proteins

Despite polyphenols' ability to serve as reducing agents, polyphenols may pose oxidative effects on heme proteins in a dose- and pH-dependent manner (Masuda et al. 2013; Figure 2). To different degrees, various phenolic compounds can accelerate the oxidation of oxymyoglobin and oxyhemoglobin to their corresponding oxidized forms (Dong et al. 2021; Masuda et al. 2013; Park et al. 2013). For example, caffeic acid at 100 mg/kg failed to slow down the spontaneous oxidation of trout hemoglobin (20 µmol/L) and accelerated the oxidation (Larsson and Undeland 2010). Despite an established positive correlation between lipid oxidation and discoloration, an extract from Willow herb (*Epilobium hirsutum* L.) that was rich in ellagic acid, myricetin, hydroxybenzoic, and hydroxycinnamic acids were found to inhibit lipid oxidation in beef patties, yet, discoloration was increased (Cando et al. 2014). Therefore, Masuda et al. (2013) concluded that the catechol moiety and ortho- and para-substituted diphenol structures are crucial for the ability of polyphenols to promote oxidation of myoglobin.

Mechanistically, it has been proposed that polyphenols can donate an electron to an oxygen molecule bound to the 6<sup>th</sup> coordination site of the heme iron, resulting in the formation of superoxide anions and, subsequently, hydrogen peroxide (Augusto and Cilento 1975; Wallace and Caughey 1975). In this regard, the oxygen affinity of heme protein may be an essential factor for polyphenols to induce the oxidation of heme proteins. Park et al. (2013) reported that at pH 5.8, the redox-destabilizing effect of caffeic acid was relatively more effective against porcine oxyhemoglobin (7-fold increase in oxyhemoglobin oxidation rate) than against perch oxyhemoglobin (less than a 1-fold increase). One explanation may be that Hb from several fish species, including perch, exhibits a Root effect, when oxygen affinity decreases under acidic conditions (Root 1931).

Another pro-oxidative mechanism of polyphenols is due to quinones, the oxidized products formed once polyphenols lose electrons, which are electrophilic and may induce redox instability of the protein in a similar way as highly electrophilic  $\alpha$ ,  $\beta$ -unsaturated aldehydes such as 4-hydroxy-2-nonenal(4-HNE) and 4-oxo-2-nonenal (Miura et al. 2014; Mohan et al. 2022; Tatiyaborworntham et al. 2012; Yin et al. 2011; Yin, Andersen, et al). However, Inai et al. (2014) proposed a mechanism in which flavonoids that show promising metmyoglobin reducing activity may form oxidized products that quickly turn into redox-stable compounds instead of reacting with the heme protein. Notably, several

amino acids could alleviate the dihydrocaffeic acid-mediated oxidation of oxymyoglobin to various degrees, and cysteine appeared to be the most effective (Masuda et al. 2013). A conjugation product between cysteine and dihydrocaffeic acid, cysteinyl dihydrocaffeic acid, where cysteine forms an S-linked bond with the C-5 of the benzene ring (see caffeic structure in Figure 1), lost the pro-oxidative activity toward myoglobin oxidation, unlike dihydrocaffeic acid. Miura et al. (2014) synthesized a cysteine-polyphenol conjugate, 2-S-cysteinylcaffeic acid, demonstrating that the conjugate was less oxidative toward oxymyoglobin while still retaining the metmyoglobin-reducing activity.

#### **4.2. The covalent and non-covalent interactions between polyphenols and heme proteins**

Polyphenol-protein interactions are common phenomena and could be another mode of inhibiting heme protein-mediated lipid oxidation. Such interactions, either of covalent or non-covalent nature, can induce changes to the structure and properties of the proteins, e.g., digestibility, antioxidant activity, solubility, and thermal stability (Das et al. 2020; Dong et al. 2021; Kroll and Rawel 2001; Kroll, Rawel, and Seidelmann 2000; Wu et al. 2022b; Xu et al. 2021).

##### **4.2.1. Non-covalent interactions**

The basis of non-covalent interactions generally relies on combinations of hydrogen bonding, Van der Waals interaction, electrostatic interaction, and hydrophobic interactions between functional groups of polyphenols and proteins (Chakraborty et al. 2012; Pahari et al. 2013). Polyphenol structures typically contain hydroxyl, carbonyl, and carboxylic groups that can form hydrogen bonding with polar groups of the protein backbone and side chains, particularly the positively-charged ones (Chakraborty et al. 2012). Meanwhile, the hydrophobic pockets of protein can accommodate the less hydrophilic near-planar structure of polyphenols, which strengthens the binding (Das et al. 2020; Xiao et al. 2011). The binding of polyphenols on the structure of heme protein can be monitored via spectroscopic techniques due to the fluorescence quenching effect of the bound phenol groups (Chakraborty et al. 2012; Das et al. 2020; Pahari et al. 2013; Xiao et al. 2011).

Regarding possible mechanisms related to the non-covalent binding of polyphenols to heme proteins, induced protein stability, and prevention of heme loss have been suggested (Park et al. 2013; Wu et al. 2022b; Yin et al. 2016). Due to its small size, phenol has been found to enter the heme cavity of sperm whale myoglobin and interact with Tyrosine-146 via hydrogen bonding and the proximal Histidine-93 via hydrophobic interactions (Huang et al. 2012). Notably, Park et al. (2013) observed that incubating caffeic acid with pork and turkey methemoglobin, respectively, resulted in declining rates of heme loss. Tian, Zhou, and Lu (2022) also reported that quercetin was better than rutin at both reducing heme loss from methemoglobin and inhibiting the pro-oxidative activity of the heme protein. Therefore, the binding of polyphenols near the heme pocket

may block access of lipid hydroperoxides to the heme iron or prevent heme from leaving.

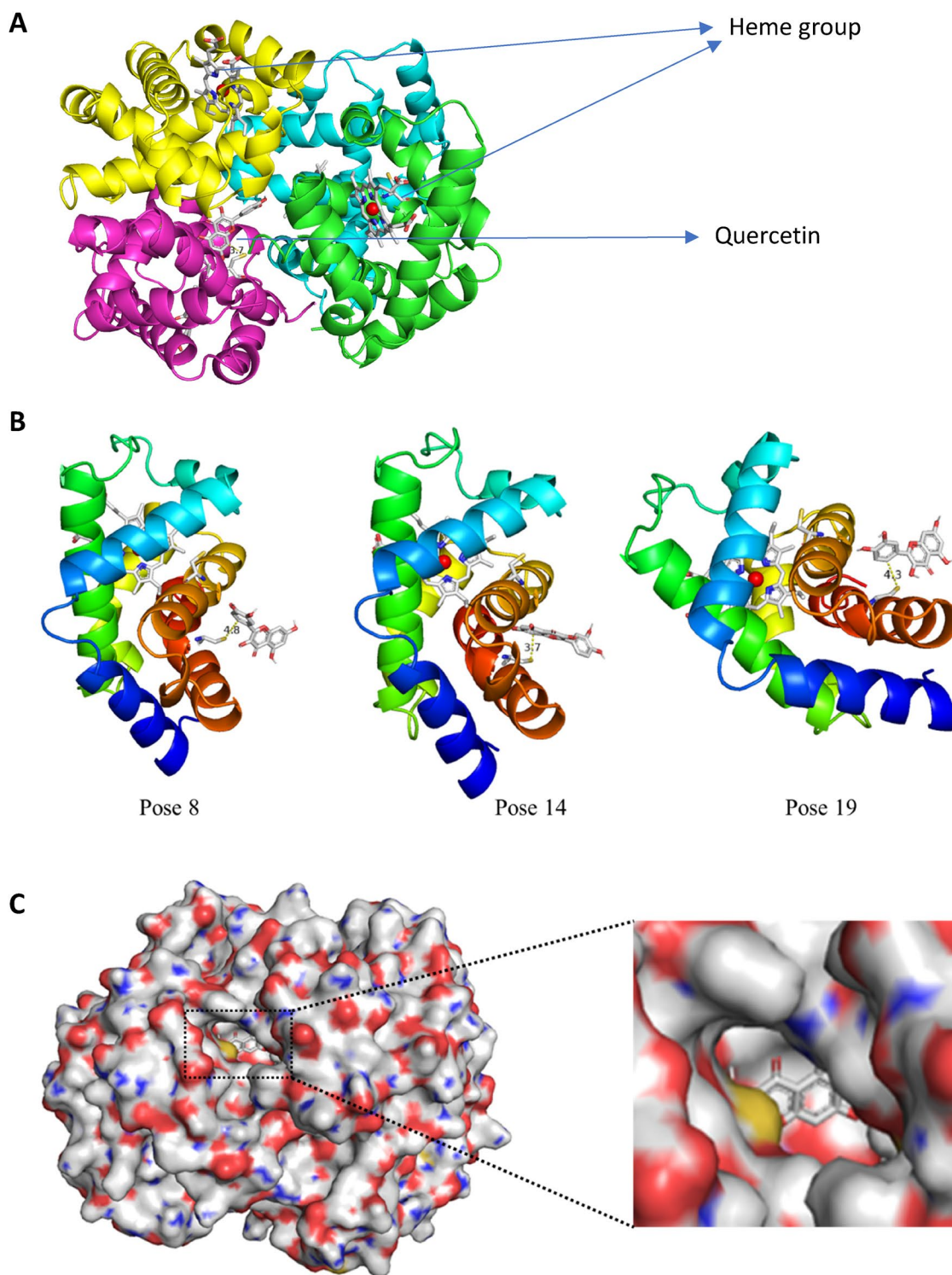
Molecular docking simulation has been employed for predicting how phenolic compounds interact with heme proteins. Dong et al. (2021) described that gallic acid could dock itself in the hydrophobic pocket to interact with the heme iron and induce structural compactness of hemoglobin. Together, these effects of gallic acid may prevent the heme release of hemoglobin. Wu et al. (2022b) also used molecular docking to predict how quercetin and its oxidized quinone form would be localized within the 5-angstrom vicinity of a cysteine residue on the H-helix of the  $\alpha$ -subunit of turkey hemoglobin A. In addition, the authors argued that direct electron transfer between the bound quercetin and the heme irons of hemoglobin was unlikely due to the distance between the two moieties. In contrast, the isoflavone genistein was predicted to localize between the subunits of human hemoglobin, which is 18 angstroms away from the heme cavity, without disturbing the structural integrity of the protein (Pahari et al. 2013).

Additionally, it was proposed that the polyphenol-hemoglobin complex could be a means of transferring water-soluble polyphenols to lipid membranes (Park et al. 2013). This might be due to the ability of hemoglobin to interact with lipid membranes (Sannaveerappa et al. 2014).

##### **4.2.2. Covalent interaction**

Conjugation between polyphenols and proteins primarily involves nucleophilic substitutions of protein side chain groups, e.g., thiol, amine, and indole groups with quinones, the oxidized form of polyphenols following a two-electron loss of phenolic compounds (Giacomelli et al. 2002; Jongberg et al. 2011; Kroll and Rawel 2001; Kroll, Rawel, and Seidelmann 2000). Quinones can form from auto-oxidation under alkaline pH conditions (Friedman and Jurgens 2000; Giacomelli et al. 2002), reactions with oxidants such as periodate,  $\text{Fe}^{2+}/\text{H}_2\text{O}_2$ , and hemoglobin (Jongberg et al. 2011; López Durán, Larsson, and Wågberg 2016), or enzymatic catalysis by polyphenol oxidase, tyrosinase, and laccase (Cheynier and Moutounet 1992; Stanic et al. 2010). Nevertheless, o-quinone-independent conjugations between proteins and curcumin and kaempferol are possible due to the keto-enol tautomerism of the phenolic compounds (Keppler, Schwarz, and Van Der Goot 2020). From Figure 3, the conjugation between the protein-bound nucleophile and o-quinone of quercetin yields a new equivalent of protein-bound quercetin with restored reducing power. Protein-bound quinone may conjugate with another protein molecule, creating protein crosslinking (Wu et al. 2022b).

Like other proteins, heme proteins can form conjugations with polyphenols, and covalent modifications can alter the properties of the heme proteins. Kassa et al. (2021) studied the anti-sickling effect of caffeic acid on sickle cell hemoglobin. Following incubation of caffeic acid with sickle cell hemoglobin, adduction sites of the phenolic acid on the hemoglobin molecule were confirmed by mass spectrometry and identified as Cysteine-93 and Cysteine-112 residues of the  $\beta$ -subunit and Cysteine-104 residue of  $\alpha$ -subunit. From



**Figure 3.** A scheme illustrated the possible role of quinone in the formation of covalent bonding between quercetin and the thiol group of hemoglobin. The tetrameric Hb view indicating the binding site of quercetin to Cys(H15) on  $\alpha$ -chain of turkey HbA (A); The monomeric views are shown to indicate the distance between quercetin and  $\alpha$ Cys(H15) of turkey HbA (B); the space-filled view of the turkey Hb tetramer is shown to illustrate the cavity for quercetin to gain access to the thiol (C) based on our previous study (Wu et al. 2022b).

these investigations, the authors attributed the anti-polymerization of the abnormal heme protein to the caffeic acid adducts and the reducing activity.

Variations in reactivity of different phenolic compounds toward proteins are structure-related. Specifically, these may depend on the number and position of the hydroxyl group

on the benzene ring. Reactions between Mb with chlorogenic acid, caffeic acid, and p-quinone under an alkaline condition (pH 9) indicated that amine and indole groups of Mb were involved in the covalent modifications (Kroll and Rawel 2001; Kroll, Rawel, and Seidelmann 2000). Based on the mass spectrometry results and losses of amine and indole

groups, the number of adducts of chlorogenic acid (2 adducts), caffeic acid (3 adducts), and p-quinone (up to 11 adducts) on Mb molecules indicate the order of reactivity of the phenols. Among ortho-, meta-, and para-hydroxyphenols, only the ortho- and para-derivatives can form quinones upon oxidation at pH 9 and form adducts on Mb via nucleophilic substitution. In contrast, the meta-derivative may react with myoglobin via a semiquinone radical intermediate (Kroll and Rawel 2001).

Additionally, the effects of polyphenol conjugations on the pro-oxidative activity of heme proteins have been investigated. Yin et al. (2016) reported mass spectrometric and protein crystallographic evidence of covalent bonding between caffeic acid and an  $\alpha$ -subunit of turkey hemoglobin A at the residue Cysteine-130. From the x-ray structure data, the site of nucleophilic substitution was likely at the C-2 carbon on the catechol unit of caffeic acid (see caffeic structure in Figure 1), which was suggested to be the most electrophilic (Kroll, Rawel, and Seidelmann 2000). In addition, the authors also reported that the caffeic acid-adducted hemoglobin was less pro-oxidative than its non-modified counterpart, and this was likely related to a higher affinity toward heme. Similar observations were made by Wu et al. (2022b), who found that turkey methemoglobin that had been pre-exposed to quercetin became less effective as a pro-oxidant in washed cod muscle, as evident by the more extended lag phase of lipid oxidation. Further mass spectrometry investigation revealed that quercetin formed a covalent adduct onto the  $\alpha$ -subunit of the hemoglobin and the quercetin-modified hemoglobin released heme 50% slower than the non-modified methemoglobin. Notably, such interactions have been linked to limiting heme loss from methemoglobin and the activity of the heme protein to promote lipid oxidation (Park et al. 2013).

#### 4.3. Partitioning of polyphenols into cellular membranes of muscle: Physical barrier and membrane fluidity change

The membrane phospholipids were widely accepted as the primary substrate of heme protein-mediated lipid oxidation

because of their high degree of polyunsaturated fatty acids and high surface area (Undeland 2016; Wu et al. 2022a). Heme proteins are water soluble and could act as a shuttle to deliver heme into membrane phospholipids, an essential step of heme proteins-mediated lipid oxidation (Grunwald and Richards 2006a). Therefore, the accessibility of heme proteins to membranes plays a crucial role in the process of heme proteins-mediated lipid oxidation (Wu et al. 2021). Several studies have demonstrated that the partitioning of polyphenols into the membrane effectively inhibits Hb-mediated lipid oxidation in hake (*Merluccius merluccius*) microsomes (Pazos et al. 2006), washed muscle of Atlantic cod (*Gadus morhua*) (Lee et al. 2006; Wang et al. 2010), washed muscle of haddock (*Melanogrammus aeglefinus*) (Ballesteros 2009), and mechanically separated turkey (Kathirvel and Richards 2009; Raghavan and Richards 2006).

Some advanced techniques have been used to detect the partitioning of polyphenols into the membrane. They include nuclear magnetic resonance (NMR) spectroscopy, differential scanning calorimetry (DSC), fluorescence anisotropy, partition coefficient, electrophysiological methods, and molecular dynamics simulations (Selvaraj et al. 2015). These techniques could provide specific information about the partitioning ways/localization, as well as membrane change on structure or fluidity. For example, De Granada-Flor et al. (2019) used fluorescence anisotropy to monitor the incorporation of quercetin into mammalian cell plasma membranes. They found that quercetin partitioned to C–O–P–O–C segment of lipid polar head groups via hydrogen bonds formed by its hydroxyl and keto groups. In addition, quercetin interaction with vacuolar membranes demonstrated similar partitioning based on NMR and Fourier-transform infrared (FTIR) techniques (Pawlikowska-Pawłęga et al. 2014). A visualization of this interaction of quercetin and membrane bilayer is shown in Figure 4. The antioxidant mechanisms of partitioning polyphenols into membranes could mainly be attributed to the following process. The polyphenols bind muscle membranes and locate in the polar region or interact at the external surface of bilayers through hydrogen bonding (Sinha et al. 2012). The exposed phenoxy group is in the aqueous region, establishing a molecular trap or physical barrier (Fabre et al.

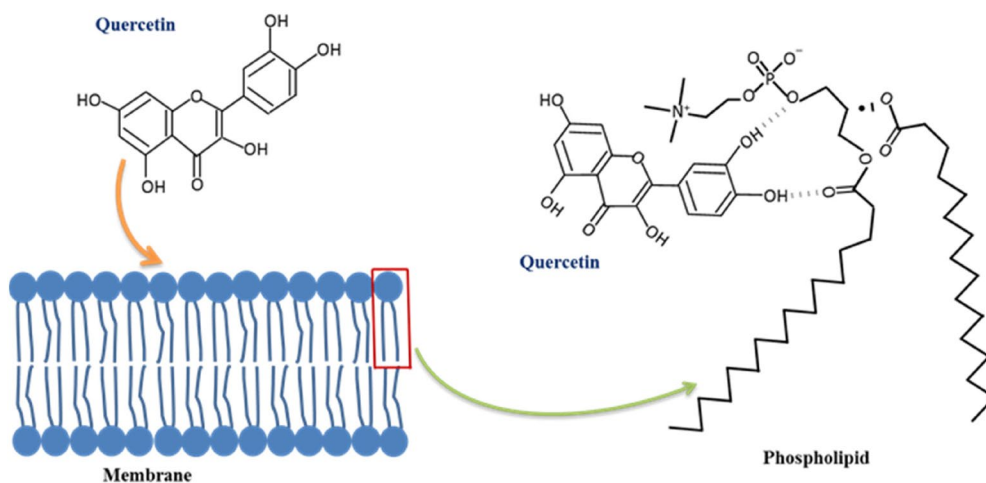


Figure 4. Interaction of quercetin and membrane bilayer via hydrogen bonds formed by its hydroxyl and keto groups.

2015). The trap or barrier could decrease the access of heme proteins or hemin to membrane phospholipids (Ballesteros 2009). In addition, Marques, Viana, and De Almeida (2014) reported the redox properties of polyphenols incorporated in the membrane are maintained or even enhanced when compared to polyphenols in solution. In this situation, polyphenols are efficiently shielded from redox processes for heme proteins in the aqueous phase, maintaining their antioxidant activity toward oxidants attacking membrane phospholipids (De Granada-Flor et al. 2019). Furthermore, the polyphenols partitioning in membranes might scavenge the hemin radicals produced near the membranes thereby inhibiting the propagation of lipid oxidation (Kathirvel and Richards 2009), which is another mechanism.

Besides the physical barrier, the membrane fluidity change induced by polyphenols could be another inhibitory mechanism of partitioning polyphenols into cellular membranes in meat systems. Membrane fluidity determines the rate of heme proteins-mediated lipid oxidation (Kathirvel and Richards 2009). Several studies suggested that polyphenols could localize in membrane interiors and decrease membrane fluidity (Singh and Rajini 2008; Tsuchiya, Tanaka, and Nagayama 2008; Wang et al. 2022). Accordingly, the membranes will become more stable with restrictions on their fluidity. This process might decrease the probability of hemin interactions with unsaturated fatty acids (Lee et al. 2006). Also, the fluidity decrease of the membrane might hinder the diffusion of the  $H_2O_2$  and alkoxyl radicals (Arora et al. 2000). Therefore, the heme proteins-mediated lipid oxidation will be inhibited in the process.

#### 4.4. Polyphenols as reactive oxygen species- and free radical-scavengers

The ability of phenolic compounds to neutralize reactive oxygen species and free radicals by donating electrons is often recognized as the primary mechanism against lipid oxidation. Heme proteins promote the propagation of lipid oxidation by decomposing pre-formed peroxides, e.g., hydrogen peroxide and lipid hydroperoxides, into free radicals via Fenton-like reactions. In addition, oxidation of the heme iron generates superoxide anion, which can undergo spontaneous dismutation to form hydrogen peroxide (Tatijaborworntham and Richards 2018). Hydrogen peroxide causes myoglobin modification, promoting pro-oxidative activity of the heme protein (Mannino et al. 2020). Therefore, adding polyphenols to meat containing oxidizable lipid substrates can delay the onset of heme protein-promoted lipid oxidation in a dose-dependent manner (Brettonnet et al. 2010; Larsson and Undeland 2010; Park et al. 2013; Thiansilakul et al. 2012; Wu et al. 2022b).

The antioxidant activity of phenolic compounds depends substantially on the chemical structure features. The number of hydroxyl groups, the number of benzene rings, and the presence of substituted groups are primary criteria that determine the compounds' reducing power (Chen et al. 2020; Platzer et al. 2022; Sun, Sarteshnizi, and Udenigwe 2022). The antioxidant activity is enhanced when the

hydroxyl groups are in the ortho- and para-positions due to the stabilization of phenoxyl radical, which is not supported by the meta-position (Platzer et al. 2021). Three criteria, known as Bors criteria, have been proposed to explain the antioxidant activity of polyphenols based on the structure-activity relationship (Bors et al. 1990). The criteria are 1) the presence of a catechol group on the B-ring, 2) the combination of 2,3 double bond and a 4-oxo group on the C-ring, and 3) the combination of hydroxyl groups at the positions 3 (C-ring) and 5 (A-ring) and a 4-oxo group on the C-ring (see quercetin structure in Figure 1). These structural features facilitate electron donations and stabilize the radicals via electron delocalization throughout the extended conjugated double bond system (Halake, Birajdar, and Lee 2016; Platzer et al. 2022).

The introduction of substitution groups onto the benzene ring of phenolic acids affects the antioxidant activities differently depending on the nature of the groups. The electron-donating groups enhance antioxidant activity by increasing the electron density and decreasing the O-H dissociation energy of the hydroxyl groups. In contrast, the electron-withdrawing groups have opposite reactions. Chen et al. (2020) found that, at the same number of hydroxyl groups, the free-radical scavenging activity of hydroxylphenylacetic acid (containing  $-CH_2COOH$  as the substituted group, which is a weak electron-donor) was superior to hydroxycinnamic acid ( $-CH_2COOH$ , a weak electron-withdrawing group) and hydroxybenzoic acid ( $-COOH$ , a strong electron-withdrawing group). Likewise, adding an electron-donating methoxyl group to phenolic acids enhances antioxidant activity due to reductions in electron transfer enthalpy and electron affinity. However, methylation of the hydroxyl groups lowers the available electron- and hydrogen-donating groups (Chen et al. 2020; Platzer et al. 2022). Following this, the antioxidant activities of cinnamic acid derivatives against lipid oxidation in cooked ground beef showed the trend of effectiveness: p-hydroxydimethoxyl cinnamic acid (sinapic acid) > o-dihydroxycinnamic acid (caffeic acid) > p-hydroxymethoxycinnamic acid (ferulic acid) > p-hydroxycinnamic acid (p-coumaric acid) (Brettonnet et al. 2010).

Limiting the formation of lipid hydroperoxides could be an indirect way of inhibiting heme protein-mediated lipid oxidation since the pro-oxidative mechanism of heme proteins relies on reactions with pre-formed lipid hydroperoxides. Additionally, to free radical-scavenging activity, polyphenols can inhibit enzymatic lipid hydroperoxide formation by inactivating lipoxygenase activity that persists in muscles even during postmortem storage and processing (Harrysson et al. 2020; Liu et al. 2019; Shang et al. 2021). Extracts from different plants are diverse in polyphenol contents and differ in their profiles and effectiveness in terms of inactivating lipoxygenase activity (Loncaric et al. 2021; Ratnasari, Walters, and Tsopmo 2017). Zhang et al. (2019) found that chlorogenic acid could bind to soybean lipoxygenase with the highest affinity, followed by caffeic acid, ferulic acid, naringenin, and chrysin. Furthermore, the binding was related to enzyme inhibition.

Polyphenols can facilitate other antioxidant entities that deal with free radicals and reactive oxygen species. One antioxidant mechanism of phenolic acids is to replenish active  $\alpha$ -tocopherol that is consumed when interfering with the lipid radical propagation (Iglesias et al. 2009; Larsson and Undeland 2010). Due to its amphiphilic nature, phenolic compounds are thought to act as a mediator that shuttles electrons from water-soluble reducing agents, e.g., ascorbic acid, to  $\alpha$ -tocopheryl radicals in the lipid phase (Iglesias et al. 2009). Caffeic acid at 10 and 100 mg/kg could delay depletion of  $\alpha$ -tocopherol during hemoglobin-mediated lipid oxidation of washed cod muscle at freezing temperature (Larsson and Undeland 2010). Importantly, polyphenols, e.g., quercetin, can also facilitate the activity of peroxide-degrading enzymes by acting as hydrogen donors (Shirasaka et al. 2005).

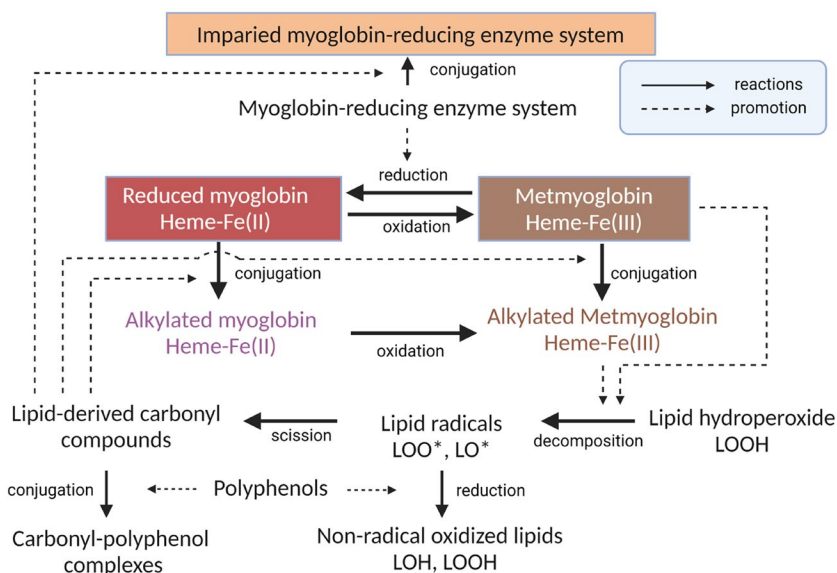
Despite the antioxidant effects, the ability of polyphenols to donate electrons can be considered as a double-edged sword. Tian et al. (2022) mentioned that factors such as concentration, pH, and presence of metal chelators can influence the antioxidant/pro-oxidant activity of tea polyphenols in oil-in-water emulsions. In terms of mechanisms, polyphenols as electron donors can undergo autoxidation generating superoxide anion and facilitate the Fenton reaction by recycling  $\text{Fe}^{2+}/\text{Fe}^{3+}$  and converting superoxides into hydrogen peroxide (De Graft-Johnson and Nowak 2016).

#### 4.5. Role of polyphenols as reactive carbonyl species scavengers

Polyphenols also show a promising ability to mitigate the deleterious effects of the reactive carbonyl species (RCS). RCS are predominately derived from oxidative degradation of lipids and, to some extent, from Maillard reaction via Strecker degradation (Zamora and Hidalgo 2016). In particular, those containing  $\alpha,\beta$ -unsaturated bonds, such as acrolein, 4-HNE, and 4-oxo-2-nonenal, are among the most reactive RCS due to their electrophilicity and ability to

adduct onto nucleophilic side chains of proteins. Additionally, they are linked with oxidative stress and several chronic diseases (Biswas and Mano 2021; Davies and Zhang 2017; Mohan et al. 2022).

The roles of RCS on lipid oxidation and their effects on compromising the oxidative stability of meat can be due to multiple mechanisms (Figure 5). Evidence suggests that RCS can partially deactivate crucial antioxidant enzymes that deal with reactive oxygen species in vitro, such as glutathione peroxidase, glutathione S-transferase, glucose-6-phosphate dehydrogenase, and superoxide dismutase, to different extents (Lesgards et al. 2011). Moreover, alkylation of heme proteins with hydroxylated  $\alpha,\beta$ -unsaturated aldehydes, e.g., 4-HNE and 4-hydroxy-2-hexenal, induced redox instability as well as enhanced pro-oxidative activity of the heme proteins (Grunwald et al. 2017; Tatiyaborworntam et al. 2012). In addition, reactive lipid oxidation-derived carbonyls can also impair Mb reducing capacity in meat by alkylating reductase enzymes, such as lactate dehydrogenase and NADH-cytochrome b5 reductase, that are responsible for the generation of NADH, a reducing entity that is important in delaying meat discoloration (Djimisa et al. 2017; Gonzales et al. 2021; Ramanathan et al. 2011; Xu, Nakano, and Ochiai 2021). An impaired enzymatic reduction system results in an accumulation of oxidized Mb, i.e., metmyoglobin and ferrylmyoglobin, which exhibit hydroperoxidase and lipoxygenase-like activity, which may enhance lipid oxidation (Lapidot, Granit, and Kanner 2005; Min et al. 2008). Moreover, aldehyde-modified myoglobin was a poorer substrate for myoglobin-reducing enzymes; the effect was more pronounced in longer and more unsaturated aldehydes (Lynch and Faustman 2000). In vitro non-enzymatic reduction of metmyoglobin with NADH was also impaired once the protein was modified by 4-HNE (Elroy et al. 2015). Structural changes induced by RCS may make myoglobin unable to accept electrons.



**Figure 5.** A representative scheme showing effects of reactive carbonyl species on redox stability of myoglobin and impairment of myoglobin-reducing enzyme system and possible roles of polyphenols as scavengers of reactive carbonyl species and lipid radicals.

Due to the pro-oxidative effects of RCS, regulation of these carbonyl compounds are essential. In vivo detoxification of RCS involves oxidoreductase enzymes, e.g., aldehyde dehydrogenases, aldehyde reductases, alkenal/alkenone reductases, and glutathione transferases (Mano et al. 2019). On the other hand, several classes of synthetic nucleophiles, e.g., thiol-based, imidazole-based, guanidine-based, and 2-aminomethylphenols-based, have been developed to target RCS as a therapeutic strategy against RCS-related chronic diseases (Davies and Zhang 2017). Meanwhile, polyphenols are considered natural candidates for RCS scavengers (Behl et al. 2022; Biswas and Mano 2021).

Several studies have demonstrated the effectiveness of polyphenols in trapping and alleviating the negative effects of RCS. Acrolein (2-propenal) is one of the most reactive and toxic RCS, and many reductases, which prefer long-chain substrates, show low affinity toward this 3-carbon aldehyde (Mano et al. 2019). Nevertheless, several polyphenols were effective at forming adducts with acrolein and attenuating the toxicity effects of the compound in vitro, e.g., phloretin from apples (Zhu et al. 2012), tea polyphenol, and soy genistein (Huang et al. 2020). Polyphenol extract from persimmon that contains epigallocatechin as the significant component was also reported to prevent acetaldehyde-induced DNA strand breaks (Matsuzaki et al. 2022). Li et al. (2022) reported insoluble fiber-bound polyphenols of different whole grains, especially black highland barley, were effective at scavenging methylglyoxal, glyoxal, acrolein, and malondialdehyde. Furthermore, the RCS-scavenging activity remained even after the fibers had undergone simulated gastrointestinal digestion. The analysis of polyphenols bound to the insoluble fibers of black highland barley indicated the presence of both phenolic acids and flavonoids with ferulic acid being the major phenolic acid and myricetin, luteolin, and quercetin accounting for 80% of all flavonoids.

The preventive effects of polyphenols against RCS modifications on protein in vitro have also been demonstrated through several investigations (Ravichandran et al. 2021; Yuan et al. 2019; Zhu et al. 2013). Related to heme proteins, a few studies exist that report protective effects of polyphenols against glycation of hemoglobin to N-terminal or  $\epsilon$ -amino groups via Schiff base (Liu et al. 2011; Ozyurt, Luna, and Estevez 2016; Wu and Yen 2005). Ozyurt, Luna, and Estevez (2016) found that the effectiveness of different tea catechins against glycation of human Hb under a simulated hyperglycemic condition: epigallocatechin (EGC)  $\sim$  epicatechin (EC)  $>$  epigallocatechin-3-gallate (EGCG), meanwhile, EGC was the best at protecting human serum albumin from carbonylation, followed by EC and EGCG, respectively. However, it was unclear whether the protective effect of these catechins was from the RCS-scavenging activity or the radical-scavenging activity due to the complicated chemistry of glucose and iron in the model system that can generate ketoaldehydes, hydrogen peroxides, and Maillard reaction products that can contribute to protein carbonylation. Liu et al. (2011) found that cranberry extracts alleviated the formation of glycated hemoglobin (HbA<sub>1c</sub>) and contributed

to the protective effect of procyanidins in the extracts. The authors demonstrated that the cranberry phytochemical extracts could effectively react with methylglyoxal, suggesting the RCS-scavenging activity as a mechanism that protects the heme protein from glycation. Furthermore, Das et al. (2020) demonstrated that EGCG could prevent glyoxal modification of bovine hemoglobin in vitro. These observations suggest the protective effect of polyphenols against changes in hemoglobin by RCS.

The structures of polyphenols and RCS play crucial roles in forming carbonyl-phenol adducts. Zhu et al. (2009) tested RCS scavenging ability in different polyphenols against acrolein and 4-HNE and found that only certain polyphenol groups, i.e., flavan-3-ols, theaflavins, cyanomaclurins, and dichlorochalcones, exhibit remarkable RCS scavenging ability. In contrast, flavones, flavanones, and flavanonols were not as effective. In addition, based on a mass spectrometry studies, Zhu et al. (2009) proposed Michael addition as the mode of alkylation of 4-HNE to phloretin via the electrophilic substitution on the A ring of the phenolic compound. Furthermore, the conjugated product is stabilized by a subsequent formation of a hemiacetal between the hydroxyl group of the polyphenol and the carbonyl group of the RCS.

The structure features of the phenol rings play essential roles in being RCS scavengers by contributing to steric hindrance and electron localization over the phenyl rings of the polyphenols (Hidalgo, Aguilar, and Zamora 2017). Therefore, the number and location of hydroxyl groups and the presence of other substitution groups on the phenol rings of polyphenols are vital factors that determine the effectiveness of polyphenols as RCS traps. The presence of an electron-withdrawing group, such as the carbonyl group, on the A ring of polyphenols may hinder the RCS-trapping activity of polyphenols (Zhu et al. 2009). Zamora and Hidalgo (2016) suggest that the location of di-hydroxyl groups at the *meta* position favors the RCS-scavenging activity and that any substitutions that result in electron delocalization yield the opposite effect. For example, in resorcinol, such orientation creates high electron densities at C-2, C-4, and C-6 on the phenolic ring (see resorcinol structure in Figure 1). Additionally, the carbons C-4 and C-6 can act as nucleophiles without steric effects from the hydroxyl groups. Zamora and Hidalgo (2016) found that methylation of either C-2 or C-5 carbon of resorcinol improved the RCS-trapping activity. However, further methylation at both carbons did not have an additional effect, possibly due to steric hindrance. Furthermore, Navarro and Morales (2015) proposed that the hydroxyl group at C-5 of hydroxytyrosol (3,4-dihydroxyphenylethanol), a main phenolic compound in olive oil with 2 hydroxyl groups at the ortho position, enhances the reactivity of the compounds with dicarbonyls such as methylglyoxal.

#### 4.6. Indirect pathways

In addition to the pathways described above, polyphenols function as antioxidants via indirect pathways.

### Regeneration of alpha-tocopherol

One of the ways in which polyphenols work synergistically with other antioxidants is via the regeneration of  $\alpha$ -tocopherol (Neunert et al. 2015; Pazos et al. 2007; Zhou et al. 2005). Alpha-tocopherol is an effective antioxidant against lipid oxidation in meat (Bolger et al. 2016). Notably, a strong synergistic effect between  $\alpha$ -tocopherol and ferulic acid was observed in a liposome system. This was ascribed to the interaction of ferulic acid with the interior of the phospholipid membrane, a common site for attacks from free radicals (Neunert et al. 2015). Additionally, alpha-tocopherol is known to have an antioxidative effect against oxidation of the phospholipid membrane (Carlsen, Møller, and Skibsted 2005). The combined impact of  $\alpha$ -tocopherol and ferulic acid was synergistic rather than additive and was ascribed to a likely regeneration of  $\alpha$ -tocopherol by ferulic acid (Neunert et al. 2015). Likewise, five different green tea polyphenols (four flavonoids and phenolic acid) were able to regenerate  $\alpha$ -tocopherol from the  $\alpha$ -tocopheryl radical in sodium dodecyl sulfate micelles, and has been suggested that electron transfer might be a factor in this reaction (Zhou et al. 2005). Regeneration of  $\alpha$ -tocopherol from the  $\alpha$ -tocopheryl radical was also established by Pazos et al. (2007), where ethanolic solutions of five benzoic acid-derived phenolic compounds and two catechins (flavonoids) were investigated in a hexane medium. From these studies, two of the benzoic acid-derived phenolic compounds and the catechins showed a significant degree of regeneration of  $\alpha$ -tocopherol (Pazos et al. 2007).

### Chelating free iron

As previously described, iron leaked from the heme proteins (or other low molecular weight transition metals) can initiate lipid oxidation via Fenton-type reactions, decompose LOOH, and generate free radical reactive species (Brewer 2011). In addition to instigating lipid oxidation on its own,  $Fe^{2+}$  has also been shown to accelerate autoxidation of ferrous Hb and oxyHb-mediated lipid oxidation (Wu, Park, and Richards 2022). Therefore, chelating free iron is an essential antioxidative mechanism in order to prevent heme protein-mediated lipid oxidation. Flavonoids are able to chelate metals, in addition to their capabilities of scavenging free radicals (Brewer 2011). The effectiveness of flavonoids in chelating free iron has been linked to the steric relationship and the locations of the  $-OH$  groups on the aromatic rings (Brewer

2011) along with the carbonyl group on the C-ring (Leopoldini, Russo, and Toscano 2011). Chelation of a transition metal such as  $Fe^{2+}$  means that this metal ion is now bound in a polyphenol-metal complex and is, consequently, unable to initiate lipid oxidation, as illustrated in Figure 6 (Leopoldini, Russo, and Toscano 2011).

The transition metal chelating effect has been reported for various flavonoids, where the effectiveness in inhibiting microsomal lipid oxidation was greatest for catechins. However, all five tested flavonoids could chelate not only  $Fe^{2+}$  but also  $Fe^{3+}$  and  $Cu^{2+}$  (Potapovich and Kostyuk 2003). On the other hand, earlier studies found that the iron-chelating effect with regard to preventing microsomal lipid oxidation was only crucial for flavonoids with a low free radical scavenging ability (Van Acker et al. 1998; Van Acker et al. 1996). Oligomeric flavonoids, known as proanthocyanidins, have been shown to contain multiple  $-OH$  groups capable of chelating transition metals and donating  $H^+$  and quenching  $O_2^{\cdot-}$  (Brewer 2011; Fukumoto and Mazza 2000).

### Decomposition of lipid hydroperoxides (LOOH)

Lipid hydroperoxides can undergo two-electron reduction, thereby decomposing LOOH to its redox-inert alcohol (LOH) and preventing the initiation of lipid oxidation (Ayala, Munoz, and Arguelles 2014; Girotti 1998). Reduced glutathione-dependent selenoperoxidases most often catalyze this reaction, but also other enzymes with peroxidatic activity may be involved in the decomposition of LOOH (Girotti 1998). This effect has been shown specifically for phospholipase  $A_2$  ( $PLA_2$ ) from pig pancreas in washed cod muscle, where Hb-mediated lipid oxidation was prevented by inhibiting the oxyHb-induced formation of LOOH (Tatijaborworntham and Richards 2018). When adding the combination of rosemary extract and  $PLA_2$  to seasoned pork sausages, it was found that LOOH was decreased more by the combination of the two antioxidants than by rosemary extract alone after 42 days of a 245-day storage period at  $-20^\circ C$  (Whalin et al. 2022). Rosemary contains various antioxidative constituents, mainly in the form of phenolic diterpenes and phenolic acids (Brewer 2011). It is unclear if the prevention of decomposition of LOOH was due to  $PLA_2$  alone or if there was a synergistic effect with antioxidative constituents from the rosemary extract. Nevertheless, rosemary extract alone has been found to stabilize LOOH in frying oil, preventing LOOH breakdown to radical species (Rěblová et al.

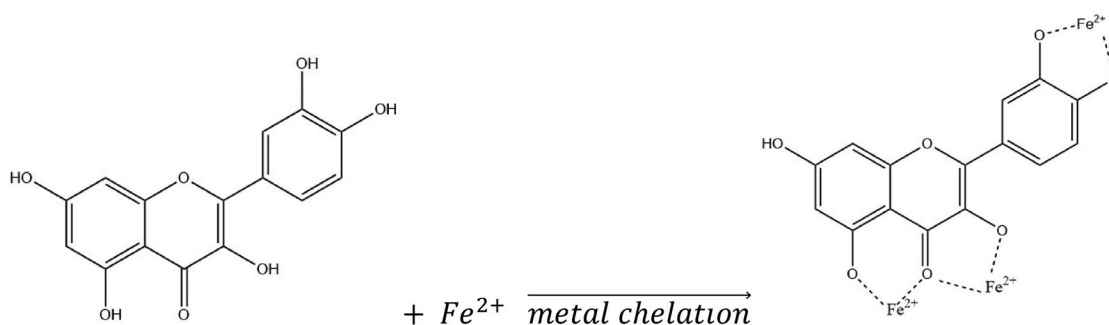


Figure 6. The chelation of polyphenol to free iron to form a polyphenol-metal complex.

1999). It is therefore plausible that in the case of the pork sausages, rosemary extract helped stabilize LOOH, and PLA<sub>2</sub> then catalyzed a reduction of LOOH to LOH.

## 5. Conclusions

Plants are rich sources of natural antioxidants that can be used to protect foods from oxidative degradation. In particular, polyphenols possess reducing power to suppress the deleterious effects of free radicals and reactive oxygen species. In muscle food, the effectiveness of polyphenols in inhibiting the pro-oxidative activity of heme proteins, primarily Mb and Hb, has been demonstrated to extend the lag phase of lipid oxidation. Recent research evidence has suggested that the mechanisms of action of polyphenols go beyond just their abilities to neutralize free radicals and reactive oxygen species. In particular, the polyphenol-protein interactions of covalent and non-covalent natures can alter the properties of proteins, including rendering the heme proteins into less effective or unable to participate in the course of lipid oxidation. Partitioning of polyphenols into cellular membranes of muscle could establish a molecular trap or physical barrier, which may decrease the access of heme proteins or hemein to membrane phospholipids. The multitude of antioxidant mechanisms of polyphenols can provide synergism that enhances their effectiveness, meaning the dose requirement is decreased. The structural diversity of both the plant polyphenols and the heme proteins from different animal species add to the complexity of the polyphenol-heme protein interactions. In this respect, knowledge gained on the structure-activity relationship and intermolecular interactions based on instrumental in silico simulations allow for tailoring of specific polyphenols for specific heme proteins. Hereby, the most effective polyphenols can be chosen for each type of muscle food.

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The authors declare no conflict of interest.

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