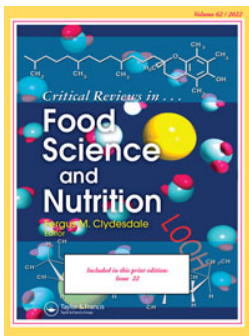# Model systems for studying lipid oxidation associated with muscle foods: Methods, challenges, and prospects

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REVIEW

Model systems for studying lipid oxidation associated with muscle foods: Methods, challenges, and prospects

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ABSTRACT

Lipid oxidation is a complex process in muscle-based foods (red meat, poultry and fish) causing severe quality deterioration, e.g., off-odors, discoloration, texture defects and nutritional loss. The complexity of muscle tissue -both composition and structure- poses as a formidable challenge in directly clarifying the mechanisms of lipid oxidation in muscle-based foods. Therefore, different in vitro model systems simulating different aspects of muscle have been used to study the pathways of lipid oxidation. In this review, we discuss the principle, preparation, implementation as well as advantages and disadvantages of seven commonly-studied model systems that mimic either compositional or structural aspects of actual meat: emulsions, fatty acid micelles, liposomes, microsomes, erythrocytes, washed muscle mince, and muscle homogenates. Furthermore, we evaluate the prospects of stem cells, tissue cultures and three-dimensional printing for future model system development. Based on this reviewing of oxidation models, tailoring correct model to different study aims could be facilitated, and readers are becoming acquainted with advantages and shortcomings. In addition, insight into recent technology developments, e.g., stem cell- and tissue-cultures as well as three-dimensional printing could provide new opportunities to overcome the current bottlenecks of lipid oxidation studies in muscle.

1. Introduction

Lipid oxidation of muscle foods (fish, poultry, and red meat) is a large research area with around 70 years of history which relates to degradation of various parameters of quality, such as odor, flavor, color, texture, and nutritional value (Dominguez et al. 2019; Undeland 2016; Wu, Richards, and Undeland 2022b). Research trends have changed according to the development of analysis methods and food scientists' efforts. In the 1950s–1980s, many studies focused on detecting links between lipid oxidation and fatty acid patterns, lipid classes/contents and endogenous pro- or antioxidants (Lee et al. 1975; Tappel 1955; Wills 1966). Then the focus shifted to investigation of free radical chain reactions (Bielski et al. 1985; Boveris, Galatro, and Puntarulo 2000; Puppo and Halliwell 1988). In the last 20 years, the greatest steps forward have been taken within the area of heme protein-(hemoglobin, Hb and myoglobin, Mb) mediated lipid oxidation (Richards et al. 2007; Undeland, Hultin, and Richards 2002; Undeland, Kristinsson, and Hultin 2004; Wu et al. 2017), as well as within the area of oxidation prevention in muscle foods using different natural antioxidants.

Muscle tissue is a complex system that contains many components, e.g., lipid substrates in the form of triacylglycerols and phospholipids, pro- and antioxidants, as well as different muscle proteins; sarcoplasmic reticulum, myofibrillar proteins and connective tissues (Medina et al. 2012). The membrane of a muscle cell contains phospholipids which are vulnerable to lipid oxidation due to their large surface area and degrees of unsaturation (Cui and Decker 2016). Muscle microstructure can affect lipid-pro-oxidant interactions, which has been shown to cause varying oxidation rates depending on the animal species from which the muscle was obtained (Wu et al. 2021b).

Because of the complexity of muscle tissues, in vitro model systems, e.g., emulsions, fatty acid micelles, liposomes, microsomes, erythrocyte, washed muscle mince and muscle homogenates have been used to study the mechanisms of lipid oxidation. However, one should exercise caution when extrapolating findings from model systems to *postmortem* muscle tissue, and it is important to discuss pros and cons of the different models used over the years to simulate muscle foods. To the best of our knowledge, there are so far no attempts to

review, summarize, or compare the different model systems used in muscle lipid oxidation research. Thus, we here review the seven most commonly applied model systems and discuss their principle, preparation, and application. The advantages and drawbacks of each model are summarized, and we provide some comments about future prospects.

2. Endogenous muscle factors associated with lipid oxidation

Before discussing individual model systems and how they can be used to study the influence of exogenous factors, we will address the critical endogenous factors relevant to lipid oxidation because that knowledge is the basis for model system design. In this review, we discuss muscle model systems that are used mainly to study lipid oxidation pathways, mechanisms, and the influence of exogenous factors; thus, we will not discuss the endogenous antioxidants in muscle foods. Many excellent reviews about endogenous antioxidants have already been published, with examples being those of Dominguez et al. (2019), Undeland (2016) and Wu, Richards, and Undeland (2022b).

2.1. Muscle structure

Although there are more than 600 different muscle types that vary in shape, size, and activity, at the cellular level, there is close resemblance among muscles from a variety of vertebrate animals (Erickson 2008). However, fish muscle structure is largely different from that of avian and mammalian muscles. For example, fibers diameter from fish muscle (>50 μm) tend to be bigger than muscle fibers from red meat (<50 μm), and fish muscle generally contains fewer mitochondria, a thinner sarcolemma, and more sarcoplasm (Erickson 2008). Also, there is significantly less of connective tissue proteins in fish given the fact that fish is supported by the surrounding water, i.e., does not need to carry its own weight.

The variability in muscle structure could contribute to the different oxidative stability between fish and red meat (Wu et al. 2021b). The complex morphologies of distinct layers of muscle are indeed difficult to replicate in a model system. Comparisons of the microstructures between washed cod muscle mince and washed pig muscle mince showed that the washed mammalian muscle had denser and wrapped structures, which was hypothesized to hinder accessibility of pro-oxidants to lipid substrates (Wu et al. 2021b). For the structure of fish muscle, myocommata is a special structure to link single muscle cell or fiber. Furthermore, myocommata has a large surface/volume ratio and is closed to fat cells, which are easier to access the pro-oxidants (e.g., Hb, and Mb) compared those wrapped fat cells in mammalian muscle (Sharifian et al. 2014). For example, it has been reported that myocommata started to deteriorate after the fish dies and then generate gaping owing to the isolation of myotomes (Chéret et al. 2005). The generating gaping in fish could better facilitate fat cells or membrane of muscle cells access oxygen and Hb. Thus,

muscle structure has an important influence on lipid oxidation.

2.2. Lipid substrates

Unsaturated fatty acids are abundant substrates for lipid oxidation in muscle foods (Vieira, Zhang, and Decker 2017). Thus, free unsaturated fatty acids have sometimes been used as lipid substrates in different models (Hajimohammadi 2020; Hajimohammadi and Bagheri 2017; Hajimohammadi and Nosrati 2018). In muscle food, lipids are primarily referred to triacylglycerols and phospholipids, with small amounts of free fatty acids (FFAs), cholesterol, and tocopherols (Pereira and Abreu 2018). Although triacylglycerol contribute to a large proportion to the total lipid in muscle food, particularly in more fatty cuts or species, membrane phospholipids have been regarded as the most important substrates in lipid oxidation of muscle, meaning that the total lipid content seems to play very little role (Undeland, Hultin, and Richards 2002; Wu, Abdollahi, and Undeland 2021a). Both the degree of unsaturation and the concentration of phospholipids have generally been considered as crucial factors in lipid oxidation in muscle food (Amaral, Da Silva, and Lannes 2018). However, we (Wu et al. 2021b) found that differently unsaturated phospholipids (polyenoic indexes of 282 vs 24) at the same concentration had a similar rate of oxidation when Mb was the pro-oxidant in a washed pig muscle mince system. Our study also suggested that the accessibility of pro-oxidants to phospholipids may be more important than their degree of saturation (Wu et al. 2021b). Similarly, lipid oxidation results retrieved from ice storage of three types of minced fish backbones derived from herring, cod, salmon did not show any significant correlation with the degree of unsaturation and the content of polyunsaturated fatty acids (PUFA), but significant correlation with Hb levels (Wu, Abdollahi, and Undeland 2021a). In addition, Richards and Hultin (2001) reported that trout Hb with 0.01% lipids generated a strong rancid odor and significantly increased TBARS values in washed cod model during ice storage, but the rate and extent of rancidity were not increased by the presence of >6 times more membrane phospholipids. These results indicated the endogenous pro-oxidants (such as Hb, and Mb) played more important roles in lipid oxidation than the degree of unsaturation and the concentration of phospholipids.

Another important point is that fatty acids exist as both free and esterified forms although the FFA concentration is low in fresh muscle food (Ahmmed et al. 2021). The classic theory asserts that FFAs oxidize more readily than their esterified counterparts (Labuza and Dugan 1971). However, we have found that the hydrolysis of lipids or the addition of FFAs appears to inhibit oxidation in turkey mince (Wu et al. 2021c) and washed cod muscle (Tatiyaborwterntham and Richards 2018; Tatiyaborwterntham, Yin, and Richards 2021). Thus, the choice of fatty acid form -free or esterified- is important when a model muscle system is designed.

2.3 Endogenous pro-oxidants

The presence of transition metals, e.g., Fe and Cu (in either free or complex forms) is an important parameter that affects the oxidative stability of muscle food (Chaijan and Panpipat 2017). The primary sources of Fe in muscle are heme proteins, Hb and Mb (Wu, Ghirmai, and Undeland 2020; Wu et al. 2017). Heme protein concentrations in meat depend on animal species, muscle type, and anatomical location of muscle (Min and Ahn 2005) as well as slaughtering and bleeding techniques (Alvarado et al. 2007; Sabow et al. 2016). Hemin release from these heme proteins is thought to be responsible for oxidation of lipids due to ability to decompose pre-formed lipid hydroperoxides (LOOHs) into lipid free radicals and secondary products (Wu, Richards, and Undeland 2022b). The contribution of free iron to lipid and protein oxidation was found to be predominant during cooking (Zhang et al. 2022).

Oxidoreductase enzymes also have impact on lipid oxidation. Lipoxygenase (LOX) has been identified as an important pro-oxidant in fish muscle (Tolasa Yılmaz et al. 2018; Wu et al. 2022a). In addition, microsomal peroxidases and dioxygenases can initiate lipid oxidation in meat (Min et al. 2008). In the presence of LOX, conjugated diene hydroperoxy products may be generated with hydrogen abstraction from the allylic methylene position of PUFA (Hui 2006). Muscle myeloperoxidase is an enzyme that catalyzes hypochlorous acid generation from H_2O_2 and chloride. Subsequently, hypochlorous acid reacts with $O_2^{\bullet-}$ to produce $^{\bullet}OH$ (Folkes, Candeias, and Wardman 1995). Interestingly,

myeloperoxidase generates $^{\bullet}OH$ six times faster than the Fenton reaction (Hui 2006).

3. Model systems

It is important to note that most models used to simulate muscle were developed from the perspective of the lipid substrate; thus, assuming the lipids are the most important principal component of muscle models. Muscle oxidation models are normally prepared by the following four approaches: 1) selecting relevant lipids of muscle and mix them to obtain a model, e.g., emulsion, fatty acid micelles, or liposomes; 2) select cells that contain both oxidants and lipid substrate, e.g., erythrocytes; 3) extract components of interest, exclude components of less interest, to simulate actual muscle structure, e.g., microsomes and washed muscle mince; 4) modify the actual muscle, e.g., diluting it such as in muscle homogenates.

3.1. Emulsions

An emulsion is a system that contains two immiscible liquids as shown in Figure 1. In general, oil-in-water emulsions consist of three different components: water (the dispersing phase), lipids (the dispersed phase), and surface-active agent (the interface) (Hu, Decker, and Mcclements 2019). Emulsion models for oxidation studies are prepared by mixing a source of unsaturated lipids (e.g., triacylglycerols from oils, oils stripped of their antioxidants, fatty acid esters or FFAs) with
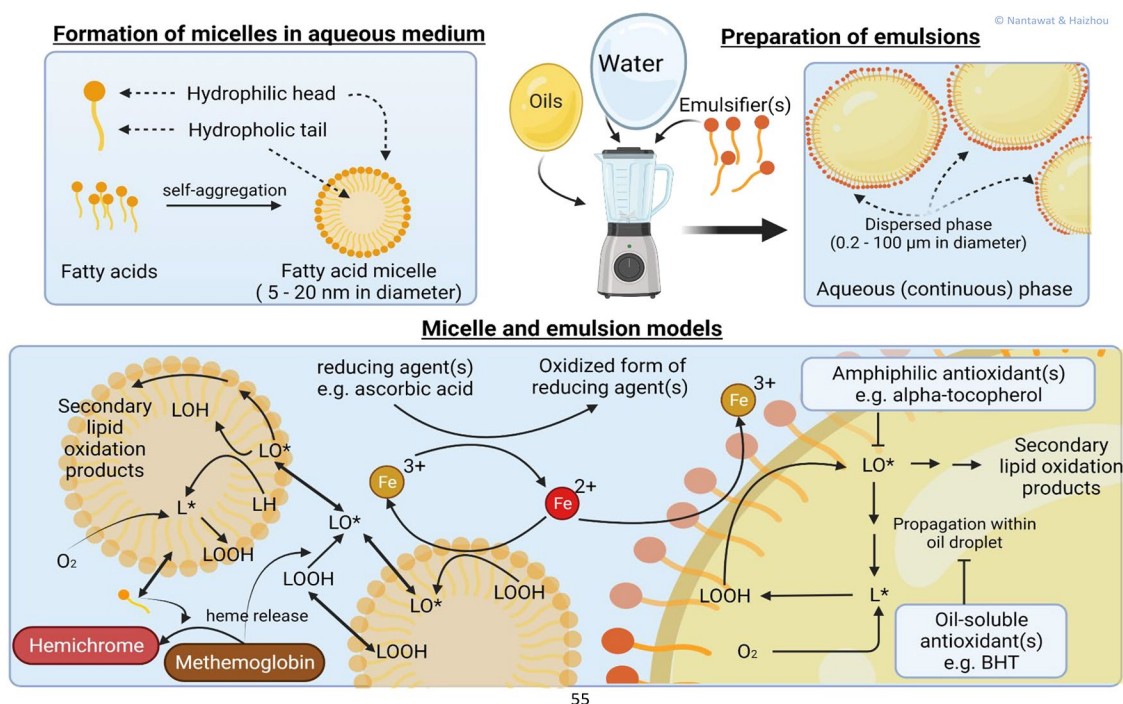
Figure 1. Fatty acid micelle and emulsion models. Above their critical micellar concentration, amphiphilic compounds tend to spontaneously self-aggregate to form lipid micelles by hiding the hydrophobic part inside and exposing the hydrophilic part to the aqueous medium. Amphiphilic emulsifiers can surround and stabilize oil droplets that are formed by physical agitation of the mixture between oil and aqueous medium. In this figure the roles of water-soluble, oil-soluble, and amphiphilic antioxidants on lipid oxidation catalyzed by free iron in the Fenton reaction scheme are presented. Due to their hydrophilic part, fatty acids and lipid hydroperoxides may jump in and out between lipid micelles and interact with aqueous compounds, e.g., Mb and Hb.

an aqueous phase containing surface-active agents (e.g., Tween-20, proteins or sodium dodecyl sulfate) into an oil-in-water (O/W) emulsion (Wills 1964; Yin et al. 1992). The mixture is typically made into a coarse emulsion with a low mixer and then particle size is further reduced using equipment such as homogenizers or sonicators. After emulsification, the prooxidants and/or antioxidants of interest can be added. The molecule of interest will partition to various degrees into the hydrophobic emulsion droplet core, the aqueous phase or it will interact with the surfactants at the emulsion droplet interface. Since some of the surfactant partitions into the aqueous phase once the droplet interface is saturated, surfactant micelles will also commonly exist in the aqueous phase. These surfactant micelles can solubilize the prooxidants and antioxidants of interest which can impact their reactivity (Inchingolo et al. 2021).

In early research on lipid oxidation of meat or fish (1955–1975), many food scientists studied oxidation from only a chemical point of view (Lee et al. 1975; Liu 1970; Tappel 1955; Wills 1966). Identification of the catalytic activity of pro-oxidants (e.g., Mb, Hb, nonheme iron and copper) and the reaction products were a large focus (Burri et al. 2020; Lee et al. 1975). Emulsion models are however also useful for studying the partitioning of oxidized lipids into environments of different polarity. Nuchi et al. (2002) reported that the polarity of LOOHs causes them to migrate to the interface of the emulsion droplet where they can interact with water soluble prooxidants, which is in accordance to what was observed in lipid bilayer modes (Junqueira et al. 2021).

The disadvantage of using oil-in-water emulsions as a model system is that they differ from cell membranes, the primary location of oxidation in muscle. For example, oil-in-water emulsions will have a larger lipid core that could host more lipid soluble components. They will also have less surface area than cell membranes at an equal lipid concentration and they could differ in charge depending on the surfactants used (Mcclements and Decker 2000). Emulsion models may be more applicable to certain muscle-derived food products, e.g., emulsion-type sausages and emulsified surimi products. However, the roles of muscle proteins in stabilizing lipid droplets should then be considered as well (Jiang and Xiong 2015).

3.2. Fatty acid micelles

Fatty acid micelles have been used in many studies on the fundamental aspects of lipid oxidation due to ease of preparation and high oxidizability thanks to high surface/volume (Table 1). Unlike emulsion models, micelles can spontaneously form upon reaching a certain concentration, the critical micelle concentration, of surface active molecules as shown in Figure 1 (Mohajeri and Noudeh 2012). Co-surfactants, e.g., sodium dodecyl sulfate or Triton X may be included to increase micelle stability (Hauville et al. 1998). Typically, fatty acid micelles are between 5 and 20 nm in diameter, i.e., a thousand times smaller than emulsion droplets (Mohajeri and Noudeh 2012).

The extent to which fatty acid micelles exists in meat and meat products is unclear, but they can still provide information to monitor processes associated with lipid oxidation (Vitrac et al. 2005). Several micellar model studies have been used to define factors that affect lipid oxidation, such as the radiation dose rate (Mekhloufi et al. 2005), the concentration of lipids (Scollo et al. 2018), the fatty acid nature and the number of double bonds (Pliss et al. 2021), the ionic strength of the medium (Raleigh and Kremers 1978) and the pH (Johnson, Inchingolo, and Decker 2018). The role of muscle food pro-oxidants, e.g., Mb and Hb in stimulating lipid oxidation has also been studied in fatty acid micelles Baron, Skibsted, and Andersen (2000).
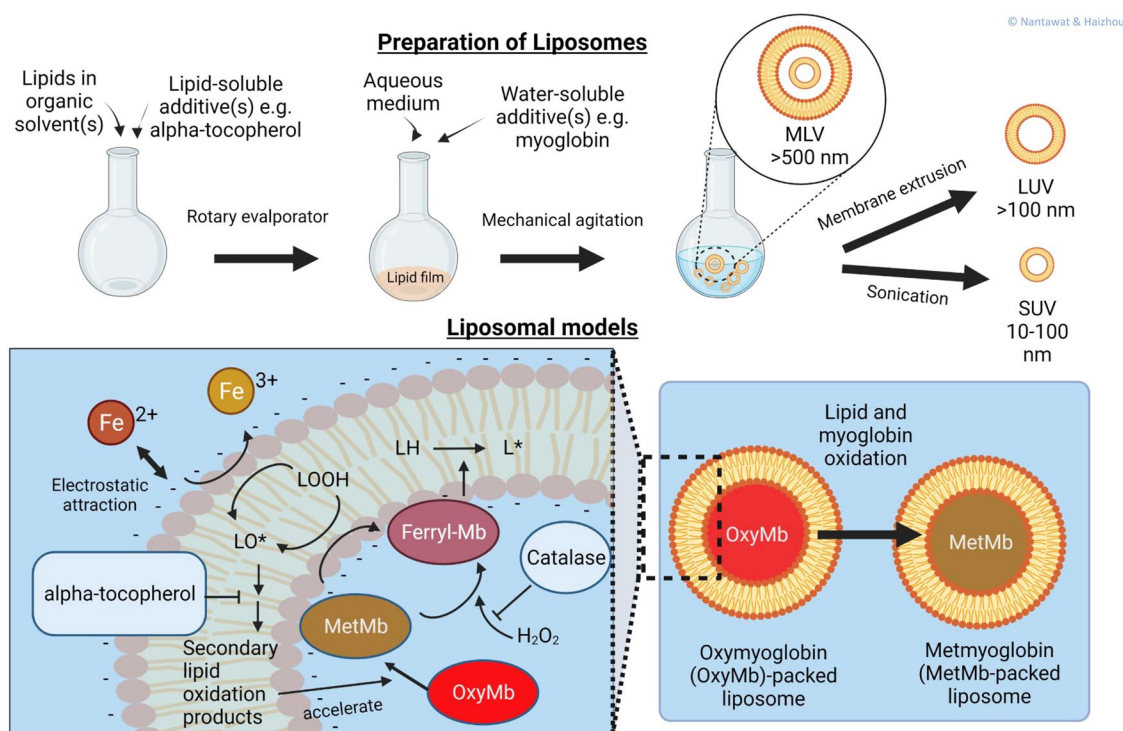
3.3. Liposomes

Liposomes are spherical phospholipid vesicles with at least one concentric bilayer encircling a hydrophilic space. Liposomes can be used as carriers for both water-soluble and lipid-soluble compounds (Akbarzadeh et al. 2013). A visualization of liposomes was shown in Figure 2. In muscle tissues, membrane phospholipids in sarcoplasmic reticulum and sarcolemma are susceptible to oxidative degradation because of the high content of unsaturated fatty acids required to maintain membrane fluidity and the large surface area in direct contact with oxidants and pro-oxidants (Heden, Neufer, and Funai 2016). Therefore, being structurally similar to phospholipid membranes, liposomes have a long history for studying kinetics and mechanisms of lipid oxidation in meat systems (Medina et al. 2012; Schnitzer, Pinchuk, and Lichtenberg 2007).

Liposomes can be prepared by several different methods. Unilamellar liposomes are prepared by hydration of dried lipid films with an aqueous medium. Multilamellar liposomes are prepared by dispersing phospholipids in aqueous media and then decreasing their size by sonication membrane extrusion, or homogenization (Frenzel and Steffen-Heins 2015; Guldiken et al. 2018). Other available methods to make liposomes include are solvent dispersion methods, e.g., ethanol injection, reverse phase evaporation vesicles, and detergent removal methods (Akbarzadeh et al. 2013). Membrane extrusion is employed for obtaining uniformly-sized lipid vesicles.

Liposomes can be prepared from synthetic or natural phospholipids. The major advantage of synthetic phospholipids is that the particular fatty acids esterified to the glycerol backbone are well defined and customizable to meet experimental requirements. Phosphatidylcholine and phosphatidylethanolamine are commonly used, being the most abundant phospholipids in cell membranes (Alberts et al. 2002; Salgo, Corongiu, and Sevanian 1992). Natural phospholipids can be obtained from muscle tissues (Genot et al. 1992). Lipid-soluble additives, e.g., alpha-tocopherol (Yin et al. 2012), cholesterol (Mosca, Ceglie, and Ambrosone 2011), and azo-radical initiator (Culbertson and Porter 2000), may also be incorporated into the bilayers during the preparation of dried lipid films. Water-soluble components, e.g., Mb may be packed within the void inside liposomes during the hydration of the lipid films (Yin and Faustman 1993).

Table 1. Main characteristics, advantages and disadvantages of emulsions, fatty acid micelle, erythrocyte, meat homogenate and washed muscle models.

Model	Main characteristic(s)	Advantages	Disadvantages	References
Emulsions	1. It is the colloidal system in which the dispersed phase and the dispersion medium both are liquid. 2. It is a mobile liquid. 3. Droplets of one liquid dispersed in another liquid. 4. No tendency to absorb a liquid. 5. Need anionic surfactants.	1. Simple preparation and usage 2. Cost effective 3. Accurate analysis of each factor that may effect on lipid oxidation 4. Oil–water interface is critically involved in the reactions	1. Storage conditions may affect stability 2. Liable to microbial contamination which can lead to cracking. 3. Uniform and accurate does my not be achieved 4. It is not appropriate model for lipid oxidation investigation reliant on animal species, muscle type, and anatomical location	(Bieri and Anderson 1960; Echegaray et al. 2021; Hu, Decker, and Mcclements 2019; Lee et al. 2020; Philpot 1963; Salvia-Trujillo et al. 2017; Shahidi and Zhong 2015; Zalkin and Tappel 1960)
Fatty acid micelle	1. contain hydrophilic/polar region 2. the polar region faces the outside surface 3. small size 4. The catalyst is needed	1. Feasibility of preparation and usage 2. High mobility 3. Suitable for measuring lipid oxidation prompted by free radicals 4. Oil–water interface is critically involved in the reaction 5. Significant surface activities and increase their ability to interact	1. lack of stability of micelles in the physiological environment 2. It is not appropriate model for lipid oxidation investigation reliant on animal species, muscle type, and anatomical location	(Barriuso, Astiasaran, and Ansorena 2013; Laguerre et al. 2020; Mcclements et al. 1992; Mitra, Cholkar, and Mandal 2017; Tzankova et al. 2017; Vitrac et al. 2005)
Liposomes	1. Lipid bilayers made of polar lipids primarily synthetic or natural phospholipids 2. Spherical shapes with one or more lipid bilayers surrounding aqueous space 3. Variation in size ranges	1. Simple preparation and usage 2. Hydrophobic core of lipid bilayers available for lipid-soluble compounds 3. Aqueous space available for packing hydrophilic compounds 4. controlled lipid composition 5. Direct spectrophotometric monitoring of lipid oxidation possible for kinetic studies	1. Instability over prolonged storage 2. Spherical shape not representing actual lipid membranes in muscle tissues 3. It is not appropriate model for lipid oxidation investigation reliant on animal species, muscle type, and anatomical location	(Akbarzadeh et al. 2013; Chan et al. 1997; Genot et al. 1992; Kaurinovic and Popovic 2012; Li, Yeo, and Tan 2000; Schnitzer, Pinchuk, and Lichtenberg 2007; Vossen et al. 1993)
Microsome	1. Reformed lipid membranes from fragmented endoplasmic reticulum obtained from actual muscle tissues 2. Containing naturally-present antioxidants, e.g., alpha-tocopherol 3. Containing membrane-bound enzyme activities	4. A better representative of lipid membranes in muscle tissues in terms of composition 5. Models for studying enzymatic and non-enzymatic lipid oxidation 6. Models for studying dietary antioxidant metabolism 7. Derived from muscle tissues; therefore, linking lipid oxidation studies with feed supplementation studies	1. Tedious preparation process 2. it is subject to inconsistency, e.g., fatty acid profile, enzyme activity, alpha-tocopherol content 3. Non-uniform in size 4. Not suitable for direct photo spectrometric studies due to turbidity	(Guengerich 1977; Mercier et al. 1998; Perez et al. 2016; Rey, Lopez-Bote, and Arias 1997; Yamazaki et al. 1997; Yin et al. 2013)
Erythrocyte	1. It is mainly composed of proteins and lipids 2. A two-dimensional (2D) structure, comprised of a cytoskeleton and a lipid bilayer, tethered together 3. Sometimes needs catalyst 4. Constantly generate O_2^- with autoxidation of Hb	1. Simplest available cell type for study 2. Talented of contain high concentrations of polyunsaturated fatty acids 3. Hb in blood gets more space in the cells so that more oxygen can be carried 4. Protected by a variety of antioxidant systems	1. During lipid oxidation the erythrocyte volume decreases with time 2. Lipid peroxide formation may also result in membrane damage 3. Change shape in response to an external force	(Cimen 2008; Greenberg et al. 2008; Jha and Rizvi 2009; Karabulut et al. 2009; Li and Lykotrafitis 2014; Li et al. 2013; Niki 2009; Pandey, Mishra, and Rizvi 2009; Wu et al. 2017)
Washed muscle mince	1. It is removed from prooxidants/antioxidant 2. Iron and Hb be eliminated to avoid undesired interference 3. Comprises myofibrillar proteins and membrane phospholipids	1. Reliable information on lipid oxidation in muscle 2. elimination of undesired contents on lipid oxidation 3. possibility of direct study of muscle 4. Appropriate model for lipid oxidation reliant on animal species, muscle type, and anatomical location 5. It is appropriate for investigation of lipid oxidation mechanism and explore of effect of different parameters on lipid oxidation in muscle	1. Preparation is laborious, high cost, and ethically eristic 2. Needs to modify washing process 3. Needs modified conditions for grown animals, sacrifice, muscle homogenization 4. Accurate analysis is difficult	(Cai et al. 2013; Cui et al. 2018; GÜner et al. 2020; Richards, Modra, and Li 2002a; Vallejo-Cordoba, Rodriguez-Ramirez, and Gonzalez-Cordova 2010; Wu et al. 2017; Xiao et al. 2018)
Meat homogenate	1. Tissue homogenates generate peroxide under endogenous condition 2. requires substrates 3. Needs catalyst	1. Lipid peroxides are formed rapidly 2. Appropriate model for lipid oxidation reliant on animal species, muscle type, and anatomical location 3. Rapid and easy screening protocol for novel antioxidant discovery	1. Preparation is laborious, high cost, and ethically eristic 2. Proteins cause to a continuous loss of malondialdehyde concentration to secondary reactions 3. Needs modified conditions for grown animals, sacrifice, muscle homogenization 4. Accurate analysis is difficult	(Ballester-Costa et al. 2017; Bieri and Anderson 1960; Jin et al. 2012; Mcmurray and Dormandy 1974; Philpot 1963; Salami 2021; Terevinto et al. 2010; Zalkin and Tappel 1960)

Preparation of Liposomes

Liposomal models

Figure 2. Liposome models. A liposome preparation scheme shows how water- and lipid- soluble additives can be incorporated into the lipid vesicles. The lipid-soluble additives stay within the lipid bilayers, while the water-soluble additives in the aqueous medium come into contact with the lipid bilayers via different modes of interactions, e.g., electrostatic attraction, hydrophobic interaction. Liposomal models for studying lipid oxidation by free iron and Mb are presented.

In addition to the degree of unsaturation, size and surface charge (zeta potential) are important physicochemical characteristics that influence oxidation of liposomes (Schnitzer, Pinchuk, and Lichtenberg 2007). Varying by size and number of lamellae, the three most common types of liposomes are small unilamellar vesicles (SUV; size 20–100 nm), large unilamellar vesicles (LUV; size > 100 nm), and multilamellar vesicles (MLV; size > 500 nm) (Chinnagounder Periyasamy et al. 2012). Compared with LUV, the small size of SUV not only increases the surface area, but also surface curvature and permeability of the bilayers which ultimately destabilize the lipid vesicles against transition metal-promoted lipid oxidation (Li, Yeo, and Tan 2000). Genot et al. (1992) compared different liposomal preparation methods and suggested that LUV are suitable models for lipid oxidation studies because of uniform size, structural integrity upon oxidation, and low spectrophotometric interference.

Surface charge of liposomes is influenced by ionic strength, and pH and may affect oxidative stability of liposomes (Mozuraityte, Rustad, and Storrø 2006). Negatively charged phospholipids attract transition metal ions, e.g., iron and copper, in close proximity to oxidizable lipids (Dacaranhe and Terao 2001; Gal, Pinchuk, and Lichtenberg 2003), although the effect of this phenomenon on lipid oxidation seems inconsistent. Thanonkaew et al. (2007) found that NaCl at 0.2–2.0% retarded iron-promoted oxidation of squid liposomes, possibly because of displacement of bound iron from the liposomal surface. However, Dacaranhe and Terao (2001) found that dipalmitoyl-phosphatidylserine at 10%mol

exhibited both iron-binding ability and an antioxidant activity against iron-promoted oxidation of egg yolk phosphatidylcholine-containing liposomes.

Related to lipid oxidation in muscle foods, free iron, free heme, and heme proteins (Hb and Mb) are often used as pro-oxidants in mechanistic studies of liposomal oxidation (Carvajal et al. 2009; Litvinko, Skorostetskaya, and Gerlovsky 2018; Lynch and Faustman 2000; Min, Nam, and Ahn 2010; Thanonkaew et al. 2007; Yamauchi et al. 2017). Furthermore, mechanisms of both lipid and Mb oxidation, related to rancidity and discoloration of meat, respectively, were studied simultaneously (Faustman et al. 2010). Abraham et al. (2016) studied endogenous antioxidant capacity of beef by extracting and incorporating Mb-containing sarcoplasm into liposomes which were stored under fluorescent illumination. The investigators found positive correlations between Mb oxidation, lipid oxidation, and oxidation-reduction potential of sarcoplasm-containing liposomes. Using oxymyoglobin-containing liposomes, Yin and Faustman (1993) found a dissimilar effect of phospholipid headgroups on redox stability of oxyMb. With a similar fatty acid profile, the phosphatidylethanolamine-based liposome promoted more lipid and Mb oxidation than the phosphatidylcholine-based liposome. Chan et al. (1997) pointed out the activity of H_2O_2 in the oxidation of both oxymyoglobin and lipid oxidation by including superoxide dismutase (SOD) and catalase (CAT) in the liposome system. Liposomes are also used in combination with meat system. Chen et al. (2017) prepared liposomes containing *Porphyra haitanensis*-derived phycobiliproteins which were added to

a liposome-meat model; the authors found that the active compounds inhibited oxidation of the composite model.

Interactions between membranes with lipid-soluble antioxidants and pro-oxidants have been studied using liposomal models. For example, Szebeni et al. (1988) investigated binding of Hb to the surface of liposomal bilayers, a phenomenon that was counteracted by inclusion of cholesterol to promote fluidity to the liposomal membranes and hinder the partition of Hb into the membranes. Small-angle X-ray diffraction is a useful technique for elucidating the relationship between membrane order and oxidizability. Using this technique, Mcnulty et al. (2007) found contrasting effects of different carotenoids on membrane structure alteration and autoxidation of liposomal lipids. The authors reported that membrane disorder caused by lycopene and beta-carotene caused increased lipid oxidation, whereas membrane structure-preserving astaxanthin exhibited antioxidant activity.

Simple and customizable liposome models enable fundamental and mechanistic research on lipid oxidation and antioxidants because components can be selectively included or excluded. Despite the benefits, liposomal vesicles may not be a true representative of muscle membranes in terms of shape and composition. Nevertheless, this lipid model can be desirable for the meat industry to gain rapid recognition of potential antioxidants (Nieto, Huvaere, and Skibsted 2011).
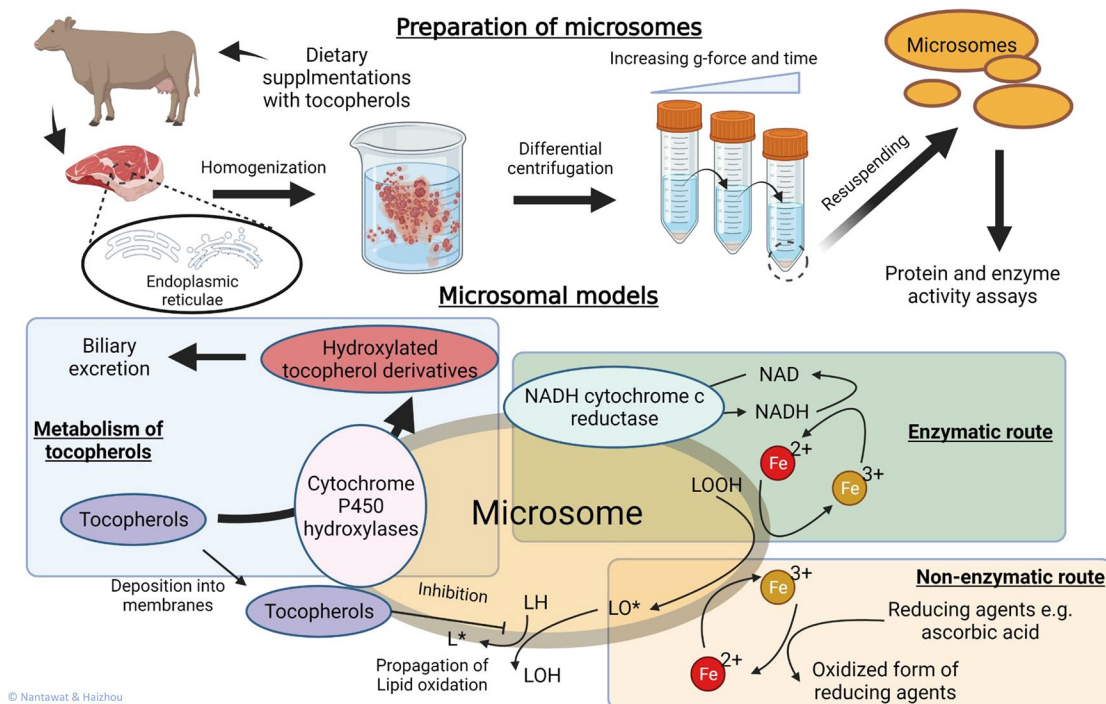
3.4. Microsomes

Microsomes (Figure 3) are vesicle-like fragments of endoplasmic reticulum (between 20 and 200 nm diameter) or other membranes (Yin et al. 2013). Being compositionally similar to cellular membranes, microsomes thus provide versatile models for lipid oxidation studies related to muscle quality. The model allows studies of the contribution of enzymatic systems to the total degree of lipid oxidation as well as the deposition and metabolism of dietary supplements.

Preparation of microsomes involves tissue homogenization and differential centrifugation to obtain the subcellular fraction. Although hepatic microsomes are common, microsomes can also be prepared from skeletal muscle (Kathirvel and Richards 2012; Rey, Lopez-Bote, and Arias 1997). Homogenization of tissue samples with a Dounce homogenizer or a Potter-Elvehjem glass with Teflon pestle should be conducted with gentle strokes to prevent foaming (Sabatini 2014). During preparation, a constant temperature below 4 °C is important to delay oxidative degradation of lipids and thermal denaturation of proteins. Isolation buffers often contain cocktails of protease- and phosphatase-inhibitors that are required to prevent unintentional proteolysis and phospholysis. At the end of the preparation, protein and enzyme activity assays are performed to assess quality and standardize the model.

Being derived from muscle, microsomes have the composition of muscle membranes and carry various types of phospholipids, cholesterol, and membrane-bound proteins. Some membrane-bound proteins integrated into microsomes possess catalytic activity, e.g., glutathione-dependent transferases, peroxidases, and cytochrome P450 enzymes (Guengerich 1977; Hosoya, Matsukawa, and Nagai 1971;

Figure 3. Microsome models. A simplified preparative procedure of microsomes from muscle tissues is illustrated. The presence of membrane-bound enzymes make microsomes versatile models for studying both enzymatic- and non-enzymatic lipid oxidation pathways as well as metabolism of dietary antioxidants can be studied using microsomal models. Muscle-derived microsomal models also connect between dietary supplementation studies and lipid oxidation studies.

Jakobsson et al. 1997). Generally, determination of micro-somal lipid oxidation can be performed in a manner similar to the methods used for liposomes. An exception is that the determination of conjugated dienes requires extraction of microsomal lipids prior to spectrophotometric measurements because of the light scattering effect of the heterogeneous microsomes (Perera et al. 1985; Srinivasan and Recknagel 1971). It should also be noted that other compounds with conjugated double bonds can interfere with the measurement; therefore, blanks prepared from non-oxidized samples are used for subtracting the background light absorption. For in situ detection of microsomal lipid oxidation, an EPR-spin trapping technique has been employed for detecting lipid radicals generated from iron-mediated decomposition of LOOHs (Boveris, Galatro, and Puntarulo 2000).

Microsomal models offer many applications in lipid oxidation-related research. Numerous mechanistic studies of antioxidants and pro-oxidants have been reported (Ikeda et al. 2011; Kathirvel and Richards 2012; Pazos et al. 2006; Pazos, Medina, and Hultin 2005; Richards, Cai, and Grunwald 2009; Shewfelt and Hultin 1983), and microsomes are unique lipid models for studying both enzymatic and non-enzymatic lipid oxidation (Lin and Hultin 1976; Rhee, Dutson, and Smith 1984; Thanonkaew et al. 2005). The enzymatic pathway involves NADH- or NADPH-mediated reduction of ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}), thereby promoting the Fenton reaction in converting peroxides to free radicals (Svingen et al. 1979). In this scheme, oxidoreductases bound to sarcoplasmic reticulum and mitochondrial membranes are responsible for recycling NAD/NADH and NADP/NADPH. In contrast, the non-enzymatic route relies on reducing agents, e.g., ascorbic acid, to promote the Fe^{3+}/Fe^{2+} conversion. In a very pure microsomal model, purified sarcoplasmic reticulum from winter flounder (*Pseudopleuronectes americanus*), Decker et al. (1989) studied whether iron and copper promoted lipid oxidation in vitro at the concentrations found in the low molecular weight (LMW) fraction of flounder muscle press juice. Several studies with this model then followed the effect of cytosol, histidine or soluble and bound iron (Erickson and Hultin 1992; Huang and Hultin 1992), providing in depth mechanistic data on fish membranal lipid oxidation. It was however revealed that the order of adding pro-oxidants, particularly iron and ascorbate, was very important for the resulting lipid oxidation in the sarcoplasmic reticulum system (Soyer and Hultin 2000).

Unlike liposomes, dietary supplementation can enrich microsomes with PUFA and lipid-soluble antioxidants. This advantage enables microsomes to be used for determining deposition of such dietary supplements and their effects on microsomal oxidation. Rey, Lopez-Bote, and Arias (1997) modified the fatty acid compositions of pork *longissimus dorsi* via feeds formulated with α-tocopherol acetate and different combinations of olive oil, sunflower oil, and linseed oil. Partial replacement of olive oil with linseed oil as a rich source of n-3 fatty acids improved the n-6:n-3 ratio in the muscle lipids but resulted in muscle microsomes with low oxidative stability. Protection was therefore required from

α-tocopherol. Lynch and Faustman (2000) and Yin et al. (2013) used microsomes prepared from tissues with different α-tocopherol content for testing the pro-oxidative activity of Mb alkylated with lipid oxidation-derived aldehydes. Their results revealed microsomes with elevated concentrations of α-tocopherol delayed lipid and Mb oxidations.

Being compositionally similar to cellular membranes, microsomes thus provide versatile models for lipid oxidation studies related to muscle quality. The model allows studies of the contribution of enzymatic systems to the total degree of lipid oxidation as well as the deposition and metabolism of dietary supplements. However, a tedious preparation process and potential lack of consistency are drawbacks of microsomal models. Care should be exercised during the handling of raw materials (liver or skeletal muscle tissues) and during the actual isolation to avoid loss of enzymatic activities. In addition, the compositional variation in the raw materials, particularly, enzyme activity, fatty acid profile, and tocopherol content, may affect oxidative stability of microsomes.

3.5. Erythrocytes

In vertebrates, erythrocytes (red blood cells) transfer oxygen from the lungs or gills to body tissues via the circulatory system (Karabulut et al. 2009). The structure of erythrocyte membrane is composed of a phospholipid bilayer and imbedded proteins, and the membrane is the direct target of lipid oxidation (Davidovic-Plavsic et al. 2021). The importance of erythrocyte as a model for lipid oxidation study is due to the fact that residual blood can promote lipid oxidation upon hemolysis and release of Hb (Richards and Hultin 2002). Therefore, the ability of erythrocytes to withstand oxidative stress and stay intact is crucial for oxidative stability of muscle.

For erythrocyte preparation, non-coagulated whole blood is centrifuged, and the plasma and buffy coat layer are removed. After further washing, the red cells are suspended in normal saline (Ghirmai et al. 2020). Experimental procedures for measuring lipid oxidation can be based on methods described by Li et al. (2016). This system to investigate external parameters of lipid oxidation utilizes physiological saline containing 1% erythrocytes and dimethyl sulfoxide. Then, oxidants (e.g., $FeSO_4$ and H_2O_2) are added to induce oxidation. After incubation, the erythrocytes are recovered to measure various analytes including O_2 concentration, H_2O_2, malondialdehyde, protein carbonyls, and the activities of SOD, CAT, and glutathione peroxidase (GPx).

There are additional examples of erythrocyte models to study effects of antioxidants, feed ingredients on lipid oxidation in muscles. Hua-Tao et al. (2019) investigated effects of extract of *Angelica sinensis* and ethoxyquin on lipid oxidation in erythrocytes and on growth, digestion, and absorptive and antioxidant capacity in carp muscle. The results indicated that *Angelica sinensis* extracts and ethoxyquin at concentrations of 0.5 and 0.25 mg/ml suppressed lipid oxidation by decreasing the generation of reactive oxygen species and restoring the activities of antioxidants in hydroxyl radical-treated erythrocytes. Li et al. (2016) revealed that

the fish erythrocyte system can be used as an experimental model to evaluate lipid oxidation in food and feed ingredients. An ethyl acetate extract of *Ginkgo biloba* leaves was used as an inhibitor in a carp erythrocyte model. They concluded that the inhibition effects of the extract on lipid oxidation occurred because of the presence of flavonoid compounds. Pig erythrocytes and their ghosts were used in studies of hemolytic and protection activities of quaternary ammonium bromides and chlorides in the presence of UV-irradiation. Hemolytic activities increased with the lipophilicity of the compounds, and each bromide salt was more hemolytic than the chloride forms (Kleszczyfiska et al. 2003). Glutamine is an important dietary supplement and a major free L-amino acid in fish (Yan and Qiu-Zhou 2006). Alanine, citrulline and proline are the important metabolites of glutamine in rats (Windmueller 1982) and pigs (Wu, Borbolla, and Knabe 1994). Li et al. (2013) showed that a mixture of glutamine, alanine, citrlulline, and proline significantly reduced ·OH-induced lipid oxidation and protein oxidation in carp erythrocytes.

3.6. Washed muscle mince

A model system of washed muscle mince is composed most of muscle components primarily myofibrillar proteins and membrane phospholipids (Wu et al. 2022c) and maintains partial muscle structure (Cai et al. 2013; Richards, Modra, and Li 2002a; Xiao et al. 2018). A visualization of washed muscle mince is shown in Figure 4.

The washing process mostly removes undesired contents such as blood, lipids, heme pigments (Hb and Mb) and iron, to concentrate muscle proteins and membranes (Karayannakidis et al. 2008; Kunyaboon et al. 2021). Washed muscles used for monitoring of muscle lipid oxidation can be prepared from muscles of different animal species (Kunyaboon et al. 2021; Tatiyaborwntham and Richards 2018; Wu et al. 2021b; 2021c; Wu et al. 2022d; Wu et al. 2017). The removal of aqueous antioxidants and pro-oxidants from the ground muscle provides rapid assessment of lipid oxidation with the capacity to examine environmental and compositional aspects (Cui et al. 2018). For example, the relative ability of different pro-oxidants that are added to incur lipid oxidation can be examined at varying pH, and the ability of added antioxidants to potentially counteract progress of lipid oxidation can also be evaluated.

There are different washing procedures that provide different qualities of washed muscle from different species primarily due to variance in heme protein contents (Vallejo-Cordoba, Rodriguez-Ramirez, and Gonzalez-Cordova 2010). In general, the preparation of washed muscles requires grinding, washing with water, and centrifugation. Muscle mince is typically washed three or more times with potable water or buffers ($< 5\,°C$) at a mince/water ratio of 1:3. Centrifugation is performed at each washing step to concentrate myofibrillar protein and lipid membranes. Any floating matters is removed manually (Halldorsdottir et al. 2013; Kunyaboon et al. 2021; Undeland, Hultin, and Richards 2002).
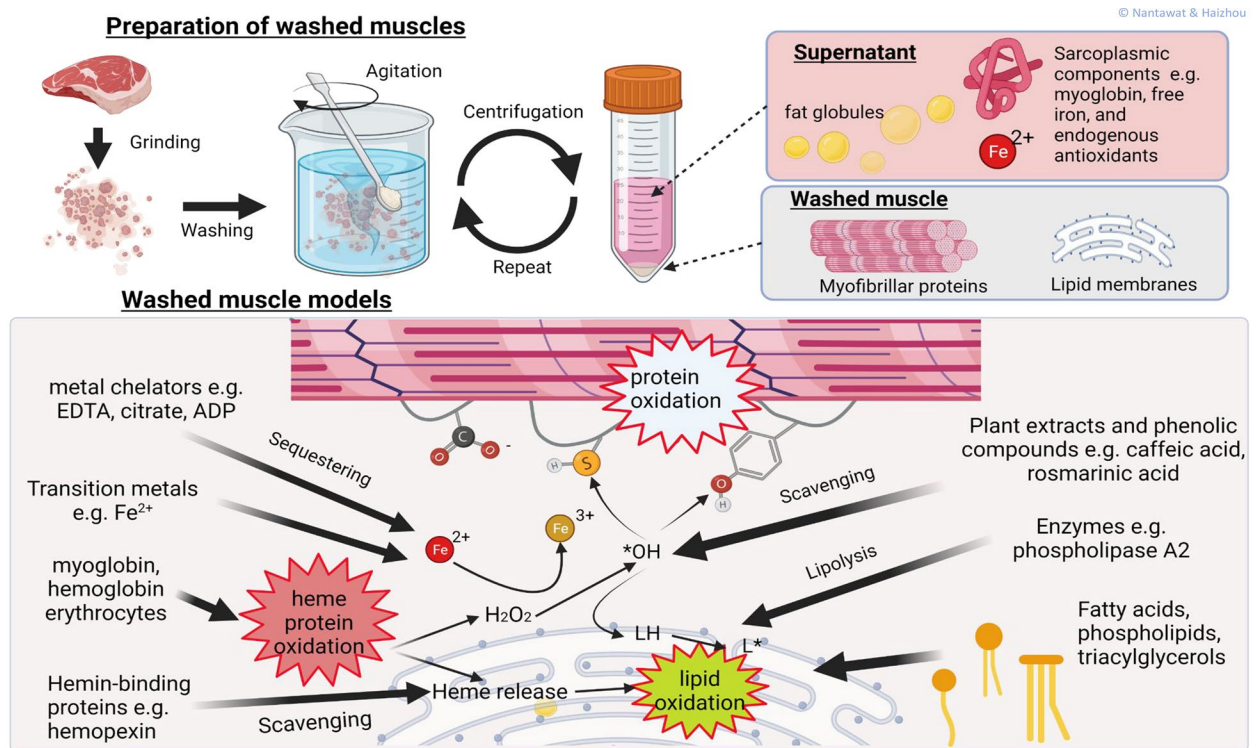
Figure 4. Washed muscle models. The washed muscles consist primarily of myofibrillar protein, connective tissues, and lipid membranes as the result of exhaustive washing of minced muscle tissues to remove water-soluble components, e.g., sarcoplasmic proteins and low molecular weight compounds. External pro-oxidants and antioxidants, as well as muscle components of interest can be added back to the washed muscle for studying their individual and interaction effects on lipid oxidation.

Washed muscles have been extensively used for studying various pro- and antioxidants. Richards, Ostdal, and Andersen (2002b) studied deoxyhemoglobin-mediated lipid oxidation by comparing the pro-oxidative activity of anodic and cathodic Hb from trout in a washed cod muscle model system. The authors proposed that deoxyhemoglobin was more pro-oxidative than its oxygenated counterpart at pH values found in postmortem fish muscle. Tatiyaborworntham and Richards (2018) and Tatiyaborworntham, Yin, and Richards (2021) studied antioxidant effects of phospholipase A2 (PLA2), an lipolytic enzyme that hydrolyzes phospholipids at the sn-2 position, against the oxidation of trout hemoglobin and lipids in washed cod muscle. In addition, they found that ferrylhemoglobin may be involved in the pro-oxidative activity of trout Hb, which was previously reported (Lee et al. 2015). In contrast, Wu et al. (2017) stated that the contribution of ferrylhemoglobin may be negligible in lipid oxidation of washed cod muscles promoted by either porcine or turkey hemolysates.

The effect of FFAs, products of phospholipid hydrolysis by PLA2, on lipid oxidation in muscles was investigated by electron paramagnetic resonance; the spectra results revealed FFA-induced modification of Hb into hemichrome which did not stimulate lipid oxidation in washed turkey muscle during the period of storage. This finding suggested that FFA was able to diminish the lipid oxidation capacity of Hb possibly through formation of hemichrome (Wu et al. 2021c). Lee et al. (2015) assessed Mb- and Hb-mediated lipid oxidation in a washed muscle model; key findings suggested that ferri-protoporphyrin IX released from metHb generated free radicals that facilitated both lipid oxidation and degradation of the heme moiety while a crosslinked form of Mb was effective in promoting lipid oxidation. In addition, mechanisms of the inhibitory effect of L-carnosine on lipid oxidation in the presence of oxidized metmyoglobin-mediated washed cod muscle was studied and results showed that the high inhibitory effect of L-carnosine was because of free radical scavenging, metal chelating, and especially its influence on pro-oxidant metmyoglobin structure (Xiao et al. 2018).

The washed muscle model is versatile in that a multitude of external factors can be examined pH, pressure, ionic strength, pro-oxidant type, antioxidant type, and storage condition) and internal factors such as type of tissue. GÜner et al. (2020) demonstrated that washed tilapia muscle samples prepared at pH 6.3 were more susceptible to lipid oxidation than samples prepared at pH 6.8. Also, they found that the ability of red onion skin polyphenols to induce a lag phase in lipid oxidation was pH dependent. Using washed muscle of pork, Papuc et al. (2018) showed that the activity of hawthorn berry ethanolic extract (100 mg kg^{-1}) was more greater than butylhydroxyanisole (100 mg kg^{-1}) in diminishing lipid oxidation and protein degradation, for preservation of firmness and lipid stability for six days at 4 °C. Grunwald and Richards (2012) described that pH and NaCl concentration are critical factors that affect the ability of hemopexin to bind ferri-protoporphyrin IX released from metHb and thereby inhibit Hb-mediated lipid oxidation in washed cod muscle. Yang et al. (2018) showed that LOX

activity and lipid oxidation were increased under high pressure conditions.

3.7. Muscle homogenates

The overall aim of preparing muscle homogenates is to break up the tissue to generate a uniform system that is compositionally similar to intact muscles. The preparation of muscle homogenates normally consists of homogenization, centrifugation, and clarification. When the system is to be used in lipid oxidation studies, the target muscle is usually homogenized with an extraction buffer (e.g., including KCl, EDTA, and butylated hydroxytoluene) at 4 °C where upon the homogenate is cooled in an ice bath and subsequently maintained at the decided study temperature.

Homogenizing the meat generates small particles and increases interactions between reactants normally contained in different compartments (Bekhit et al. 2013; Wang et al. 2019), which shortens the lag phase of lipid oxidation and duration of experiments. Min and Ahn (2009) investigated how free ionic iron and Mb affected muscle lipid oxidation in chicken breast and beef homogenates. In addition, Terevinto et al. (2010) investigated factors such as the initial oxidative status, metal content and activities of SOD, CAT, and GPx on lipid oxidation of rhea (*Rhea americana*) muscle homogenates. Also, ferrous ion-chelating ability, ferric reducing antioxidant power assay, ABTS radical cation-scavenging activity and DPPH radical-scavenging activity of essential oils from *Thymus zygis* was analyzed in homogenates of minced beef, cooked ham or dry-cured sausage (Ballester-Costa et al. 2017). Ahn and Kim (1998) showed that ionic iron-, ferritin-, and Hb-catalyzed oxidation of turkey muscle homogenates were different from those in an oil-based emulsion and cooked-meat homogenate. The changes were ascribed to heat sensitive compounds such as reducing enzymes which contributed to the redox potentials in the muscle homogenates. The investigators found that ferrous iron was the main pro-oxidant among all the iron sources, and, during storage, heme pigments and ferritin did not have a significant catalytic impact on oxidation in the studied homogenates.

Using muscle homogenates, investigators have also assessed the role of storage conditions, pH, chelating agents, salts, temperature, and dietary factors on lipid oxidation. Chen et al. (2021) used duck breast muscle homogenates and revealed that curing by vacuum tumbling decreased the lipid oxidation compared with static brining and pulsed pressure salting. Also, Tongnuanchan, Benjakul, and Prodpran (2011) evaluated the effect of lipid oxidation and pH on the structure and yellow discoloration during storage of a red tilapia (*Oreochromis niloticus*) muscle homogenate. They found that lipid oxidation significantly stimulated yellow discoloration, mostly by modification of the carbonyl groups involved in the Maillard reaction, and that pH controlled the rate of this reaction. Furthermore, Jin et al. (2012) showed that both temperature and NaCl significantly affected lipid oxidation in a pork belly muscle homogenate. Results indicated that < 5% NaCl (w/w) reduced the

activation energy for lipid oxidation and that high temperature as well as moderate concentration of NaCl accelerated lipid oxidation. Moroney et al. (2012) reported that iron-induced lipid oxidation was amplified in liver, heart, kidney, and lung tissue homogenates during 24 h storage 4 °C, while a dietary seaweed extract containing laminarin and fucoidan reduced the degree of lipid oxidation particularly in the liver tissue homogenates. The results confirmed the potential of incorporating marine-derived natural antioxidant in muscle foods via the animal's diet (Moroney et al. 2012). In another similar study, Jeronimo et al. (2020) investigated the influence of *Cistus ladanifer* L. plant and vegetable oils in the diet for lamb on intramuscular fat composition and muscle antioxidant status. The results indicated that *Cistus ladanifer* increased α-tocopherol content in the lamb muscle and also limited lipid oxidation in a lamb muscle homogenate during 7 days of storage at 2 °C.

Overall, muscle homogenates are closest to the actual muscle tissue based on composition and structure among all models. This may aid food scientists to obtain more reliable presumptions for muscle oxidation process compared other models. However, the moisture content of muscle homogenates is significantly higher than the actual muscle. In addition, the homogenizing process may result in more exposed cell membranes and destruction of protein structure. These factors could lead to different lipid oxidation features between muscle homogenates and actual muscle.

4. Comparison of model systems

Table 1 summarizes the main characteristics of the seven muscle models reviewed here, together with their advantages and disadvantages. In general, models that do not include a lipid substrate from actual muscle tissue are easy to prepare and have fewer disturbing factors. For example, lipid monolayer models as emulsions and fatty acid micelles and lipid bilayer models as liposomes are all three simple models to simulate muscle cell membranes (Akbarzadeh et al. 2013; Echegaray et al. 2021; Laguerre et al. 2020). The fact that these models are rapid and easy to prepare as well as to standardize results in universal application, and the results from different researchers can be compared and discussed. Another advantage is that it is relatively easy to monitor the oxidation products and reaction processes in these models. For example, some more advanced analytical techniques, e.g., chemiluminescence, fluorescence emission, Raman spectroscopy, infrared spectroscopy and magnetic resonance are more compatible with these simple models compared with models that include proteins, e.g., microsomes, erythrocytes, washed muscle mince and muscle homogenates (Barriuso, Astiasaran, and Ansorena 2013; Laguerre et al. 2020). In addition, electron spin resonance and electron paramagnetic resonance can directly be used to monitor the generation of free radicals during oxidation of emulsions, fatty acid micelles, and liposomes (Ikeda et al. 2011), but not in the more complex models. Although the three simpler models have many advantages, they do not include any components from actual muscle tissue, which indeed can result in

incorrect conclusions when extrapolated results to actual muscle. Yet, these simple models have a value in understanding, e.g., membrane interactions with anti- and pro-oxidants or interfacial phenomena between aqueous/lipid phases in processed muscle products.

Conversely, microsomes, erythrocytes, washed muscle mince, and muscle homogenates have the obvious advantage of containing muscle components and/or muscle structure. For example, microsomes are compositionally similar to muscle cell membranes, while erythrocytes can simulate intact cell membranes. Further, washed muscle mince and muscle homogenates have many structural and compositional elements of actual muscle. These models are therefore appropriate models for lipid oxidation investigations that depend on animal species, muscle type and anatomical location, while more simplistic models cannot be used for these aims.

5. Caution in extrapolating findings from model systems to postmortem muscle tissue

Muscle contains cytosolic, membrane-bound, myofibrillar and stromal proteins as well as trace amounts of carbohydrates, vitamins, and minerals (at less than 1% of muscle wet weight). All these molecules that are to varying degrees excluded or modified in the model systems described in this review. Besides compositional interactions between the different macro- and micro-molecules, structural organization is often overlooked in simple models such as lipid micelles, emulsions, liposomes, and microsomes. Although washed muscle minces are subjected to some physical alteration during their preparation, this model still provides a level of structural organization that cannot be achieved by simply mixing lipid models and myofibrillar components. Using washed muscle mince as study models, studies have related variations in the muscle microstructures to the oxidative stability of lipids (Sannaveerappa, Sandberg, and Undeland 2007b; Wu et al. 2021b).

Caution must be exercised when comparing lipid models (microsomes, washed muscles, and muscle homogenates) prepared from different sources due to variations in endogenous compounds, e.g., the tocopherol content which should be determined. Increasing concentrations of tocopherols in muscle tissue extends the lag phase prior to formation of lipid oxidation products (Russell et al. 2004). Varying the concentrations of endogenous carotenoids in muscle tissue will also influence the onset of lipid oxidation (Jensen et al. 1998), which can be an issue, e.g., in salmonoid fish (*Salmo gairdnerii gairdnerii*). Most of the tocopherols and carotenoids will not be removed by washing with aqueous solutions as they are bound to membranes and to some degree to myofibrillar proteins (carotenoids).

The pH is a very important factor to consider in lipid oxidation model systems and in *postmortem* muscle tissue. The pH for a model system should be near the pH of the muscle tissue or muscle food product of interest. In a turkey deli meat product, formation of hexanal during refrigerated storage was suppressed 2.4-fold as the pH was increased

0.36 units because of addition of sodium tripolyphosphate (STPP) (Bak, Rankin, and Richards 2020). The ability of STPP to inactivate metals and change muscle structure could contribute to the antioxidant effect of STPP in addition to the pH increasing the effect of STPP. Ammonium hydroxide (0.5%) increased pH in raw buffalo patties from 5.6 to 6.4 and decreased formation of lipid oxidation products 3 to 4-fold during 4°C storage (Naveena et al. 2011).

Muscle tissue contains co-factors that facilitate iron-mediated lipid oxidation (e.g., phosphorylated nucleotides and free amino acids) that are often absent in model systems. Nevertheless, co-factors can be added to model systems. For example, Erickson and Hultin (1992) reported the ability of adenosine diphosphate and histidine to activate added iron to instigate lipid oxidation in a sarcoplasmic reticulum preparation. The ability of copper to bind to Mb and thereby increase metmyoglobin formation should be noted in the context of LMW metals increasing the pro-oxidative capacity of heme proteins (Moiseeva and Postnikova 2001).

The activity of copper ions can be underestimated when added to a model system if critical endogenous muscle co-factors are excluded. For example, the ability of Cu^{2+} to decompose linoleic acid hydroperoxide increased greater than three orders of magnitude when a physiological concentration of ascorbate was added to the model system (O'brien 1969). This effect was likely because of the ability of ascorbate to facilitate redox cycling of copper between the 2+ and 1+ oxidation state (Khan and Martell 1967). The formation of Cu^+ may facilitate decomposition of linoleic acid hydroperoxide, in that reduced metals decompose peroxides up to five orders of magnitude more effectively than the higher valence state of the metal (Mcclements and Decker 2017).

Soluble components of muscle (e.g., press juices and cytosolic fractions) can be pro-oxidative or antioxidative toward lipids depending on compositional attributes and possibly the type of oxidizable lipid. For example, addition of the low molecular weight (LMW) and high molecular weight (HMW) soluble fractions of ordinary mackerel muscle to liposomes generated maximal lipid oxidation that was partly attributed to the ability of metals in the LMW fraction and heme proteins in the HMW fraction to collectively oxidize the liposomes (Decker and Hultin 1990). However, the press juice from, e.g., chicken breast muscle, cod muscle and herring muscle were inhibitory to Hb-mediated lipid oxidation in washed muscle (Li, Richards, and Undeland 2005; Sannaveerappa et al. 2007a; Undeland, Hultin, and Richards 2003). This inhibitor effect can be attributed to the ability of antioxidants in the soluble fraction to inhibit Hb-mediated lipid oxidation that outcompeted the ability of pro-oxidants in the press juice to facilitate lipid oxidation. The greater ability of fish Hbs and Mbs in the soluble fraction to oxidize lipids compared with mammalian and avian heme proteins should be noted (Lee et al. 2015). Further, Hb from perch was more oxidative toward lipids than Hb from trout (Aranda et al. 2009). And the concentration of heme proteins in cytosol from ordinary muscle (also called light or white muscle) will be lower than that from dark muscle and muscle that is a mixture of light and dark fibers. Heat labile/non-dialyzable and heat resistant/dialyzable factors in the cytosol of white muscle from rainbow trout protected against lipid oxidation in microsomes (Han and Liston 1989). Thus, adding the soluble components from different muscles to a selected model system may provide improved understanding of factors that contribute to oxidative stability of the lipids in postmortem muscle.

It should be emphasized that many models are used to increase the speed of oxidation. This is often necessary to observe oxidation before tissues are spoiled by bacterial growth. Many intact meats will spoil from microbial growth before oxidation occurs. Frozen storage or addition of antimicrobials as steptomycin are routes to avoid microbial spoilage however for the former, prolonged time is required to incur oxidation products. Cooked meat will oxidize rapidly so that screening of antioxidants can be examined fairly efficiently after a thermal step with this in mind.

6. Prospects

Technology development always brings expectations to existing challenge. For example, with growing interest in cellular agriculture, the production of meat and fish from stem cell- and tissue-cultures is emerging as an approach to address current ecological challenges (Rubio et al. 2019; Tuomisto 2018). These technologies may be used also to assess the mechanisms of muscle lipid oxidation. Stem cells are cultivated in a bioreactor under strict control of environmental factors; thus, the endogenous components could be controlled by adjusting the nutrient medium. For example, many investigators reported that Mb is a strong endogenous pro-oxidant in red meat (Faustman et al. 2010; Yin, Zhang, and Richards 2017; Zhou et al. 2016). The addition of Mb into washed muscle is a common approach for this study. However, Mb is located within muscle cells (e.g., myocytes) (Richards 2010), which could prevent the interaction between Mb and lipid substrates in situ. Thus, cultured meat or fish could be a good model to identify the activities of important endogenous pro- and antioxidants at the cell scale. In addition, three-dimensional printing stands as a developing technology for food manufacturing (Dick, Bhandari, and Prakash 2019) and offers the opportunity to design a new tailored model for lipid oxidation study. This three-dimensional model could be schemed into expected components and muscle structures that meet special needs for lipid oxidation study. The pathways and relationships involved in lipid oxidation are complex in muscle. Existing studies normally just identify affecting factors one-by-one. Simultaneous analysis of multiple factors is a challenge. Mathematical modeling provides a chance to integrate the synthesis of data from many experiments into one system, which could calculate quantitative changes in many factors (Kaczmarek and Muzolf-Panek 2022). Thanks to advances in quantitative analysis and computation, chemometrics and machine learning algorithms can be useful for classification, optimization, and prediction in the analysis of complex

dataset (Gu et al. 2017; Khoshnoudi-Nia and Moosavi-Nasab 2019; Rosario et al. 2020).

7. Conclusion

Muscle foods has complex composition and structures, which explain why the mechanisms and pathways of lipid oxidation are still not completely confirmed. The seven models discussed in this review have been used as tools to aid food scientists getting answers or indications on, e.g., oxidation pathways, oxidation product formation and roles of endogenous pro-/antioxidants or lipid substrates, in indirect ways. It is however vital to distinguish the main characteristics, advantages, and disadvantages of each model to make the right selection. Particularly, it is necessary to pay attention to the following points: 1) feasibility of preparation and analysis of lipid oxidation results; 2) the speed and accuracy of monitoring lipid oxidation products, e.g., tentative interference from model system components; 3) cost of preparing the desired model and related analyses; 4) stability and robustness of the model, i.e., the possibility to get reproducible results across different experiments. Based on this reviewing of oxidation models, tailoring correct model to different study aims could be facilitated, and readers are becoming acquainted with advantages and shortcomings. In addition, insight into recent technology developments, e.g., stem cell- and tissue-cultures as well as three-dimensional printing could provide new opportunities to overcome the current bottlenecks of lipid oxidation studies in muscle.

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