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Molecular Changes of Meat Proteins During Processing and Their Impact on Quality and Nutritional Values

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Abstract

Meats are rich in lipids and proteins, exposing them to rapid oxidative changes. Proteins are essential to the human diet, and changes in the structure and functional attributes can greatly influence the quality and nutritional value of meats. In this article, we review the molecular changes of proteins during processing, their impact on the nutritional value of fresh and processed meat, the digestibility and bioavailability of meat proteins, the risks associated with high meat intake, and the preventive strategies employed to mitigate these risks. This information provides new research directions to reduce or prevent oxidative processes that influence the quality and nutritional values of meat.

1. INTRODUCTION

Meat and meat products are prone to oxidation due to their high lipid and protein content. Lipid oxidation (LOx) is characterized by a free-radical chain reaction that produces arrays of oxidation derivatives mainly linked to color and flavor deterioration, including loss of muscle protein functionality and stability. Similarly, proteins are prone to oxidation by reactive oxidative species (ROS) and secondary by-products of oxidative stress. According to D. Zhang et al. (2020a), protein oxidation (POx) is a process that leads to conformational and structural alterations, aggregation, and fragmentation, which consequently impairs the functional properties of proteins and thus affects meat quality.

The LOx–POx coexistence in a meat system is inseparable, as LOx products may induce POx. As LOx derivatives, α,β-unsaturated aldehydes such as acrolein, 4-hydroxy-2-nonenal, and malondialdehyde are electrophiles and can interact with nucleophilic groups in proteins (Wang et al. 2019b). These accumulated oxidized proteins and lipids, including their secondary products, have been suggested to pose health risks to humans upon the consumption of meat products and subsequent digestion. Therefore, it is crucial to control POx in meat and meat products.

Numerous digestibility trials and related risks have been studied to elucidate the molecular changes associated with meat proteins. Protein digestion is a complex process from the collective actions of digestive enzymes on dietary proteins. It is attributed to several factors such as protein diets, peptic activity, intestinal and gastric pH, motility, and endogenous secretions (Bouzerzour et al. 2012). Animal models have demonstrated that excessive processed meat intake aids the proliferation of proteolytic bacteria involved in nonalcoholic fatty liver disease (NAFLD) and obesity (Ahmad et al. 2019, 2020; Ge et al. 2021; Ijaz et al. 2018). It has also been reported that oxidation reactions can be stimulated in the colon following high red meat intake (Ijaz et al. 2018). The accumulation of oxidized lipids in colon tissues is an integral proposed mechanism that links red meat intake to colorectal cancer (CRC) development (Corpet 2011). Every process is interlinked so that an excessive introduction of meat-derived oxidized products may promote intestinal dysbiosis, impair the colon's metabolic ability, and promote harmful effects on colonic mucosa (IJssennagger et al. 2012).

This review highlights the molecular changes in meat proteins, effects on the nutritional value of fresh and processed meat, digestion and absorption of meat proteins, risks associated with high meat intake, and preventive strategies employed to ameliorate these occurrences.

2. MOLECULAR CHANGES IN FRESH MEAT AND INFLUENCE ON MEAT QUALITY

Meat quality is commonly affected by the physicochemical and metabolic changes during muscle-to-meat conversion. These changes primarily include pH decline, myofibrillar protein (MP) degradation, POx, and post-translational modification (PTM) of proteins (Warner 2016) (**Figure 1**). Quality attributes such as color, tenderness, pH, and water-holding capacity (WHC) are measured by colorimeter, texture analyzer, pH meter, and sensory analysis or drip loss change postmortem. However, these tools cannot provide insights into the mechanisms that alter meat quality traits or predict meat quality changes.

2.1. Impact of Myofibrillar Proteins

MPs account for 60–70% of total muscle protein (Zhang et al. 2021a) and contribute mainly to muscle contraction during rigor mortis (Li et al. 2015). The intra- and intermolecular interactions of MPs, such as hydrogen bonding and hydrophobic, ionic, and van der Waal's interactions, greatly impact the texture, structural ability, and quality of meat (Feng et al. 2017). According

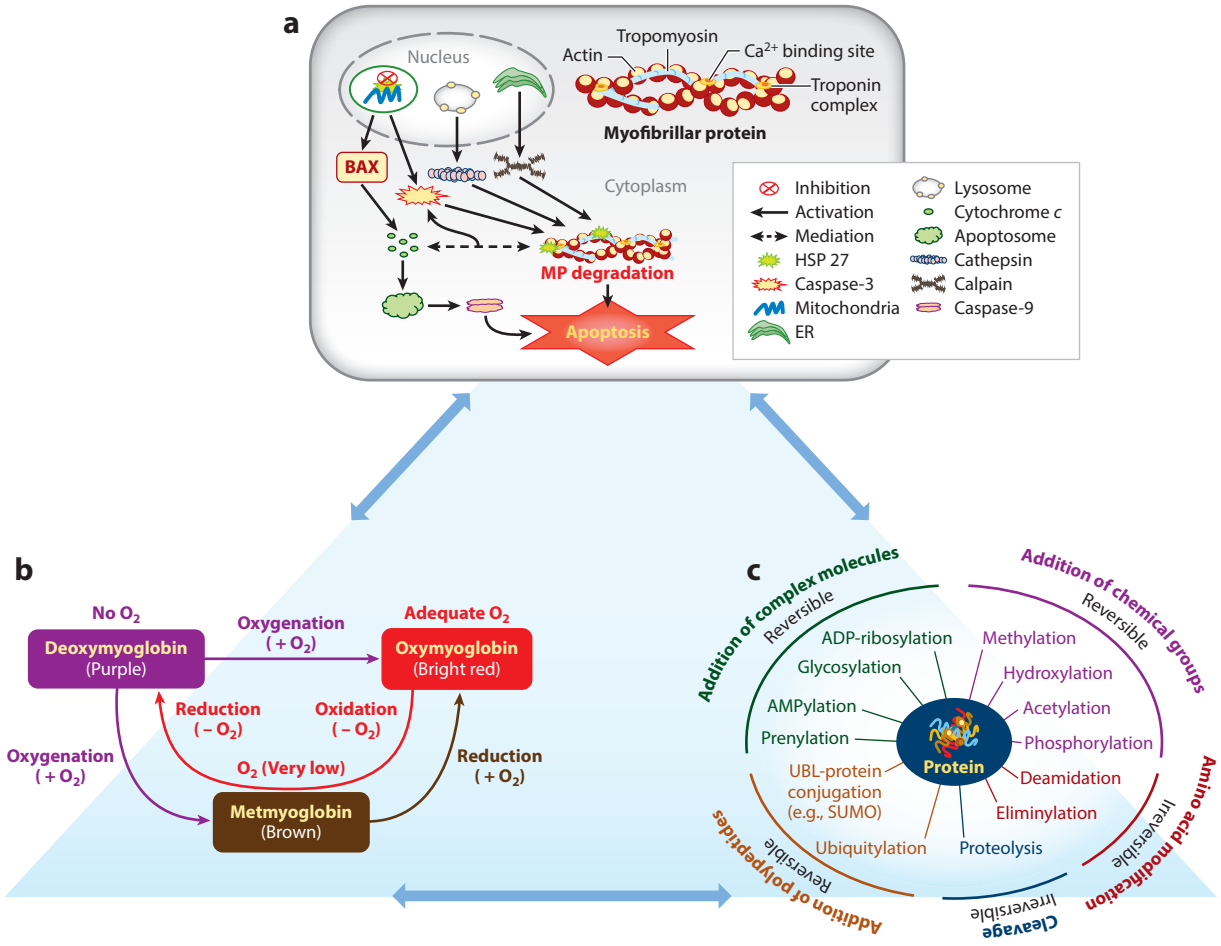

Figure 1

Schematics of changes in fresh meat and impact on meat quality. (*a*) Mitochondria are the first organelle affected by postmortem changes and are integral to meat tenderization. Mitochondrial apoptosis is mediated by the BAX protein, leading to cytochrome *c* release and activation of apoptotic caspases. Cytochrome *c* and HSP27 mediation have been implicated in muscle breakdown. During postmortem proteolysis, the ER releases calpains and lysosomes activate cathepsins, which then hydrolyze MPs. (*b*) Myoglobin oxygenation determines color changes. The native pigment is deoxymyoglobin (no O_2), which is purple. Fresh-cut muscle is bright red (oxymyoglobin), and metmyoglobin, which is brown, indicates excess O_2 exposure and quality deterioration. (*c*) PTM is integral to postmortem meat quality. Specifically, phosphorylation and proteolysis are linked to actomyosin dissociation, protein degradation, and μ-calpain activity postmortem, whereas acetylation is involved in cell apoptosis during muscle-to-meat conversion. Abbreviations: ER, endoplasmic reticulum; HSP, heat-shock protein; MPs, myofibrillar proteins; PTM, post-translational modification; SUMO, small ubiquitin-related modifier; UBL, ubiquitin-like.

to Koohmaraie & Geesink (2006), collagen concentration and solubility (background toughness), the extent of meat shortening, and the proteolytic changes of MP during postmortem aging are integral factors associated with meat tenderness. Aging initially provides for buffering against mechanical stresses. It is aided by freezing via the enzymatic structural degradation of muscle tissues and subsequent swelling of muscle cells (Kim et al. 2018). Most water in the muscle fiber is confined in the myofibrils, and MP degradation can be associated with water reduction.

Recently, C. Chen et al. (2021) reported that lysosomal Fe^{2+} promoted lipid peroxidation and mitochondrial swelling, causing mitochondrial dysfunction, which subsequently aided cytochrome

c oxidation and mitochondrial Ca^{2+} accumulation, thus inducing MP denaturation. Mitochondria are the primary organelles initially impaired by postmortem changes and are integral to further cellular responses and final postmortem meat tenderization (Sierra & Olivan 2013). ROS are inevitably generated during postmortem aging and further invade the mitochondrial membrane via peroxidation of polyunsaturated fatty acids, resulting in mitochondrial damage as affirmed by Ca^{2+} influx and swelling of mitochondria (Wang et al. 2018).

Additionally, ionic strength and pH may cause conformational modifications in protein structure, exposing hydrophobic residues to the surface and affecting surface hydrophobicity (Lin & Park 2008). This corroborated the study by Zhang et al. (2021b) showing that pH decreased and ionic strength increased in unfrozen water during freezing, causing a disruption of the inner structure of myosin filaments and aiding their conformational changes and consequent dissolution and denaturation.

2.2. Post-Translational Modifications

In muscles, oxygen loss causes an early postmortem transformation from aerobic to anaerobic metabolism. The following complex changes accompany such a process.

2.2.1. Phosphorylation/dephosphorylation. Phosphorylation is a PTM that plays an integral role in postmortem muscle quality attributes. Particularly, protein phosphorylation is a major PTM of threonine, serine, and tyrosine residues and regulates the signaling transduction, metabolism, and other essential biological processes, such as differentiation and proliferation. It impacts meat quality via the regulation of actomyosin dissociation, protein denaturation, and μ-calpain activity postmortem (Gao et al. 2017, Li et al. 2017). Franco et al. (2015) and Lana & Zolla (2016) provided interesting insights into this, stating that the phosphorylation status of myosin regulatory light chains greatly influenced the structural integrity of thick filaments, including their association with the thin filaments of myofibrils.

Previous studies have demonstrated that the phosphorylation state of sarcoplasmic proteins and MPs changes postmortem and that the changes are linked to rigor mortis and meat quality (Huang et al. 2012). Li et al. (2012) earlier illustrated that electrical stimulation promoted meat tenderization postmortem by facilitating glycolysis and pH decline, leading to increased metabolic enzyme activity via protein phosphorylation. In a phosphoproteomic study, Li et al. (2015) reported that the season also contributes to meat quality changes, including pH decline and WHC. Changes in temperature during season transitions may cause cold or heat stresses in pigs by overexpression of some chaperones (Pennarossa et al. 2012), inducing pale, soft, exudative defects. Y. Zhang et al. (2020) recently outlined that L-lysine and L-histidine introduction may have influenced meat quality via protein phosphorylation at varying NaCl concentrations, providing an understanding of the regulation of postmortem biological processes that enhance meat quality via the addition of exogenous amino acids.

On the other hand, Graves & Krebs (1999) asserted that reversible protein phosphorylation was the primary PTM associated with all aspects of cellular biological processes. This corroborated the study by Mato et al. (2019) showing that reversible phosphorylation was a relevant mechanism involved in preslaughter stress response and downstream impacts on meat quality, thereby unraveling the complex molecular puzzle underlying the conversion of muscle to meat in response to preslaughter stress. Li et al. (2018) also reported that MP dephosphorylation by a protein kinase inhibitor promoted the denaturation of several proteins, resulting in muscle tenderization. According to Borovikov et al. (2000), the denaturation of filament proteins into fragments by proteases facilitated modifications in orientation and conformation, affecting filament structure.

2.2.2. Acetylation/deacetylation. Mitochondrial proteins are post-translationally altered in various ways, including acetylation. Itami et al. (2018) asserted that protein acetylation is promoted by a constantly high acetyl-CoA level in mitochondria. Additionally, Li et al. (2016) showed that protein acetylation played an integral regulatory role in postmortem glycolysis as antemortem injection of histone acetyltransferases and deacetylases inhibitors modulated glycogen utilization, pH decline, and protein acetylation in mouse muscle postmortem. Bonora et al. (2015) reported that because lysine acetylation regulates protein intermolecular associations and protein functions, the rapid acetylation/deacetylation of transition pore complex components early postmortem could participate in mitochondrial membrane permeabilization and cell apoptosis in muscle-to-meat conversions.

Although protein acetylation regulated gene expression, metabolism, cell signaling, and disease, Jiang et al. (2019) provided an overview of protein–lysine acetylation in postmortem muscle and outlined its significance in the muscle-to-meat conversion. This followed direct involvement in regulating the cellular response to stress and apoptosis, glucose utilization and ATP generation, muscle contraction, and rigor mortis occurrence. Lundby et al. (2012) highlighted that lysine acetylation was more conserved across tissues than animal species, with the expression regulated by physiological states. According to Rardin et al. (2013), acetyl-proteins involved in cellular metabolism were enriched in metabolically active liver, heart, and brown fat, whereas muscle metabolism was linked to skeletal muscles involved in contraction, with their expressions being regulated by exercise and energy stress.

In contrast to protein phosphorylation, there is limited information about the biological relevance of protein acetylation in muscle development and function. Ryder et al. (2015) outlined that lysine acetylation was attributed to the progression of skeletal muscle atrophy, corroborating the findings of Viswanathan et al. (2015) that actin hyperacetylation at K328 and/or K326 by pseudoacetylation impaired actin interaction with tropomyosin and/or myosin, aiding muscle denaturation. Samant et al. (2015) also demonstrated that acetylation of myosin heavy chains modulated actin-activated ATPase activity and actin-sliding velocity of cardiac myosin. This corroborated the findings of Yan et al. (2022) showing that the acetylation process is readily realized in the muscles with lower glycolytic and higher oxidative fibers. Zhou et al. (2019) asserted that acetylation and phosphorylation of myosin impact meat quality, supporting the result of Zou et al. (2020) that mild handling affects muscle contraction and energy metabolism by regulating phosphorylation and acetylation levels in muscles, promoting meat quality.

2.3. Chemical State of Myoglobin

Meat color is an integral quality attribute and the first point of judgment for consumers, with variations highly linked to the likelihood of purchase. Fresh meat color is commonly characterized by the concentration of colorants (i.e., saturation) and the stability of a desirable color over the storage period or retail display. Although the CIE L*a*b* system describes L^* (lightness) as a chromatic contribution to perceived meat color, the hue (a^* = redness) and chroma (b^* = yellowness) profiles are dominated by myoglobin, with variations depending on its biochemical state and, particularly, the oxidation or reduction degree (Purslow et al. 2020).

Myoglobin is the main oxygen-carrying heme protein in muscle, whereas hemoglobin transports oxygen in the blood. Although the hemoglobin content in postmortem muscle is low, it may contribute up to 50% of the color in trout and salmon (Richards & Hultin 2002). Myoglobin has a higher oxygen affinity than hemoglobin. However, to prevent its oxygenation, mitochondrial respiration can convert oxymyoglobin to deoxymyoglobin by decreasing the oxygen partial pressure. This conversion is a two-step process requiring oxygen consumption and metmyoglobin

reduction (Mancini & Ramanathan 2020). Metmyoglobin formation usually begins within the meat core, where oxygen partial pressure is not high enough for oxymyoglobin or adequately anaerobic for deoxymyoglobin.

Recently, biochemical investigations have been carried out to elucidate meat color mechanisms. Utilizing mitochondria isolated from dark-cutting beef (muscle pH > 6), McKeith et al. (2016) noted that dark-cutting beef had higher electron loss than the control (i.e., mitochondria isolated from normal beef muscles, pH 5.6). This suggests that muscles with more mitochondria, e.g., psoas muscles have more than longissimus muscles, can generate ROS and engender oxidative changes (Ramanathan et al. 2020b). Yu et al. (2020) outlined that high abundances of hypoxanthine and inosine were detected in psoas major, whereas adenosine, carnosine, and L-histidine were observed in longissimus lumborum, indicating distinct purine metabolism rates between muscle types. Ramanathan et al. (2020a) similarly reported higher mitochondrial protein and DNA content in dark-cutting beef. The findings also corroborated a recent proteomic study showing that changes in proteins linked to mitochondrial electron transport and glycogenolysis facilitate high oxygen intake and pH increase, respectively, thereby inhibiting myoglobin oxygenation in dark-cutting beef (Kiyimba et al. 2021).

2.4. Proteolytic Enzymes and Heat-Shock Proteins

Enzymes are essential in the biochemical changes of meat such as carbohydrate degradation, proteolysis, amino acid degradation reactions (deamination, transamination, decarboxylation), Strecker degradation, Maillard reactions, lipolysis, and LOx (Flores & Toldrá 2011). During postmortem aging, noticeable quality improvements such as juiciness, flavor, and/or tenderness occur via endogenous proteolytic actions denaturing cytoskeletal MPs in meat. Calpains and cathepsins are the enzyme systems involved in postmortem proteolysis. Both μ/m-isoforms of the calpain system are activated during postmortem aging and are critical to meat tenderization by degrading desmin and troponin-T (Goll et al. 2003). Cathepsin, on the other hand, is released from the lysosomes upon the weakening of the lysosomal membrane as the muscle pH decreases postmortem, making them available to hydrolyze MPs (Sancho et al. 1997). Hence, cathepsin-treated MPs have varying denaturation patterns compared to MPs occurring during postmortem muscle storage.

Lysosomes, regarded as the digestive system of the cell, digest many complex molecules such as carbohydrates, proteins, lipids, and nucleic acids, using enzymes (proteases, amylases, nucleases, lipases, acid phosphatases, etc.) for specific cell functions. According to Wang et al. (2013), fasting stimulated the release of lysosomal enzymes but delayed the activation of μ/m-calpains. Wheeler et al. (1992) demonstrated that injection of Ca^{2+} (calpain activator) in muscles promoted postmortem proteolysis, whereas calpain inhibitors prevent postmortem proteolysis and hence tenderization. Unlike other endogenous proteases, μ/m-calpains are substrate specific, as they usually cut proteins at a few sites and do not completely break them into small peptides (Bhat et al. 2018). This is because their specificity is mostly determined by protein conformation rather than amino acid sequence.

The heat-shock protein (HSP) family is known for its significance in cell protection. A high abundance of HSPs is integral to muscle antiapoptosis and potentially inhibits meat aging, affecting meat tenderness. Small HSPs have been reported to protect cytoskeletal structures, such as titin, actin, and troponin T in postmortem muscles (Lomiwes et al. 2014). They could simulate an actin monomer and bind to the actin–actin binding sites, acting effectively as a cap to hinder actin polymerization. Lomiwes et al. (2013) asserted that μ-calpain proteolytic activity was affected by ultimate meat pH via the inhibitory regulation of small HSPs.

Moreover, activated caspase-3 can promote autolytic μ-calpain activity and partially denature MPs, which encourages the breakdown of muscle structure (Huang et al. 2009) via the mediation of cytochrome *c* and HSP27 (Ding et al. 2021). Cytochrome *c* serves as a regulator of apoptotic protease-activating factor-1 once released to the cytoplasm from the mitochondria, engendering mitochondrial oligomerization to produce apoptosomes (Jiang & Wang 2004). HSP27 is a molecular chaperone protein that is abundantly present in skeletal muscle and is associated with meat quality. Morzel et al. (2008) found that HSP27 appeared to inhibit the initiation of proteolysis, but as meat aging progressed from 7 to 14 d postslaughter, HSP27 presence contributed to meat tenderness. Ma & Kim (2020) reported that HSP27 may regulate proteolytic activities via interaction with enzymes, substrates, or both.

3. MOLECULAR CHANGES IN PROCESSED MEAT AND THE IMPACT ON MEAT QUALITY

Several structural changes occur to different degrees during meat processing, depending on superimposed time–temperature conditions and technological processes (**Table 1**). Muscle cells are degraded and encapsulated by oxygen during mechanical alterations, aiding LOx–POx

Table 1 Processing methods and their impacts on meat quality

Methods	Advantages	Disadvantages
Heating	Promotes protein denaturation; extends shelf life; releases aromatic compounds; induces meat browning via Maillard reaction	Induces protein aggregation and polymerization; promotes rapid oxidation processes; induces Schiff bases and Maillard fluorescent products; damages protein cleavage site; decreases digestibility
Salting	Promotes binding of meat proteins; enhances flavor intensity; improves water–protein interaction; aids myoglobin digestion by pepsin; promotes MP stability and gel strength; exhibits antioxidant properties	Reduces textural attributes, protein functionality (excess); induces protein polymerization and insolubility ($CaCl_2$ or $MgCl_2$); induces oxidation and protein degradation (KCl); expands myofiber gap, reducing WHC
Drying	Decreases FA oxidation and protein denaturation (cold-drying); extends shelf-life; promotes meat redness; inhibits myoglobin oxidation (dry aging); improves sensorial traits	Alters nutritive value; causes protein carbonylation/cross-linking; reduces protein digestibility; reduces MP susceptibility to pepsin activity
Packaging	Inhibits LOx–POx processes; improves color stability (low O_2); promotes meat functionality (edible coating/film); provides health benefits (bioactive compounds in films)	Aids protein cross-linking and polymerization (high O_2); reduces meat color (VP); causes migration/permeation of volatile and nonvolatile metabolites; promotes absorption of nutrient components from meat to packaging material
Nonthermal treatments	Promotes essential biochemical and functional properties; HPT lowers cooking loss by promoting reticular network within muscle fibers; HPT and PEF influence enzymatic activity of meat proteins; HPT promotes aromatic profile, textural attributes, and microstructure in meat products; UT reduces MP aggregation and promotes peptide production	Impedes product uniformity (presence of bubbles in chambers); alters nutritive composition (high treatment) and protein molecules/structures; requires high-level standard equipment; has a relatively high cost

Abbreviations: FA, fatty acid; HPT, high-pressure treatment; LOx, lipid oxidation; MP, myofibrillar proteins; PEF, pulsed electric field; POx, protein oxidation; UT, ultrasound treatment; VP, vacuum packaging; WHC, water-holding capacity.

possibility. Heat treatment promotes severe changes to main protein constituents, resulting from protein denaturation, amino acid oxidation, and aggregation processes (Di Luccia et al. 2015).

3.1. Heating

Heating causes conformational changes known as denaturation of proteins. It also induces protein–protein interactions, resulting in protein aggregation. Protein aggregate formation in cooked meat primarily affects the technological and nutritional properties of the final products (He et al. 2018). It varies significantly in comminuted and noncomminuted products. For example, emulsion sausages (Di Luccia et al. 2015) contain a larger amount of insoluble protein residues compared to cooked ham (Di Luccia et al. 2017). The presence of collagen signifies high-molecular-weight protein aggregates, possibly as a result of heat treatments and distinct technological processes. These aggregates are characterized by a high myofibrillar-to-sarcoplasmic ratio, suggesting the collusion of MPs, particularly actin, in the building of a heat-induced supramolecular protein assembly (Rutigliano et al. 2019).

When studying the cooking effect on meat proteins, Deb-Choudhury et al. (2014) observed an uptrend in the amino acid oxidative changes, particularly in the soluble collagen, whereas myosin in the insoluble fraction was most vulnerable to other heat-induced modifications such as Maillard reactions. He et al. (2021) recently found that van der Waals forces and hydrogen bonds engendered myosin–aldehyde binding interactions, thereby providing new insight into the mechanism of maintaining/controlling meat flavor. In a proteomic study, Yu et al. (2016) revealed that dry heating aided aggregation of some meat proteins that varied markedly in three-dimensional structures, e.g., creatine kinase M-type and myosin heavy chains. Although a substantial loss in total protein extractability was detected in the urea–thiourea solution, major collagens in skeletal muscle, type I and III, displayed relatively better extractability after longer cooking in contrast to other proteins. M. Zhang et al. (2020b) reported that heat-induced partial unfolding or oxidation of type I collagen at a lower temperature may expose more active sites for pepsin digestion, whereas overheating leads to aggregation, polymerization, cross-linking, and oxidation of proteins, inducing resistance to enzymatic degradation. Consistently, Jiang et al. (2022) illustrated that sous vide cooking for 12 h increased the number of antioxidant-active peptides, which could markedly reduce LOx and POx occurrences. This indicates that peptides with potential antioxidant properties and biological activity that could penetrate cells may be generated at low temperatures and short times.

3.2. Drying

Dried meat and meat products are commonly achieved by a hot-air-drying technique. Generally, successive and intense processing of meat proteins causes nutritional changes due to the loss of essential amino acids and impaired digestibility. Because of this, drying is often followed by other processes such as curing, salting, or smoking. To reveal changes in LOx, MP oxidation, and protein digestibility, Ma et al. (2021) found that the decline in protein digestibility of air-dried yak meat was attributed to oxidation-induced protein cross-linking and carbonylation, which influenced the binding of the substrate to pepsin.

Alternatively, cold drying has also been reported to extend shelf life by reducing rapid oxidative processes of heat-sensitive foods due to reduced temperature. Lewicki (2006) demonstrated that protein degradation and fatty acid oxidation declined in cold-air-dried fish, whereas Kilic (2017) reported greater efficacy of anchovy and trout samples cold dried at 4°C than those dried at 10°C, 15°C, and 20°C under constant airflow. Recently, to minimize the organoleptic limitations of conventional drying, Aykın-Dinçer & Erbaş (2019) designed a novel dryer operating at low temperatures (≤20°C) and reported remarkable results in cold-dried beef slices.

3.3. Salting

Salt is an integral ingredient in processed products. It promotes the solubilization of meat proteins and acts as a binder between meat and fat, improving texture, tenderness, aroma, and palatability. The perceived saltiness is attributed to the Na^+ cation and Cl^- anion, and flavor intensity is dependent on salt level. Salt level played a significant role in the oxidation, structure, and digests of actomyosin, demonstrating a large influence on meat nutrition and protein digestibility (Zhao et al. 2020). Following myoglobin's rigidity and low digestion efficiency (Li et al. 2020), an NaCl treatment decreased protein binding capacity, causing rapid myoglobin digestion by pepsin (Liu et al. 2021). Nonetheless, NaCl decrease reduces yield and induces inferior texture in the final product, whereas excessive NaCl impairs protein functionality, as MPs are highly salt-soluble. NaCl treatment was recently reported to change the heme structure and myoglobin hydrophobic cavity, decreasing protein digestibility (Liu et al. 2022). Hence, the impact of NaCl reduction on POx varies, which is related to the association between chloride ions and protein residues, proteolysis, and myofibril conditions.

Various chloride salts such as calcium ($CaCl_2$), potassium (KCl), and magnesium ($MgCl_2$) chlorides have been studied to determine their potency as NaCl substitutes in meat products. Accordingly, monovalent (potassium) and divalent cations (magnesium and calcium) were observed to enhance the functionality of meat proteins during gelation (Zheng et al. 2019). To assess the impact of NaCl partial substitution with KCl, $MgCl_2$, or $CaCl_2$ on MP, Ge et al. (2020) demonstrated that NaCl was able to unfold MP structure and enhance gel quality, especially at 0.60 M, whereas 25% KCl increased MP hydrophobicity and particle size, disulfide, and carbonyl contents, enhancing gel structure and gel strength better than other salt combinations at similar ionic strength. Although $MgCl_2$ or $CaCl_2$ contributed to protein insolubility and polymerization, the former greatly affected gel properties.

D. Zhang et al. (2020b) reported that K^+ had a faster mass transfer rate than Na^+ during salting, replacing NaCl with KCl-aided oxidation and denaturation in salted pork proteins. These results corroborated the findings of Ge et al. (2020) showing that a high KCl substitution rate increased water content in salted pork, plausibly enhancing the mobility of water molecules because KCl may promote POx. Xing et al. (2017) asserted that changes in proteins influence the electrostatic repulsion among myofibers in meat products and expand the gap in myofibers, thereby affecting the distribution and state of water.

Notably, tenderness, water–protein interactions, gel properties, MP stability, and oxidative status have also been markedly improved in salted meat products following the application of high-pressure treatment (HPT) (Yang et al. 2021a,b), ultrasound (Gao et al. 2022, Gómez-Salazar et al. 2021), and plant extracts (Mancini et al. 2020, Zhao et al. 2021).

3.4. Packaging

Researchers have developed various packaging technologies such as controlled, modified, active, and intelligent packaging to reduce oxidative processes and enhance meat quality (Fang et al. 2017, Pirsa & Shamusi 2019). Ye et al. (2020) demonstrated that low O_2 (10% O_2/90% N_2) inhibited POx, corroborating the result of Chen et al. (2015) showing that high-O_2 packaging increased centrifuge loss of pork and reduced meat tenderness. In high-O_2 (80% O_2/20% CO_2) packaged beef, Moczkowska et al. (2017) revealed the generation of high-molecular-weight protein polymers, which was consistent with Lund et al. (2007), who showed that high oxidation and cross-linking caused myosin polymerization in high-O_2 packaged pork.

Interestingly, edible films and/or coatings have significantly improved packaging by incorporating food, preservation, and packaging systems into edible, biodegradable, and

moisture-resistant films. Such packaging can prevent color deterioration, oxidative changes, and off odors, extend shelf life, and impart functionality to meat and its derivatives (Umaraw et al. 2020). Different coatings enriched with antioxidant-rich extracts, polysaccharides, and essential oils have been reported to enhance the mechanical properties of films and inhibit the formation of metmyoglobin and the LOx–POx processes in meat products (Martillanes et al. 2021, Priyadarshi et al. 2021, Sani et al. 2021, Tàkma & Korel 2019). Previous studies on the application of natural antioxidants in the meat industry have also been reviewed (Domínguez et al. 2018). These bioactive substances also offer health benefits to consumers once ingested.

3.5. Nonthermal Processing Methods

Recently, consumer attention has shifted progressively beyond nutrition and toward foods that impart a positive physiological response in the body. Innovative tools such as ultrasound, HPT, and pulsed electric field (PEF) have been acknowledged to enhance essential biochemical and functional properties of meat and meat products. HPT was found to improve meat batters via the formation of a filamentous reticular network, even within the muscle fibers, which contributed to low cooking loss (Yang et al. 2021b). In a proteomic study, López-Pedrouso et al. (2019) revealed that HPT accelerated proteolysis, suggesting a differential denaturation of actin, unlike myosin. They also confirmed that HPT positively affected linear aldehyde formation (hexanal, nonanal, heptanal, and pentanal), thereby improving the taste and aroma of dry-cured ham. HPT and PEF were also shown to positively affect the enzymatic hydrolysis of meat proteins during digestion in vitro (Bhat et al. 2021, Kaur et al. 2016).

J. Chen et al. (2021) recently revealed that an ultrasound-assisted epigallocatechin gallate covalent reaction group exhibited increased digestibility, which was linked to the accessibility of digestive protease and reduced MP aggregation. Also, Li et al. (2021) demonstrated that integrated ultrasound and low-temperature short-time heating (40 kHz, 0.2W/cm^2 at 55°C for 15 min) synergistically promoted the inactivation of essential meat proteases (cathepsin B, calpain, and total proteases). This markedly reduced meat protein degradation, improving the texture and microstructure of chicken breast. Likewise, results from liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) illustrated the promotion of peptides with small molecular weight via ultrasound treatment, which may be linked to an uptrend in mitochondrial energy metabolism (Jiang et al. 2021).

4. MOLECULAR CHANGES RELATED TO NUTRITIONAL VALUES OF MEATS

4.1. Digestibility and Bioavailability of Meat Proteins

Meat is a fundamental source of dietary proteins and has a favorable balance and high bioavailability of essential amino acids. However, POx and meat structure changes can influence protein hydrolysis rate, affecting protein bioavailability.

Although mild POx may induce partial unfolding, promoting the binding of proteolytic enzymes to protein substrate, severe POx conditions reduce protease susceptibility by altering the protein binding site to the proteolytic enzyme and causing the protein structure to become compact via polymerization. A typical example, as illustrated in rhea meat, showed that cooking inhibited MP susceptibility to pepsin activity (Filgueras et al. 2011). The increase in the proteolysis rate by pancreatic enzymes after cooking supported the significance of protein aggregation in the nutritional traits of meat proteins.

The nutritional quality of meat on a consumer's plate depends on several factors, ranging from animal and muscle type to maturation and cooking conditions. In a proteome study, Zou

et al. (2018) demonstrated that biceps femoris muscle in pork exhibited the highest susceptibility to digestion, and interaction analysis revealed that differential proteins were primarily linked to glycolysis and muscle contraction. Hence, variations in protein components and digestion susceptibility could be attributed to fiber types. Nevertheless, nutritional quality must also consider both the fatty acid composition of the meat and the peroxidation processes that can generate harmful substances.

According to Goethals et al. (2020), higher contents of POx derivatives in raw-cooked and precooked-cooked meat products during processing were potentially attributed to a high fat–protein ratio, low protein level, and/or intense mincing and cooking methods. POx occurrence during cooking and the release of oxidized sequences during further digestion resulted in bioactivity changes primarily from peptides detected from collagen and titin and newly produced peptides during digestion (Xiao et al. 2020). Ding et al. (2022) recently demonstrated that protein source and fat content influenced the rheological properties and microscopic state of the food matrix, further affecting the degree of protein hydrolysis and digestibility.

A systematic study also compared the efficacy of the in-bag dry-aging process of lamb to its wet-aged equivalents in terms of consumer acceptance, oxidative stability, quality, and in vitro digestibility (R. Zhang et al. 2020). Lee et al. (2020) recently investigated beef protein digestibility in an in vitro digestion model and concluded that the digesta level after digestion improved the digestibility of beef proteins upon aging. Dry aging of Australian beef loins produced products with less myoglobin oxidation, intense redness, and preferred organoleptic traits, and stepwise (wet-then-dry) dry-aged beef was preferred to wet types for palatability, flavor, and general acceptance by Japanese consumers (Ha et al. 2019). Álvarez et al. (2021) recently demonstrated biochemical changes associated with dry aging, which improved technical and organoleptic meat properties highly appreciated by niche consumers.

D. Zhao et al. (2019) also demonstrated that actomyosin heating at 100°C caused the formation of a disulfide bond, aggregation, and oxidation of residues, which resulted in lower digestibility by damaging partial cleavage sites, largely changing peptide composition in protein digests. Myoglobin was also shown to have a relatively low degree of hydrolysis in pancreatin and pepsin digestion (Li et al. 2020). The low digestibility and digestion efficiency may inhibit protein bioavailability and its accumulation in the cecum and colon, where the protein or its fragments are fermented by gut microbiota (GM). Gallego et al. (2020) assessed the impact of gastrointestinal digestion on the profile of bioactive peptides produced from meat and meat products. According to Sayd et al. (2018), the simulation of bioactive peptides in the gastrointestinal tract (GIT) demonstrated that meat proteins are a source of antidipeptidyl-peptidase activity, angiotensin-converting enzyme inhibition, and antioxidant activity to some extent. Thus, for meat to release bioactive peptides and exhibit any physiological effect, the peptides must pass the GIT intact.

4.2. Impact of Balanced Meat Intake on Human Health

Diet composition and dietary habits are important for gut health, including GM composition and balance (Rinninella et al. 2022). During digestion and absorption, the GIT extracts nutrients from foods consumed for basic nutrition and health. Although some foods are rich in anti-inflammatory bioactive compounds (AIBCs), others possess proinflammatory compounds (PICs) (Losso 2021). Regular intake of AIBC-enriched foods aids the prevalence of beneficial GM that degrade food components into metabolites to maintain homeostasis. In contrast, ingestion of PIC-enriched diets favors dysbiosis and GM dominance, generating disease-inducing metabolites that can pose health risks (Losso 2021) (**Figure 2**).

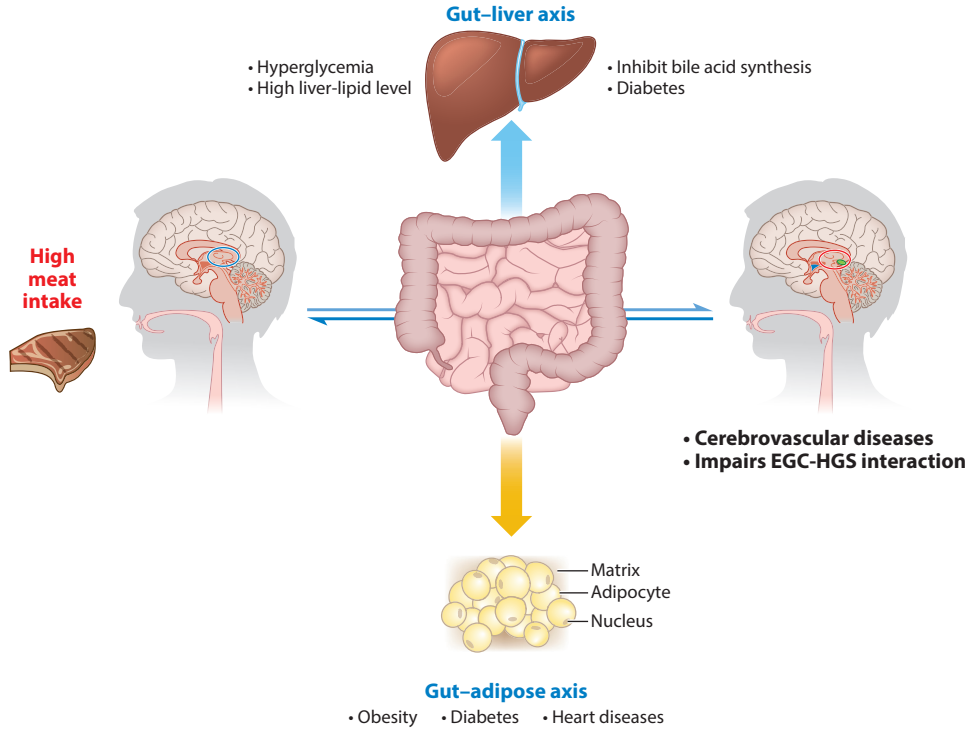

Figure 2

Adverse health risks associated with excessive high-fat meat intake in humans. Abbreviations: EGC, enteric glial cell; HGS, hippocampal glutamatergic system.

In a balanced diet (**Table 2**), intake of meat proteins has been shown to positively affect GM composition, energy metabolism, and antioxidation. Zhu et al. (2015, 2017) reported that during long-term consumption of protein sources (casein, beef, chicken, and soy), meat proteins maintained a more balanced GM composition and reduced GM's antigen load and inflammatory response to the host. Song et al. (2016a,b) demonstrated that dietary meat proteins could downregulate gene expression at proteomic and transcriptomic levels associated with energy metabolism, fatty acid metabolism, essential amino acid metabolism, and Pparα signaling pathways. However, the same diets upregulated gene expression related to oxidoreductive transformation reactions (Huang et al. 2021, Shi et al. 2021). Moreover, Song et al. (2016c) revealed differences in liver proteome profiles among different dietary protein groups (fish, pork, and chicken). Song et al. (2018) also reported that meat proteins were beneficial for the metabolism and growth of young rats compared to soy and casein. Zhu et al. (2021) recently asserted hepatic antioxidative stress was markedly induced in chicken and fish meat proteins compared to beef, pork, and soy proteins. Thus, at a recommended dose, meat proteins may promote triglyceride decomposition and cholesterol degradation and maintain energy balance at a healthy level (Shi et al. 2021).

Furthermore, as oxidative stress is the primary propellant of chronic diseases, including obesity, cancer, and diabetes, individuals seek preventive alternatives to reduce meat-related health risks without impairing nutritional value. Although Liu et al. (2020) recently reviewed the valuable impacts of dietary polyphenols on high-fat diet (HFD)-induced obesity associated with GM modulation, several studies also demonstrated positive findings. In a study by F. Zhao et al. (2019),

Table 2 Recent studies on the impact of balanced meat intake on health

Ingredient	Model	Animal type	Dose	Prevention	Reference
Soy, pork, chicken	Liver metabolic enzymes	4-week-old male Sprague-Dawley rats	200, 190, 192 g/kg, respectively, for 12 weeks	CP and pork diets downregulated AA metabolizing enzymes and induced higher levels of serum AAs, ribosome assembly, and protein synthesis than soy	Huang et al. 2021
Fish, pork, chicken, beef, casein	Liver metabolic enzymes	4-week-old male Sprague-Dawley rats	193, 190, 192, 191, 200 g/kg, respectively	Fish and pork upregulated the gene expression linked to esterification and cholesterol synthesis; pork also upregulated the gene expression of HDL and LDL receptors; chicken, pork, and beef diets upregulated the gene expression involved in bile acid production and cholesterol reverse transport; pork and beef diets lowered the total cholesterol levels in the liver	Shi et al. 2021
Casein, soy, chicken, fish, beef, pork	Oxidative stress	3-week-old male Sprague-Dawley rats	200, 203, 190, 195, 192, 191 g/kg diet, respectively, for 14 d	Pork and soy induced higher hepatic oxidative stress; fish and chicken promoted hepatic-superoxide-dismutase activity and total antioxidant capacity; beef-fed rats showed hepatic steatosis with small vacuoles	Zhu et al. 2021
Casein, chicken	Induced-obesity	4-week-old male Sprague-Dawley rats	Mineral mixes (g/kg diet) for 7 d	Promoted abundance of beneficial bacteria; upregulated obesity-prevention genes	F. Zhao et al. 2019
Soy protein	Colonic bacteria and metabolites	4-week-old male Sprague-Dawley rats	20% protein/kg diet for 90 d	Balanced GM composition; reduced antigen load and inflammatory response	Zhu et al. 2017
Casein, beef, pork, chicken, fish	Physiological and transcriptome responses	4-week-old male Sprague-Dawley rats	200 g protein/kg diet for 7 d	Pork protein reduced ATM and LTC; fish protein suppressed plasma cholesterol and cofactor metabolism; beef and chicken mostly aided pathway responses	Song et al. 2016a
Casein, soy, pork, beef, chicken, fish	Gene expression and physiological changes	3-week-old male Sprague-Dawley rats	200 g protein/kg diet for 7 d	Meat proteins improved insulin resistance index; SP reduced body weight gain and ATM; both proteins reduced LTC and changed plasma AA patterns	Song et al. 2016b
Casein, soy, pork, beef, chicken, fish	Growth and metabolic responses	3-week-old male Sprague-Dawley rats	200 g protein/kg diet for 14 d	WMP increased plasma essential and total AA concentrations; RMP increased plasma HDL cholesterol concentrations; SP increased PT, TC, and LDL cholesterol	Song et al. 2018
Casein	Induced-obesity	8-week-old male C57BL/6J mice	90 g/100 g diet for 8 weeks	Reduced fat mass; prevented obesity risk	Liisberg et al. 2016

Abbreviations: AA, amino acid; ATM, adipose tissue mass; CP, chicken protein; GM, gut microbiota; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LTC, liver triacylglycerol contents; PT, plasma triacylglycerol; RMP, red meat protein; SP, soy protein; TC, total cholesterol; WMP, white meat protein.

dietary casein, compared to dietary chicken protein, increased *Lactococcus lactis* abundance and upregulated gene expression linked to obesity repression in the cecum of experimental animals. Consistently, among dietary protein sources (soy, beef, skinless chicken, casein, cod filets, or pork) fed to C57BL/6J mice, a casein diet greatly reduced fat mass and prevented obesity development when compared to other diets (Liisberg et al. 2016). Fernández et al. (2019) also illustrated a reduction in polyps and uptrends in anti-inflammatory and fiber-fermentative microbiota in two CRC animal models fed inulin-rich, traditionally processed pork products (fermented sausage and cooked ham). Notably, unlike starches, fructans such as inulin are not modified in the GIT of humans until they reach the colon, where they are used as energy and carbon sources by probiotic bacteria such as *Bifidobacterium*, *Lactobacillus*, and other short-chain fatty acid (SCFA)-producing species (Roberfroid 2007).

In C57BL/6JRj mice with cyclically induced chronic inflammation, Burri et al. (2021) reported marked changes in microbiota and immune responses after being fed processed meat products with plant antioxidants. The study provides proinflammatory responses upon the ingestion of processed meat by aiding bacterial diversity and regulatory T-cell levels. Carob fruit extract–enriched meat product was also found to provide preventive and curative treatments in a late-stage Type 2 diabetes mellitus model, such as inducing higher GM richness, enhancing colonic barrier integrity, promoting adequate levels of SCFAs, and causing mild modifications at the distal colonic mucosa (Macho-González et al. 2021).

Butyrate, a preferred energy source for colonocytes, possesses colonic health–promoting and antineoplastic benefits, supports mucosal integrity, and prevents inflammation and carcinogenesis via its influence on epigenetic modulation, immunity, and gene expression (O'Keefe 2016).

4.3. Excessive High-Fat Meat Intake and Human Health

In HFDs, the body may respond differently to meat proteins (**Table 3**). M. Zhang et al. (2020a) reported that a high-pork or high-chicken diet (40% or above) with a high-fat content could impair the glutamatergic system and neurotransmitter balance and exert a huge influence on the association between the hippocampal glutamatergic system and enteric glial cells. Likewise, excessive meat protein consumption in an HFD may promote metabolic disorders, systemic inflammation, alterations of central nervous system function, and ultimately the development of neurodegenerative diseases (Sandhu et al. 2017). Zhao et al. (2017) also reported rapid alterations in cecum microbiota composition of dietary-protein-fed rats, and Koeth et al. (2013) illustrated an association between meat intake and GM, which showed that excessive meat consumption promotes cardiovascular disease risks and arteriosclerosis. Consistently, Lang et al. (2020) attributed high protein ingestion to histological disease activity in NAFLD patients, which results directly from gut inflammation (Reccia et al. 2017).

Processing method may also exert a certain influence on the nutritional attributes of meat proteins. Xie et al. (2020b) explored the digestion of processed meat protein in vivo and its connection with GM and intestinal morphology. The results showed that the bioavailability of meat proteins was altered by processing methods and influenced the intestinal morphology and cecum microbiome and function. Additionally, Ge et al. (2021) recently evaluated the effects of cooked pork with different oxidative injury degrees on glucose metabolism in mice and concluded that intake of a high-oxidative injury pork diet (HOP) impaired glucose tolerance and caused hypoinsulinemia and hyperglycemia, indicating a glucose metabolism disorder.

Moreover, HOP-mediated hyperglycemia was partially involved in elevated hepatic glucose, as demonstrated by elevated glycogenolysis and gluconeogenesis and reduced glycolysis and glycogen level. Vik et al. (2015) revealed that the hypotriglyceridemic characteristic of a chicken protein

Table 3 Recent literature associated with excess high-fat meat intake and health effects

Diet	Model	Duration	Dose	Risks	Reference
Plant antioxidant mixtures	Cyclically induced chronic inflammation in 8-week-old female wild-type C57BL6/7JRj mice	87 d	20% meatball feed + antioxidant mixtures (OP, OS, SBT, SS, BCL) with cyclic DSS treatment	Standardized intestinal microbiota at early inflammation stage; increased bacterial diversity and regulatory T-cells levels	Burri et al. 2021
Dietary protein, carbohydrate, fat mix	6-week-old male and female C57BL/6J mice	12 weeks	HFD (24, 41, 24 g/100 g diet), LFD (19.2, 67.3, 4.3 g/100 g diet)	HFD-induced glucose intolerance and obesity in male mice; glutaredoxin1 deficiency exacerbated HFD-induced liver injury, oxidative stress, and GM alteration	Zou et al. 2021
Casein, fish, mutton	6-week-old male C57BL/6J mice	12 weeks	HFC (260.44), HFF (261.5), HFM (260.58) g/kg	Mutton diet impaired GM composition, intestinal inflammatory gene expression, hepatic metabolic profile, and serum endotoxin level	Ahmad et al. 2020
Casein, chicken, pork	Male Wistar rats	12 weeks	High-fat (45% calorie) low-protein (20%) and high-fat (45%) high-protein (40%) diets	High chicken and pork diets altered glutamatergic system and neurotransmitter balance; markedly influenced the interactions between hippocampal glutamatergic system and EGCs	M. Zhang et al. 2020a
Carob fruit extract	Late-stage Type-2 diabetes mellitus in 2-month-old male Wistar rats	8 weeks	4 g/kg diet	Promoted colonic barrier integrity; enhanced SCFA formation; induced GM richness and mild modifications at the distal colonic mucosa	Macho-González et al. 2021
LOP/HOP diets	4-week-old male C57BL/6 mice	12 weeks	LOP (296.11) and HOP (276.67) g/kg diet	HOP impaired glucose tolerance; induced hyperglycemia and hypoinsulinemia	Ge et al. 2021
Beef and chicken	7 male, 3 female nonvegetarians (22–75 years)	24 h	4.5 g in 10 fecal inocula ($n = 2 \times 3 \times 10$ simulated meat digestion)	Detected NOC- and/or LPO-related DNA adduct formation, indicating red meat induced CRC risks	Hemeryck et al. 2018

(*Continued*)

Table 3 (*Continued*)

Diet	Model	Duration	Dose	Risks	Reference
Soy protein, chicken, pork	7-week-old male C57BL/6J mice	12 weeks	184.87, 189.56, and 184.70 g/kg diet	HFP increased inflammatory cells infiltration, disorganized liver structures, and potential serum markers for NAFLD, ALT, and AST; HFCH/HFP induced hepatic lipid accumulation	Hussain et al. 2020
Inulin	Induced-CRC in 5-week-old male FIscher 344 rats	20 weeks	15.7 g/day of feed (cohort 4) and 10% inulin (cohort 5)	Reduced colon polyps; increased cecum weight; increased anti-inflammatory and fiber-fermentative bacteria	Fernández et al. 2019
Casein, chicken, beef, pork	7-week-old male C57BL/6J mice	14 weeks	189.56, 189.71, 189.57, and 184.70 g/kg diet	HFCH and HFB diets induced mitochondrial biogenesis, adiposity, visceral obesity, and dyslipidemia	Ijaz et al. 2020
Dietary protein intake	180 NAFLD patients	14 days	Low- (<17.3%) versus high- (≥17.3%) protein diet	HPD decreased *Bacteroides* abundance; caused severe histological disease activity, inducing NAFLD development and/or progression	Lang et al. 2020
Casein, chicken, pork	Male SPF Wistar rats	12 weeks	LFLC (190), HFLC/HFLCH/HFLP (233), and HFHC/HFHCH/HFHP (466) g/kg diet	HFHP and HFHCH diets impaired liver ability to metabolize skatole; induced GM dysbiosis and tryptophan metabolism, causing colon inflammation	Shi et al. 2020
Cod, beef, chicken, pork	C57BL/6J mice	11 weeks	89, 76, 90, and 87 g/100g diet	Pork-based diet highly induced obesity via accentuated fat mass gain and decreased UCP1 expression	Liisberg et al. 2016

(*Continued*)

Table 3 (*Continued*)

Diet	Model	Duration	Dose	Risks	Reference
Red, white, and non meat	113 adults (21–65 years old)	2–7 weeks	Red and white (12% meat + 4% VP + 9% DE each), nonmeat (16% VP + 9% DE)	Chronic dietary red meat increased systemic TMAO levels capable of causing CVD	Wang et al. 2019a
Chicken, red, and red processed meat	3-week-old castrated male piglets	4 weeks	145 g/kg diet (red = 62%; red processed = 38%)	Red meat diet induced hepatic mRNA expression related to TMAO formation	Thøgersen et al. 2020
Soy protein and pork	4-weeks-old male C57BL/6J mice	240 days	178.6 g protein and 70 g fat/kg diet	Pork diet altered GM composition; increased fat deposition linked to CVD	Xie et al. 2020b
Pork, beef, chicken, fish, soy, or casein	3-week-old male Sprague–Dawley rats	14 days	20% protein/kg diet	Diets rapidly altered microbial composition in rat cecum, associated with CVD risks and arteriosclerosis	Zhao et al. 2017
Lean seafood and meat	7-week-old male C57BL/6 J Bom Tac mice	12 weeks	16% protein/kg diet	Lean meat impaired glucose clearance; increased plasma insulin, liver lipid levels, and fasting blood glucose	Holm et al. 2016

Abbreviations: ALT, aspartate aminotransferase; AST, alanine aminotransferase; BCL, lyophilized blackcurrant leaves; CRC, colorectal cancer; CVD, cardiovascular disease; DE, dairy and eggs; DSS, dextran sodium sulfate; EGCs, enteric glial cells; GM, gut microbiota; HFB, high-fat beef; HFC, high-fat casein; HFCH, high-fat chicken; HFD, high-fat diet; HFF, high-fat fish; HFHC, high-fat high-casein; HFHCH, high-fat high-chicken; HFHP, high-fat high-pork; HFLC, high-fat low-casein; HFLCH, high-fat low-chicken; HFLP, high-fat low-pork; HFM, high-fat mutton; HFP, high-fat pork; HOP, high-oxidative injury pork diet; HPD, high-protein diet; LFD, low-fat diet; LFLC, low-fat low-casein; LOP, low-oxidative injury pork; LPO, lipid peroxidation products; NAFLD, nonalcoholic fatty liver disease; NOC, N-nitroso compounds; OP, olive polyphenols; OS, onion skin; SBT, sea-buckthorn leaves/sprouts; SCFA, short-chain fatty acid; SPF, specific pathogen-free; SS, summer savory leaves; TMAO, trimethylamine N-oxide; VP, vegetable protein.

water-soluble fraction was mainly attributed to its influence on triacylglycerol synthesis and mitochondrial fatty acid oxidation, asserting that chicken protein's cholesterol-lowering effect may be associated with accelerated bile acid production.

Ahmad et al. (2020) reported that protein in an HFD markedly influenced GM composition, hepatic metabolic profile, intestinal inflammatory gene expression, and serum endotoxin level, with many metabolites affecting serum endotoxin, inflammation, and intestinal permeability. The findings of Hussain et al. (2020) also illustrated that gut inflammation induced hepatic injury in C57BL/6J mice via gut-vascular barrier dysfunction with an HFD, underlining the relationships among GM, intestinal barriers, and diet that aid NAFLD development. According to Xie et al. (2020a), specific GM may impact protein digestion and absorption by modulating the secretion of digestive proteins from the host, particularly after long-term consumption of meat proteins. The assertion corroborated the results of Shi et al. (2020) showing that high dietary meat proteins, compared to alternatives, lowered the activity of indole and skatole metabolizing enzyme (CYP2E1) in the liver.

High-fat chicken or beef significantly influenced mitochondrial biogenesis and adipocyte differentiation in obese mice by upregulating diacylglycerol lipase α, N-acyl phosphatidyl ethanolamine-selective phospholipase-D, and cannabinoid 1 receptor in adipose tissue and decreasing the immunoreactivity of mitochondrial uncoupling protein 1 (UCP1) in brown adipose tissue (Ijaz et al. 2020). Pork-fed mice also caused considerable fat accumulation in interscapular brown adipose tissue, followed by decreased UCP1 expression (Liisberg et al. 2016). Kiilerich et al. (2016) highlighted that dietary fat content was a more important driver of GM composition than obesity, as mice fed HFDs (high sucrose and protein diets) exhibited similar GM profiles, notwithstanding the variations in obesity development. This was consistent with changes linked to colon cancer progression (Li et al. 2014), demonstrated to be caused by high-fat feeding due to obesity and not diet. Zou et al. (2021) recently asserted that GM composition was altered by diet but not gender or genotype, providing a novel insight into the differences between males

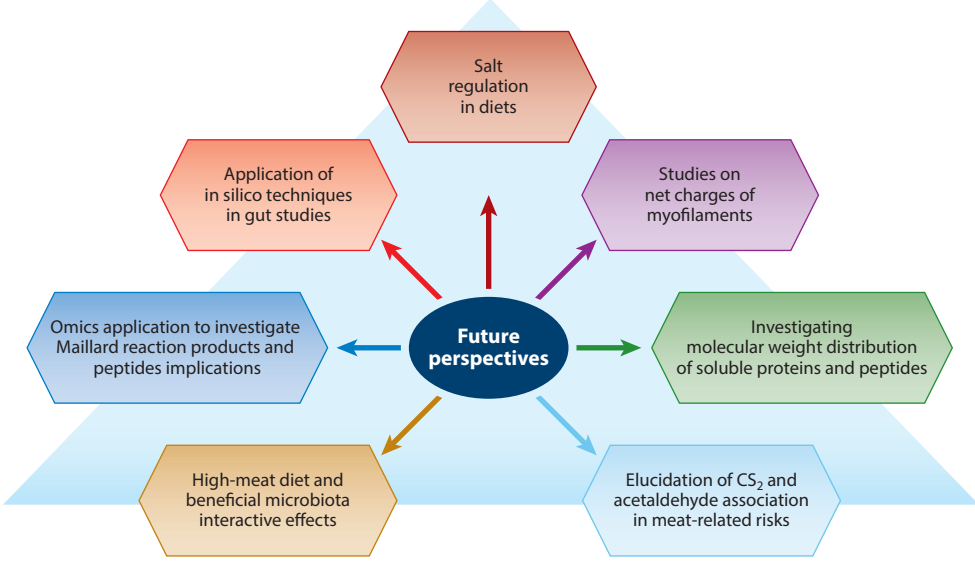

Figure 3

Flowchart on future research directions to reduce oxidative reactions and meat-related health risks in humans.

and females in obesity vulnerabilities induced by an HFD. These findings highlight the need to separate the impact of high-fat feeding from obesity.

The GM also engenders trimethylamine (TMA) generation in meat and other dietary lecithin sources. TMA is oxidized by hepatic flavin-containing monooxygenases to trimethylamine N-oxide (TMAO) from L-carnitine in the diet, which may inhibit bile acid synthesis and secretion but promote atherosclerosis. Bile acid is crucial for the host to change GM composition, as it has a strong interaction with L-carnitine (Zhao et al. 2017). According to Mohseni et al. (2020), the elevation of secondary bile acids such as lithocholic and deoxycholic acids was attributed to the intake of HFDs, which can prompt CRC risks. Thøgersen et al. (2020) found that meat-induced TMAO formation was regulated by mechanisms other than changes at the hepatic gene expression level, possibly involving GM alteration. Importantly, the study revealed that switching red meat–enriched diets to either a white meat or nonmeat protein source (yet maintaining the same calories and dietary protein proportion) led to a substantial decrease in TMAO levels within several weeks.

Wang et al. (2019a) explored the interaction of dietary protein source to plasma TMAO levels with defined isocaloric randomized diets, and the time needed to decrease TMAO levels with dietary changes, highlighting that, beyond quantity, diet composition (with respect to the protein source but not saturated fat content) affects overall TMAO metabolism and excretion. This corroborated the recent study by Shi et al. (2021) showing that meat proteins at the recommended dose could enhance cholesterol degradation and triglyceride decomposition and maintain energy synthesis at a healthy state. **Figure 3** provides perspectives that may be helpful in satisfying further objectives and technological interests.

SUMMARY POINTS

1. The high nutrient levels (e.g., lipids and proteins) in meat and meat products make them susceptible to oxidative changes.
2. Lipid oxidation is induced by a free-radical chain reaction that generates several oxidative by-products that are primarily associated with the deterioration of meat flavor and color.
3. Protein oxidation, caused by reactive oxidative species and derivates of oxidative stress, engenders structural and conformational changes, altering protein functions and affecting meat quality in the process.
4. The inseparable co-existence of lipids and proteins in the meat system exacerbates the generation of oxidized secondary by-products that could adversely affect human health upon meat intake and subsequent digestion.
5. The importance of meat in the daily diet underlines the growing interest in elucidating the molecular changes that may negatively impact its nutritional value and create health risks.

FUTURE ISSUES

1. In silico techniques can be applied to track the outcome of meat proteins in the gastrointestinal tract to better understand their bioavailability and satisfy physiological benefits upon consumption.

2. Because protein sources with the same in vitro digestibility can vary in the release of free amino acids or di- and tripeptides, investigating the change in molecular weight distribution of soluble proteins and peptides before and during trials might provide a deeper insight into both in vitro and in vivo meat protein digestion.
3. Investigating the net charges of myofilaments may engender a new perspective to elucidate oxidation-induced meat quality changes.
4. Although sodium and processed meat intake are highly correlated, the latter is an independent contributor to colorectal cancer risk. Nonetheless, future research should also focus on promoting compliance and adherence to reducing high salt intake in diets.
5. Applying omics technologies singly or in combination will help elucidate the various aspects/implications of peptides and Maillard reaction products from meat proteins.
6. To elucidate the recent involvement of acetaldehyde and CS_2 in meat-related chronic diseases, in vitro studies should complement in vivo studies, concentrating on the complete diet.
7. Studies should also focus on the interactive effect of probiotic GM and a high-meat diet, as this can help develop biocidal agents to decrease meat-related health risks.
8. As the inclusion of meats in diets is expected to keep rising, strategies to reduce/avoid oxidative processes and consequent loss in nutritional values should be intensified.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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