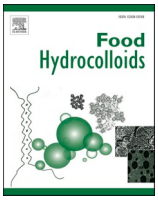
Food Hydrocolloids 131 (2022) 107748

Contents lists available at ScienceDirect

Food Hydrocolloids

journal homepage: www.elsevier.com/locate/foodhyd



Collagen and its derivatives: From structure and properties to their applications in food industry

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ARTICLE INFO

Keywords:
Collagen
Gelatin
Collagen peptides
Structure and functionality

ABSTRACT

Collagen is the most abundant extracellular matrix protein in food-producing animals. Gelatin is partially degraded collagen. Collagen peptides refer to the peptides with specific properties identified from collagen hydrolysate who produced by hydrolysis of collagen/gelatin. Due to the specific structural and bio- and physical-chemical properties, collagen and its derivatives are used in the field of food industry. In this review, the structure of the collagen molecule and its biosynthetic process *in vivo* are introduced, and the production methods and structures of gelatin and collagen peptides described. Then the inherent self-assembly property of collagen, the mechanical properties of collagen and gelatin gels, functional properties of collagen and gelatin, and bioactive properties of collagen peptides are reviewed. Finally, the applications of collagen and its derivatives that are correlated with their properties in food industry are summarized. The mechanisms and advantages of the applications of collagen and its derivatives in food industry are raised, and the limitations and challenges of these applications are also discussed. And possible studies to address the challenges of the applications in different areas are indicated.

1. Introduction

Due to the energy and food challenges caused by the rapid growth of the global population, minimizing waste and making high-value use of by-products from the slaughter and processing of food-producing animals, such as livestock, poultry, and fish, have been important challenges. Statistics show that the annual output of pork was >49 million tonnes in China, producing nearly 5 million tonnes of viscera, 7 million tonnes of skins, and 8 million tonnes of bones (Shen, Zhang, Bhandari, & Gao, 2019). These by-products contain large amounts of proteins, among which collagen is the most abundant. Therefore, the utilization of collagen in these by-products will provide opportunities to potential produce high-value by-products from slaughtered animals.

Collagen represents the most abundant structural protein in all animals (accounting for 30% of the total protein content), and can be found in skin, tendons, bones, cartilage, ligaments, and other tissues and organs (Gisbert, Benaglia, Uhlig, Proksch, & Garcia, 2021; Li et al., 2013). So far, ~28 different types of collagen have been identified and described, among which type I collagen is the most common (Hennet, 2019). All types of collagen consist of three identical/different α-chains, and contain at least one triple helix domain (Silver, Jaffe, & Shah, 2018). Collagen self-assembles into highly diverse morphologies in different tissues *in vivo* (Sorushanova et al., 2019), and, with certain conditions, a considerable number of collagen molecules with intact triple-helical structures can be separated. On the other hand, the intramolecular and intermolecular covalent bonds stabilizing the collagen fibrils and the hydrogen bonds stabilizing the collagen triple helix may be broken during the extraction process of collagen, and the resulting polypeptide mixture is gelatin, i.e., gelatin is partially degraded collagen (Duconseille, Astruc, Quintana, Meersman, & Sante-Lhoutellier, 2015). Collagen and gelatin have many functional properties related to their groups of protein side chains, such as gelling, emulsifying, foaming, and film-forming properties (Gómez-Guillén, Giménez, López-Caballero, & Montero, 2011). All these properties make them the functional

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https://doi.org/10.1016/j.foodhyd.2022.107748
Received 10 November 2021; Received in revised form 2 April 2022; Accepted 18 April 2022
Available online 21 April 2022

ingredients in various food systems (Baziwane & He, 2003; Santana, Perrechil, Sato, & Cunha, 2011), or the edible packaging materials (Cao, Wang, Ma, Bao, Yu, Duan, 2020; Moula Ali, Caba, Prodpran, & Benjakul, 2020; Suurs & Barbut, 2020).

Collagen and gelatin can provide potential health benefits by releasing bioactive peptides encrypted in their sequences during gastrointestinal digestion and food processing (Gómez-Guillén et al., 2011). Moreover, low molecular weight collagen hydrolysates have higher digestibility and bioavailability, and show greater biological activity than collagen/gelatin (Hong, Fan, Chalamaiah, & Wu, 2019), which promotes the preparation of collagen hydrolysate from various animal by-products. Collagen hydrolysates are usually prepared by acid, alkali, or enzymatic hydrolysis of collagen/gelatin (Fu, Therkildsen, Aluko, & Lametsch, 2019). Ingestion of collagen hydrolysates has a variety of beneficial effects, such as improving skin health (Zhao, Zhang, & Liu, 2021) and alleviating cardiovascular disease (Cao, Wang, Hao, et al., 2020; Tometsuka, Funato, Mizuno, & Taga, 2021; T.-Y.; Wang, Hsieh, et al., 2015). Some collagen peptides with specific biological activities have been identified and characterized from collagen hydrolysate. Collagen hydrolysates/peptides have great potential to be used in improving the qualities of processed foods and the development of functional foods (Lv et al., 2019).

The insufficient utilization of collagen in animal by-products not only can lead to an increase in disposal costs but also the loss of potential revenues. The global collagen market value had reached ~4.7 billion dollars in 2020, of which ~80% of the collagen and its derivatives are used in the food and beverage (~32%) and the health management (~48%) industries (Cao, Xiao, Ge, & Wu, 2021). And it is estimated that the global collagen market value will reach ~7 billion dollars by 2027 (Cao et al., 2021). To fully exploit the application potential of collagen and its derivatives in food industry, it is necessary to understand their basic structure, key properties, and application features. To this end, we reviewed the recent research regarding the structure and properties of collagen, gelatin, and collagen peptides, and further summarized and discussed the representative applications and challenges of collagen and its derivatives in food industry. This review can provide a comprehensive understanding of collagen and its derivatives, and prospects their applications in food industry.

2. Structure of collagen and its derivatives

2.1. Structure of the collagen molecule

The structure of collagen was suggested by Ramachandran and Kartha (1954, 1955) as a triple helix using X-ray diffraction in the 1950s, which laid a foundation for better understandings of the function and properties of collagen. Although there are considerable differences in size, function, and tissue distribution among different types of collagen (Gelse, Pöschl, & Aigner, 2003), the general structural feature of collagen is a right-handed triple helix formed by the supercoiling of the three parallel α-chains each of which adopts a polyproline II (PPII)-like left-handed conformation (Fig. 1A) (Exposito, Valcourt, Cluzel, & Lethias, 2010; Shoulders & Raines, 2009). The monomeric collagen molecule is known as tropocollagen, which exists in either fibrillar or non-fibrillar types (Hulmes, 2008). The mature fibrillar collagen is essentially a long triple-helix domain composed of over 1000 amino acids residues with short non-helical telopeptides at both ends, exemplified by type I collagen (Sorushanova et al., 2019). Meanwhile, all non-fibrillar collagens have interruptions (containing a large number of residues) or imperfections (one to three residues) in the triple helix (Exposito et al., 2010; Shoulders & Raines, 2009). Another important structural feature of collagen is that each α-chain contains one or more regions of repeating amino acid motifs, Gly-X-Y (Hulmes, 2008), where X and Y are often occupied by Pro and 4-Hyp, respectively. Every third amino acid residues of each α-chains are in the center of the collagen triple helix, so the smallest amino acid Gly occupies every three positions in the primary structure (Gaar, Naffa, & Brimble, 2020). Moreover, the higher abundance of Pro and Hyp residues preorganizes the α-chain into a PPII conformation, thereby reducing the entropic cost for collagen folding (Shoulders & Raines, 2009). The hydrogen bonds formed between the amino group of Gly residues and the carboxyl group of the residues in the X position of adjacent chain are the main interactions for stabilizing the collagen triple helix (Fig. 1B) (Liu, Zheng, Luo, Wang, & Jiang, 2019; Shoulders & Raines, 2009). Also, 4-Hyp in the Y position of α-chain stabilizes the collagen triple helix *via* a stereoelectronic effect (Bretscher, Jenkins, Taylor, DeRider, & Raines, 2001).

The biosynthesis of collagen molecules and the subsequent self-assembly of collagen into collagen fibers, which builds up the dermis, tendons, bones, ligaments, and cornea, are shown in Fig. 2. The mRNA

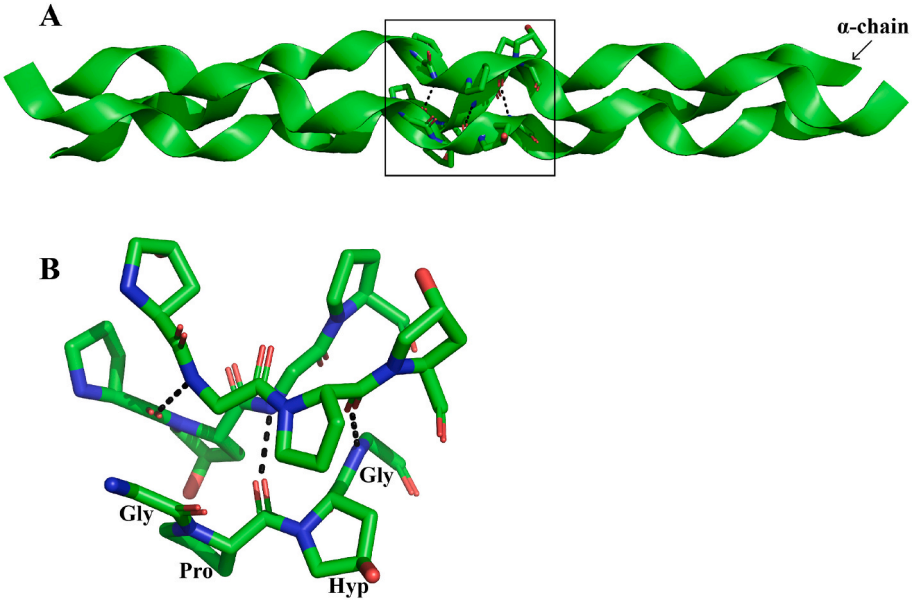

Fig. 1. The triple helix structure (A) of collagen with the three α-chains depicted in cartoon and partial stick representation (PDB code 1CAG). B shows a repeating region of the Gly-X-Y motif in the black box in A, and the interchain hydrogen bonds are labeled with a dashed line in black.

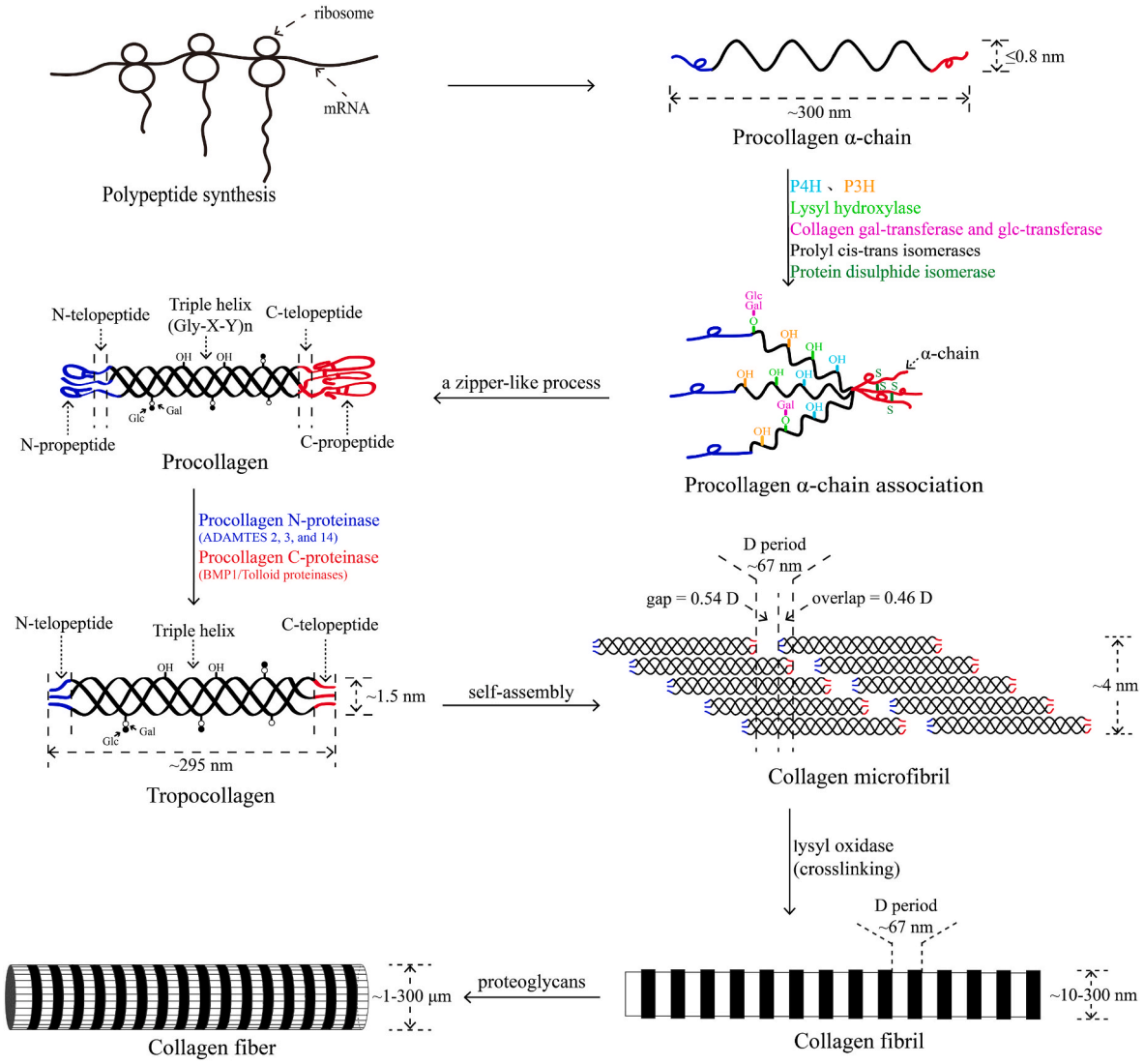

Fig. 2. Schematic diagram of the biosynthesis process of collagen and collagen fiber *in vivo*. P4H: prolyl 4-hydroxylase; P3H: prolyl 3-hydroxylase; ADAMTES: a-disintegrin-and-metalloproteinase-with-thrombospondin-like-motifs family; BMP1: bone morphogenetic protein 1.

carrying genetic information for collagen translates to the corresponding amino acid sequence of procollagen α-chains at the ribosome. The procollagen α-chains undergo post-translational modifications (such as hydroxylation and glycosylation) in the lumen of the endoplasmic reticulum after removing the N-terminal signal peptide by a signal peptidase (Yamauchi, Sricholpech, Terajima, Tomer, & Perdivara, 2019; Yamauchi, Terajima, & Shiiba, 2019). The modified procollagen α-chains align at the C-terminal domains (Gelse et al., 2003), and the disulfide bonds between the C-terminal domains of α-chains are formed by the catalysis of protein disulphide isomerase to prevent the slippage of three α-chains against each other in the formation process of triple helix (Sorushanova et al., 2019). Then the triple helix extends from the C-terminus to the N-terminus of the α-chains (Exposito et al., 2010), resulting in a procollagen molecule. The newly synthesized procollagen molecules are secreted to the extracellular matrix and transformed into tropocollagen molecules (~1.5 nm in width and ~295 nm in length) by the site-directed and restrictive cleavage of biological enzymes called the procollagen N-proteinase (PNP) and the procollagen C-proteinase (PCP) (Mienaltowski & Birk, 2014). In the case of type I procollagen, PNP cleaves the N-propeptide at specific Pro-Gln and Ala-Gln sites, and PCP cleaves between Ala and Asp (Greenspan, 2005). PNP belongs to the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) family (e.g., ADAMTS 2, 3, and 14) (Kelwick, Desanlis, Wheeler, & Edwards, 2015), while PCP is classified as bone morphogenetic protein-1(BMP-1)/Tolloid-like proteinases (Greenspan, 2005). After the enzymatic removal of the N-/C-propeptides, tropocollagen molecules are laterally packed into quarter-staggered or quasi-hexagonal units, which are then longitudinally incorporated into collagen microfibrils (Orgel, Irving, Miller, & Wess, 2006; Silver et al., 2018). Subsequently, the microfibrils are interdigitated and cross-linked to form collagen fibrils. With the help of proteoglycans, multiple fibrils make up a collagen fiber, which is the structural basis of tendons and ligaments (Gautieri, Vesentini, Redaelli, & Buehler, 2011).

The extraction of collagen molecules from the by-products of food-producing animals usually includes two procedures: pretreatment and extraction. The pretreatment procedure may include soaking raw materials in alkaline solution for the removal of impurities and non-collagenous proteins (Z. Song, Liu, et al., 2021), in organic solution to remove lipid material (Zhang et al., 2016), and in EDTA solution for decalcification (Yousefi, Ariffin, & Huda, 2017). The extraction procedures could be divided into three categories: salt extraction, acid extraction, and enzyme extraction. The products correspond to salt-soluble collagen, acid-soluble collagen, and enzyme-soluble collagen, respectively. Generally, these products all retain the inherent

triple helix structure of natural collagen molecules (Zhou et al., 2016). Moreover, enzymatic hydrolysis tends to remove the non-helical telopeptides, which increases the extraction rate and solubility of collagen (Z. Song, Fu, et al., 2021). However, collagen molecules with intact telopeptides have better self-assembly properties *in vitro* (Zhang et al., 2016).

2.2. Structure of gelatin

Partial hydrolysis of collagen results in gelatin with different molecular weights ranging from 15 to 250 kDa (Abedinia et al., 2020). Depending on the pre-treatment procedures, namely, acid or alkaline pretreatment conditions, two types of gelatin can be obtained, which are commercially known as type A (pI ≈ 8–9) and type B (pI ≈ 4–5) (Gómez-Guillén et al., 2011). Enzymatic pre-treatment procedures which target the disruption of specific labile peptide bonds are also used to produce gelatin (Zhu et al., 2022). The combination of different pre-treatment and extraction procedures makes the final gelatin product a mixture of polypeptides with different conformations and molecular weights. It may consist of α-chains, small subunits of the α-chain, and the fractions of higher molecular weights, e.g., β-chains (covalently linked α-chain dimers), γ-chains (covalently linked α-chain trimers), and even higher orders called microgels (Duconseille et al., 2015). As gelatin derives from denatured collagens, the amino acid composition is similar to that of collagen molecules. However, when collagen is hydrolyzed to gelatin with alkaline, glutamine may be de-amidated to glutamic acid and asparagine to aspartic acid (Duconseille et al., 2015). Although collagen is denatured and loses its native structure during the gelatin manufacturing process, the resulting fragments can still form partially ordered collagen-like triple helical structures during the cooling process (Maki & Annaka, 2020).

Gelatin gels are a cold-setting and thermo-reversible gel, which allows it to transform from gel to sol by adjusting the temperature above its critical gel temperature (Avallone et al., 2021). The gel formation of gelatin is related to the structural transition of the gelatin polypeptide chains from random coils to ordered collagen-like triple helices (Qiao, Wang, Zhang, & Yao, 2021). In the sol state, the polypeptide chains are random coils. Upon cooling, some parts of the different chains or parts of the same chain intertwine with each other to form a triple helix region, which is called a junction zone (Guo, Colby, Lusignan, & Whitesides, 2003). At this time, the gelatin molecules partially revert to the ordered collagen-like triple helical structure with the rest remaining a disordered coil structure. And the increase in the number of junction zones results in the gel network (Fig. 3). Hydrogen bonds are the main source of the stability of these triple helices, and hydrophobic and electrostatic interactions were also found to have important roles in stabilizing the helical structure (Duconseille et al., 2015).

2.3. Structure of collagen peptide

Collagen hydrolysate represent a mixture of various amino acids and peptides of different sizes obtained by chemical or enzymatic hydrolysis of collagen or gelatin. And some identifiable peptides with specific properties obtained from the mixture after isolation, screening, and identification are called collagen peptides, and the preparation routine is shown in Fig. 4. Chemical hydrolysis, such as acid/alkali hydrolysis, can decompose the peptide amide bonds, and the products of hydrolysis are amino acids and small peptides that vary in molecular weight based on the conditions and time (Anal, Noomhorm, & Vongsawasdi, 2013). The advantages of chemical hydrolysis that they are cost-effective and simple operations, but the hydrolysis process is difficult to control, the products are unpredictable, and the reagents may cause some environmental problems (Chen, Li, & Huang, 2020). The advantage of enzymatic hydrolysis is that the reaction conditions are milder than chemical hydrolysis, and the products are relatively controllable and predictable which due to enzymes usually cleave specific peptide bonds (M. Chen, Li, Li, & Huang, 2020), but the enzymatic hydrolysis is less effective in hydrolyzing highly cross-linked collagen (Hong et al., 2019). Some re-pretreatment procedures, e.g., the use of pepsin (Hong et al., 2017), formic acid (Hong, Roy, Chalamaiah, Bruce, & Wu, 2018), and amylase (Hong, Fan, Roy, & Wu, 2021), could improve the efficiency of enzymatically hydrolyzing collagen. Hong et al. (2019) concluded that enzymatic hydrolysis was the preferred method for the preparation of collagen peptides after reviewing the procedures and influencing factors for the preparation. The collagen hydrolysates generated using different enzymatic hydrolysis conditions have different biological activities (Offengenden, Chakrabarti, & Wu, 2018). And the hydrolysis mixtures are separated *in vitro* and screened for the most active peptides which are then analyzed using mass spectrometry to identify the amino acid sequence (Liang et al., 2022; Y.; Song, Fu, et al., 2021). Synthetic peptides with the same sequence can be prepared and used to verify the biological efficacy of the specific peptides (S. Cao, Wang, Hao, et al., 2020). Collagen peptides are usually inactive within the sequences of their parent proteins and, after they are released show biological activities such as antioxidant activity (Y. Song, Fu, et al., 2021), angiotensin-I converting enzyme (ACE-I) inhibitory activity (Fu et al., 2016), dipeptidyl peptidase-IV (DPP-IV) inhibitory activity (Jin, Teng, Shang, Wang, & Liu, 2020), and antifreeze activity (Cao et al., 2016).

Collagen peptides consist of 2–20 amino acid residues, and are rich in Gly, Pro, Ala, Hyp, and Glu residues (Li, Jia, & Yao, 2009). The hydrophilic amino acids in the collagen peptides of tilapia skin exceeded 58% of the total amino acid residues (Hu, Yang, Zhou, Li, & Hong, 2017). The specificity of protein enzyme can result in specific amino acids at the restriction enzyme sites of the collagen peptides. For example, collagen peptides isolated from the papain hydrolysates of skin of hen, bovine, porcine, and tilapia all contain Lys, Arg or Gly residues at the N-terminal (Hong et al., 2021). Collagen peptides are rich in repeat amino acid

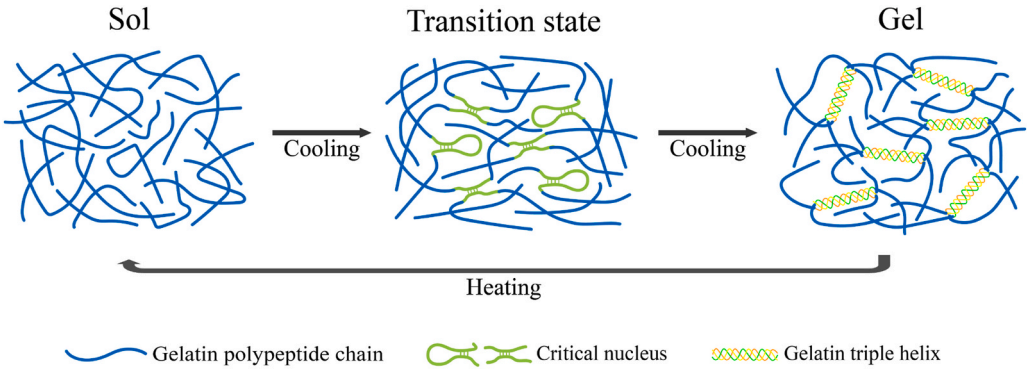

Fig. 3. The gel formation process of gelatin. The transition from coil to triple helix could convert gelatin from sol to gel, which depends on the temperature.

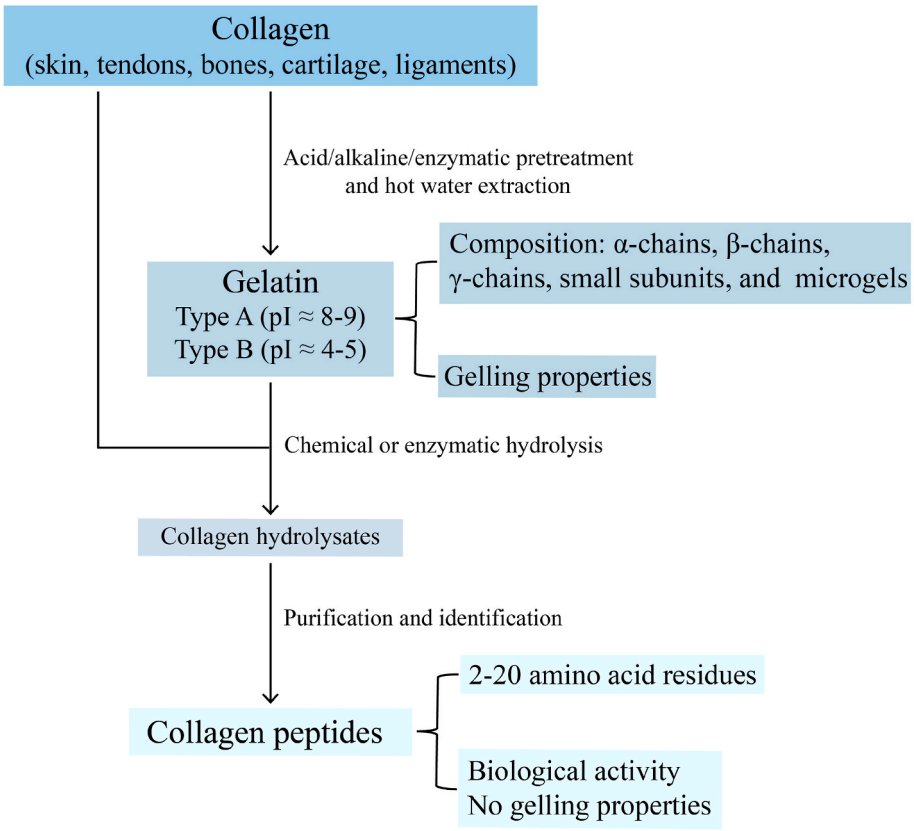

Fig. 4. Scheme for the production of gelatin and collagen peptides.

sequences of Gly-X-Y. For example, AGER, GIAGER, GPAGPAGPR, GVVGPEGAR, and GFSGLDGAK with good antioxidant activities isolated from cowhide collagen hydrolysates (Xie et al., 2021). However, the collagen peptides (FDAEYY and VGFDAEY) identified from chicken skin hydrolysates are not the case, and they may be generated from the non-helical telopeptide regions of collagen (Hong et al., 2017). The secondary structure of collagen peptide (GLPGPLGPAGPK) was mainly composed by β-turn and β-sheet (Ennaas et al., 2016). Moreover, Lin et al. (2021) found that the secondary structure of tilapia skin collagen peptides was mainly random coil and changed to β-sheet after chelating with iron ion. By studying the structure-activity relationship of bioactive collagen peptides, targeted enzymatic release of new collagen peptides with specific bioactivities can be realized (O'Keeffe, Norris, Alashi, Aluko, & FitzGerald, 2017).

3. Properties of collagen and its derivatives

The unique properties of collagen and its derivatives are closely associated with their structures, such as self-assembly, gelling and functional properties, and biological activities. In this section, recent researches concerning the properties of collagen and its derivatives will be reviewed.

3.1. Self-assembly of collagen

The ability to self-assemble is an inherent property of collagen. Type I collagen self-assembles into microfibrils *in vivo* and further results in fibrils, which could further hierarchically assemble into larger fiber bundles that are organized differently in different tissues and organs (Jiang et al., 2016). With physiologically analogous temperature and pH, collagen molecules containing the intact triple-helical domain can also spontaneously and orderly assemble into fibrils with the characteristic D-periodicity *in vitro* (C. Xu, Liu, Goff, & Zhong, 2020). The structure of the fibrils formed *in vitro* is similar to those assembled *in vivo*. By changing the environmental conditions, collagen can self-assemble into various products such as fibrils, gels, and sponges (Yan, Li, Zhao, & Qin, 2012), and the physical and biological properties of these self-assembled aggregates are predominantly attributed to their distinctive multi-hierarchical organization (S. Zhu, Yu, et al., 2021).

The self-assembly process of collagen *in vitro* follows a nucleation-growth mechanism, i.e., the cores are formed by the gathering of a limited number of collagen molecules, which then grow into mature fibrils in length and diameter (Zhu et al., 2018). Yan et al. (2012) proposed that the self-assembly of collagen includes a two-phase kinetic process, namely, (1) nuclear center formation, and (2) nuclear growth. The typical results of turbidity experiments showed that collagen self-assembly is a process with a lag stage (where monomer molecules aggregate to form the cores), growth stage (where cores growth in length and diameter to form the fibrils), and linear plateau phase (where the growth of fibrils reaches saturation) (Gunasekaran et al., 2020). Gisbert et al. (2021) visually recognize the initial stage of collagen self-assembly using a high-speed bimodal atomic force microscope (AFM) and identified four stages: (1) the nucleation and growth of collagen precursors, (2) the formation of tropocollagen molecules, (3) the assembly of tropocollagen into microfibers, and (4) the arrangement of microfibers to give microribbons.

Many factors may affect the self-assembly process of collagen (Table 1). From the collagen molecule itself, the source (He, Lan, Wang, Ahmed, & Liu, 2019), extraction method (Yan, Qin, & Li, 2015; Zhang et al., 2016), and concentration (Yan et al., 2012) all have a significant impact on the molecular self-assembly process. External factors include temperature (S. Zhu, Yu, et al., 2021), pH (Li, Asadi, Monroe, & Douglas, 2009), ionic conditions (Tian et al., 2021), amino acid composition (Liu, Dan, & Dan, 2017), molecular chirality (W. Zhu, Li, et al., 2021), sulfonated chitosan (Ran, Su, Ma, Wang, & Li, 2021), phytic acid (Tu et al., 2018), and ultrasonic treatment (Jiang et al., 2016). These factors may

Table 1
Factors affecting collagen self-assembly.

Factors	Results	Reference
Collagen source	The nucleation speed of grass carp scale derived collagen was faster than that of both tilapia skin and bovine dermal derived collagens.	He et al. (2019)
Extraction method	In the range of 4–37 °C, a lower extraction temperature was beneficial to maintain the natural structure of collagen and improve its self-assembly ability.	Yan et al. (2015)
	Enzymatic extraction of collagen led to the loss of non-helical telopeptides, which could inhibit fibrillogenesis.	Zhang et al. (2016)
Concentration	In the range of 0.01–2.0 mg/ml, a higher concentration helped to form fibrils with larger diameters.	Yan et al. (2012)
Temperature	In the range of 20–37 °C, a higher temperature could accelerate the collagen self-assembly process.	S. Zhu, Yu, et al. (2021)
pH	At low pH (≤6.6), fibrils of different sizes were formed and with the increase of pH (6.9–9.2), the fibrils were more uniform.	Y. Li, Jia, and Yao (2009)
Ionic strength	In the range of 65–160 mM, a higher concentration of NaCl could increase the lag time in the collagen fibril formation and decreased the fibril forming degree.	Tian et al. (2021)
Amino acid composition	Lysine increased the size or number of self-assembled fibers, and glutamic acid limited collagen self-assembling to a higher-order structure.	Liu et al. (2017)
Molecular chirality	The self-assembly rate in the presence of D-glutamic acid was faster than that of L-glutamic acid, whereas L-glutamic acid treatment led to a larger diameter of the resulting fibrils.	W. Zhu, Yu, et al. (2021)
Sulfonated chitosan	The addition of sulfonated chitosan could promote the lateral aggregation of fibrils resulting in larger fibrils, but in the range of 10–50%, a higher addition concentration reduced the self-assembly rate.	Ran et al. (2021)
Phytic acid	The addition of phytic acid could improve nucleation rate and degree of self-assembly, but reduced diameter of resulting fibrils.	Tu et al. (2018)
Ultrasonic treatment	Ultrasonic treatment could lead to a higher collagen fibrillogenic rate, smaller fibril diameters, and larger network pore sizes.	Jiang et al. (2016)

lead to differences in the kinetics of self-assembly, and the structure and property of self-assembled aggregates by adjusting the driving forces, such as hydrogen bonding, hydrophobic interactions, or electrostatic interactions (Y. Li, Asadi, et al., 2009). For example, the increase of temperature (20–37 °C) leads to the transformation of the secondary structure of collagen from highly hydrated PPII structure to ordered β-sheet, which enhances the hydrophobic effects and promotes the collagen self-assembly process (S. Zhu, Yu, et al., 2021). And the self-assembly behavior of collagen molecules will be more easily initiated when the pH is closer to the isoelectric point, as the net charge of the protein is decreased and the reduced electrostatic repulsion leads to a faster interaction between collagen molecules (Zhu et al., 2020).

3.2. Gel formation of collagen and gelatin

3.2.1. Collagen gels

The gel formation of collagen refers to a continuous process, including self-assembly of collagen, fibril formation, and fibril intertwining *in vitro*, which may be initiated by changes in ionic conditions, pH, or temperature (Djabourov, Lechaire, & Gaill, 1993). The three-dimensional structure of a collagen gel is together by an elastic network made of collagen fibrils (Yan et al., 2020). The collagen fibrils that make up the collagen gel network are usually ~100 nm in diameter (Nomura, Toki, Ishii, & Shirai, 2000) and have similar D-periodicity structures to natural collagen fibrils (Yan et al., 2020). The initiating conditions for the collagen sol-gel transition have been used to control the gel formation of collagen. Tian et al. (2021) found that the fibril network structure of collagen gels became denser with the increase of NaCl concentration in a simulated body fluid. Due to the chloride ion neutralize the surface charge of collagen molecules, thus reducing inter-molecular repulsion which in turn promotes the formation of heterogeneous and tightly packed collagen fibril aggregates. Moreover, chloride anions could induce the formation of collagen fibrils with D-periodicity structures (Zhu et al., 2018). Shi et al. (2020) studied the effect of pH on the gel formation of acid-soluble collagen (pI = 5.27) and found that the diameter and number of fibrils of collagen gel increased with the increase of pH in the range of 5.0–8.0. The collagen gel network showed smaller fibril diameters and pore spaces with the increase of ambient temperature from 4 to 37 °C (Raub et al., 2007). C. Xu et al. (2020) recently developed a collagen gel induced using ultraviolet radiation at a low temperature. They found those collagen molecules were degraded and cross-linked in that gel formation process, which led to the collagen fibrils having more "branches" and promoting the intertwining of fibrils.

Generally, the size and number of microfibrils formed during the nucleation phase affect the structure of the final self-assembled collagen fibrils, resulting in the difference in the structure of the collagen gel network, as are the density and size of the fibers, and the uniformity of the distribution of gel pores. For example, Jiang et al. (2016) found that ultrasonic treatment can reduce the diameter and diameter uniformity of fibrils by increasing the number and homogeneity of microfibers formed during nucleation, which leads to more heterogeneous pore structures with larger pore sizes of collagen gels.

3.2.2. Gelatin gels

Gelatin can form gels by a conformational transformation from coil to helix at low temperature, and the structure of these helices is similar to that of the collagen triple helix. The final helix configuration, single-looped helix or non-looped helix, is contingent on the concentration of gelatin and the annealing temperature (Guo et al., 2003). When the concentration is >1%, the gelatin will undergo the process of gel formation at a temperature lower than the sol-gel transition temperature (Avallone et al., 2021). The gel formation temperature of cold-water fish gelatin (~4–12 °C) is lower than that of warm-water fish gelatin (~18–19 °C), both of which are lower than those of mammalian gelatin and poultry gelatin (~30 °C) (Gómez-Guillén et al., 2011). The difference in gel formation temperature among the different kinds of gelatin mentioned above may be due to the differences in amino acid content (Abedinia et al., 2020). The gel formation mechanism of gelatin is related to the coil to collagen-like triple helix conformational transition and the most direct method to monitor such a process *in situ* is to measure the optical rotation (Joly-Duhamel, Hellio, & Djabourov, 2002). The specific optical rotation obtained by normalization of the optical rotation value can be directly converted into the amount of helices in the gelatin chains (Djabourov, Leblond, & Papon, 1988). For example, Qiao et al. (2021) used a polarimeter to study the change of triple-helix content with time during gel formation of gelatin solutions in the presence of different Hofmeister salts, in which kosmotropic ions could promote gel formation of gelatin solution, while chaotropic ions hindered this process. Normand, Muller, Ravey, and Parker (2000) found in a range of temperature, molecular weight, and concentrations that the gel formation kinetics of gelatin had four common rheological stages: (1) the gelatin solution is in the liquid state (loss modulus G'' > elastic modulus G'), (2) a gel network is established and strengthened by the formation of new cross-links (G' and G'' increase rapidly), (3) the gel network continues to be strengthened by the expansion of existing cross-links (G' slowly increases, G'' remains constant), and (4) due to the fusion of growing cross-links, the number of junction zones decreases and the elasticity of the gel increases significantly (the rate of G' increase

is faster than that of the third stage).

Gel formation time is defined as the corresponding time of transition from sol to gel, which can be determined by linear oscillatory time sweep tests and corresponds to the cross-over time of G′ and G′′ (Ross-Murphy, 1991). Kinetic analysis showed that the gel formation time of gelatin depended on gelatin concentration and temperature. Avallone et al. (2021) modified the Ross-Murphy equation by confirming that the critical q exponent in the temperature-dependent model proposed by Ross-Murphy (1991) is only related to the gelatin concentration. They obtained an empirical model which can simultaneously evaluate the influence on gel formation of both concentration and temperature. However, the empirical model has yet to be investigated with varying concentrations and sources of gelatin.

In gelatin gel-formation process, the polypeptide chains connect with each other through hydrogen bonds and maybe other interactions to form a macroscopic gel network. Salem et al. (2020) studied the effects of different pretreatment methods on the microstructure of gelatin gel from dogfish skin using the scanning electron microscope (SEM). The microstructure of all gelatin gels was sponge or coral-like. And the gelatin concentration and pH had a strong influence on the gel structure (Pang, Deeth, Sopade, Sharma, & Bansal, 2014), where the microstructure of the gel with higher gelatin concentration or at higher pH was relatively denser and no clear gelatin strands could be seen.

3.3. Mechanical properties of collagen and gelatin gels

3.3.1. Mechanical properties of collagen gels

Collagen gels are entangled networks consisting of self-assembled fibrils, which have mechanical strength and viscoelasticity (Mori, Shimizu, & Hara, 2012). The mechanical properties on the macro scale are ascribed to its inherent hierarchical structure from the nano to the macro level. Latinovic, Hough, and Daniel Ou-Yang (2010) investigated the mechanical properties and structural changes of a collagen solution transforming to a gel, which showed that the spatial changes in the viscoelastic properties of the collagen gels were closely related to the structural heterogeneity. The gels formed by collagen from different species showed different mechanical properties. Bao et al. (2018) found that higher amounts of Hyp and Cys can cause more cross-linking and led to a more homogeneous structure, e.g., tilapia collagen gels had higher mechanical strength and elasticity than porcine collagen gels. The preparation approaches of collagen are highly empirical. And there are differences in the purity, composition, and structure of produced collagen, which can lead to significant differences in the mechanical properties of the corresponding collagen gels. For example, the gels formed by collagen with telopeptide had higher storage moduli than that formed by non-telopeptide collagen, which may be due to the telopeptide increases the affinity between collagen molecules, resulting in a longer-range intermolecular structure (Slyker, Diamantides, Kim, & Bonassar, 2021).

Because a high concentration of collagen is not able to gel, the proportion of collagen in a collagen gel is relatively low (0.2–0.5% (w/v)) which leads to weak mechanical properties of the gel. Generally, native collagen gels are usually not strong enough to meet the needs of various applications (Andriakopoulou, Zadpoor, Grant, & Riches, 2018). For example, sufficient strength and elasticity are required for the gel used as a tissue engineering scaffold and collagen gels have not been strong enough (Jiang et al., 2016). Common methods to improve the mechanical properties of collagen gels include physical, chemical, and enzymatic cross-linking, have been reviewed in detail by Adamiak and Sionkowska (2020). However, many of these methods (the use of glutaraldehyde, carbodiimide, formaldehyde, and other chemical cross-linking agents) are potentially toxic (X. Liu, Zheng, et al., 2019). Recently, Andriakopoulou et al. (2018) proposed a self-compression technique to increase the density of collagen fibril and thus increase the mechanical properties of collagen gels (the compression modulus was increased by ~3 times).

3.3.2. Mechanical properties of gelatin gels

Studies have shown that the mechanical property of gelatin gels have a strong correlation with the amounts of α-chains in gelatin that a large ratio of polypeptides/peptides with molecular weights higher/lower than the a-chains would diminish gel strength (Liu, Li, & Guo, 2008; Normand et al., 2000). Also, the gel strength of gelatin from aquatic animals is generally lower than that of gelatin from terrestrial animals, which seems to suggest the effect of the amount of different amino acid on gel strength (Karim & Bhat, 2009). Gelatins with different gel strengths are utilized in different applications. For example, type B gelatin with a gel strength of 125–250 g is usually used in confectionery products, and type A gelatin with low gel strength (70–90 g) can be used for the fining of wine and juice (Mariod & Fadul, 2013).

Viscoelasticity is another important mechanical property of gelatin gels, which is usually characterized using a rheometer (Ge, Wu, Woshnak, & Mitmesser, 2021). The small amplitude oscillatory shear (SAOS) tests have become the common approach for exploring the linear viscoelastic properties of gelatin gels, as viscosity and elasticity can be evaluated without disrupting the gel structure (Burey, Bhandari, Rutgers, Halley, & Torley, 2009; Hyun et al., 2011). However, foods containing gelatin often undergo large and fast deformations during manufacturing and mastication (Netter, Goudoulas, & Germann, 2020; Pu et al., 2021). Therefore, the nonlinear viscoelastic regions obtained using large amplitude oscillatory shear (LAOS) tests could provide a more comprehensive understanding of the rheological behaviors of gelatin gels with practical application conditions. Ge et al. (2021) investigated the effect of gummy formulation on the rheological behaviors of gelatin gummy networks in both linear and nonlinear viscoelastic regions using SAOS and LAOS tests, respectively. Sun, Huang, Yang, Liu, and Tong (2015) reported the strain-stiffening behavior of gelatin gel with LAOS deformations.

3.4. Functional properties of collagen and gelatin

Collagen and gelatin have properties related to their surface behaviors, such as emulsifying, foaming and film-forming properties, that may be due to charged groups, and hydrophilic and/or hydrophobic groups of the protein side chains (Gómez-Guillén et al., 2011). These functional properties of collagen and gelatin are strongly influenced by the source and the extraction process (Ahmad et al., 2017).

3.4.1. Emulsion formation and stabilization

An emulsion can be defined as a system consisting of two immiscible liquids, i.e., one of which (the dispersed phase) is dispersed in another (the continuous phase) in the form of droplets (Zhang, Xu, et al., 2020). Emulsions exist in many food systems (such as mayonnaise, ice cream and milk). And emulsion-based foods are a mixture of oil and water and show a high tendency to separate, which can be slowed down using emulsifiers (K. K. Kumar, Singh, et al., 2019). Emulsifiers are surface-active substances that have an important in the production of emulsions by facilitating emulsion formation and improving emulsion stability (Liu, Li, Diao, Kong, & Liu, 2018). As an insoluble protein, collagen is generally considered to be an ineffective emulsifier (Gómez-Guillén et al., 2011). However, processing treatments can make insoluble collagen into soluble forms, such as acid-/pepsin-soluble collagen or gelatin, which do show its emulsifying properties (Akram & Zhang, 2020; Aksun Tümerkan, Cansu, Boran, Regenstein, & Özoğul, 2019).

Soluble collagen or gelatin contained sufficient hydrophilic and hydrophobic amino acid residues, can absorb to oil-water interfaces and promote emulsion formation by lowering interfacial tension during emulsification (Tan, Karim, Uthumporn, & Ghazali, 2020). They also improve emulsion stability by generating electrostatic repulsion between droplets and/or forming interfacial membranes around the droplets to prevent the aggregation of droplets (Surh, Decker, & McClements, 2006). And the rupture resistance of interfacial

membranes can be extra improved by gel formation of gelatin (Gómez-Guillén et al., 2011). Moreover, gelatin can improve emulsion stability by increasing the viscosity of continuous phase (Tan et al., 2020). Soluble collagen or gelatin from different species have different emulsion formation and stabilization potential, which can be measured by the emulsifying activity index (EAI) and emulsifying stability index (ESI) (Zhang, Sun, et al., 2020). For example, the emulsifying ability of gelatin from fish is usually lower than that from mammals (Gómez-Guillén et al., 2011). The EAI and ESI of type II collagen from chicken sternal cartilage are higher than that of collagen from soft-shelled turtle calipash at pH 7, while the results at pH 4 or 10 are opposite (Akram & Zhang, 2020; Zou et al., 2017). However, the differences in the emulsifying properties of soluble collagen or gelatin from different species sources may be unable to compare due to different preparation processes. Aksun Tümerkan et al. (2019) measured the EAI and ESI of gelatin extracted from tuna (defatted), frog (non-defatted), and chicken skins (defatted), and the results suggested that frog skin gelatin showed better emulsifying. However, Sae-leaw, Benjakul, O'Brien, and Kishimura (2016) proposed that the degreasing treatment can directly affect the emulsifying properties of the gelatin.

3.4.2. Foam formation and stabilization

Foam can be defined as a two-phase system composed of air bubbles separated by liquid regions (Phawaphuthanon, Yu, Ngamnikom, Shin, & Chung, 2019). Soluble collagen and gelatin can quickly migrate and adsorb to the air-water interface, by diffusion and resetting at the interface to show good foaming properties (Jin et al., 2019). The basic functions of soluble collagen and gelatin in foam formation are to reduce interfacial tension (Gómez-Guillén et al., 2011), and to form protective films around air bubbles (Jin et al., 2019). Moreover, gelatin can form a three-dimensional network by gelation to increase the continuous phase to stabilize the foam (Mardani et al., 2019). Foaming capacity of acid- and pepsin-soluble collagens were much lower when pH was adjusted to the isoelectric point, as that pH made "soluble" collagen insoluble, which led to the reduction of interaction between protein and water needed for foaming (J. Chen, Li, et al., 2019). The gelatin molecules with lower molecular weights can more easily access the air-liquid interface, resulting in increased foaming capacity (Casanova et al., 2020). Foaming stability is determined by the physical properties of the film once formed. For example, catfish gelatin had better foaming stability than calf bone gelatin, as it had more high molecular weight components and could form more stable protein films (Duan, Zhang, Liu, Cui, & Regenstein, 2018). Moreover, foaming capacity and stability were both positively correlated with gelatin concentration, which may be because that higher protein concentration increased the viscosity of gelatin and facilitated a multilayer cohesive protein film at the interface (Abdelmalek et al., 2016; Jin et al., 2019).

3.4.3. Film formation

Edible and biodegradable casings, films, and coatings prepared using collagen or gelatin have been developed for their economic benefits and environmental protection (Antoniewski & Barringer, 2010). Collagen casings/films are usually made by extrusion or casting of colloidal aqueous dispersions containing pretreated collagen fibers (Xu et al., 2020). The effects of various pretreatments on the fiber structure and the properties of final casings/films are normally measured. Xu et al. (2020) found that the films made by casting collagen fiber dispersions pretreated at high temperatures (>39 °C) have lower tensile properties and higher barrier properties. The effect of acid swelling (pH = 1.5–4.0) on the properties of the final collagen films showed that the swelling ratio of collagen fibers was the highest at pH = 3.0, which gave the films good mechanical and thermodynamic properties (Xu et al., 2020). Ma et al. (2020) prepared micro/nano collagen fibers using high-pressure homogenization to study the impact of fiber size on the properties of the final films. With decreased fiber size, the mechanical and water repelling properties of the collagen films were increased. Meanwhile, the fiber size hardly affected the thermal stability of the film.

Gelatin has good film-forming properties and could be applied to form a film for covering or wrapping, or form a coating on the surface of products (Abedinia, Ariffin, Huda, & Mohammadi Nafchi, 2018; Cardoso et al., 2019; Jridi et al., 2020). The content of Hyp residues and the molecular weight distribution are factors determining the mechanical and barrier properties of gelatin-based films/coatings (Gómez-Guillén et al., 2011). For example, the water vapor permeability (WVP) of gelatin-based films from duck feet were lower than those from bovine skin because of the difference in the Hyp whose hydroxyl can usually form a hydrogen bond with water (Abedinia et al., 2018; Abedinia et al., 2020). Moreover, gelatin with more low molecular weight fragments, caused by degradation in hot water (Nagarajan, Benjakul, Prodpran, & Songtipya, 2012) or drying for the formation of films (Liu et al., 2016) tends to form weaker and more deformable films.

3.5. Biological activities of collagen peptides

Collagen peptides with different molecule weights and sequences, which are derived from enzymatic hydrolysate of collagen/gelatin, have various biological activities, such as antioxidant, ACE-I inhibitory, DPP-IV inhibitory, and antifreezing activities.

3.5.1. Antioxidant activity

Free radicals can oxidize lipids, proteins, DNA, and enzymes in the human body, resulting in destructive and lethal cellular effects (Ailen & Oscar, 2013). In the food industry, food deterioration may often be related to the lipid oxidation and the formation of excessive secondary lipid peroxidation products (Pal & Suresh, 2016). Antioxidants play important roles in both food systems and in the human body to reduce oxidative stress. Collagen peptides from various sources, such as bovine (Y. Song, Fu, et al., 2021), yak (Wang et al., 2022) and skipjack tuna (Ding, Du, Zhang, Zaman, & Huang, 2019; Yang, Zhao, Qiu, Chi, & Wang, 2019) bone, fish skin (e.g., tilapia (Ren, Wu, Chi, Deng, & He, 2020), cod (Ngo et al., 2011), salmon (Wu et al., 2018), and mackerel (Zhang, Zhao, Wang, Chi, & Wang, 2019)), and fish scale (e.g., tilapia (Shiao et al., 2021), tuna (Qiu et al., 2019), and redlip (Wang, Zhao, Zhao, Chi, & Wang, 2020) and croceine (Wang et al., 2013) croaker), have all shown antioxidant activities, shown in Table 2. Two or more methods are needed for evaluating the antioxidant activities of collagen peptides, due to the differences in the mechanism of interaction between reactive molecules and peptides. For example, the results of DPPH radical scavenging assay showed that the antioxidant activities of peptides from pepsin-soluble collagen was higher than that from bromelain-soluble collagen, but there was no difference in the results obtained by reducing power test (Devita, Nurilmala, Lioe, & Suhartono, 2021). The antioxidant activities of collagen peptides generally involve scavenging free radicals (Y. Song, Fu, et al., 2021), inhibiting lipid peroxidation (Yang et al., 2019), and/or chelating iron or copper ions (Nakchum & Kim, 2016; Sarbon, Badii, & Howell, 2018). The antioxidant activity of protein hydrolysates cannot be attributed to a single antioxidant mechanism (Ailen & Oscar, 2013), which means that the total antioxidation of collagen peptides is likely to be the synergistic interactions involving the above. Sarbon et al. (2018) evaluated the antioxidant mechanism of collagen peptides from chicken skin gelatin and found that they showed free radicals scavenging and metal chelating properties, and could inhibit the lipid oxidation by reducing peroxide formation. And the peptides with a molecular weight of 200–800 Da showed better antioxidant activity than commercial antioxidants (BHT, Trolox, and ascorbic acid) at the same concentration (10 mg/mL).

As shown in Table 2, structure-activity relationships of collagen peptides with antioxidant activity have also been studied. For example, all of the five antioxidant peptides identified by Y. Song, Fu, et al. (2021) from bovine bone collagen showed the typical collagen Gly-X-Y repeat sequence. The antioxidant collagen peptides purified from cod skin gelatin hydrolysates were high in Gly and Pro (Ngo et al., 2011). The

Table 2
Collagen peptides with antioxidant activity.

Source	Enzyme used	Sequence[a]	ABTS radical scavenging activity (%)/IC_{50}/EC_{50}	DPPH radical scavenging activity (%)/IC_{50}/EC_{50}	Hydroxyl radical scavenging activity (%)/IC_{50}/EC_{50}	Superoxide anion radical scavenging activity (%)/IC_{50}/EC_{50}	Reference
Bovine bone	Recombinant collagenase from *Bacillus cereus*	GPIGPVGAR	47.16 ± 1.36 at 5 mg/mL	29.69 ± 1.25 at 5 mg/mL			Y. Song, Fu, et al. (2021)
		GPIGSRGPS	12.28 ± 1.03 at 5 mg/mL	17.11 ± 0.78 at 5 mg/mL			
		GPQGIAGQR	15.06 ± 0.43 at 5 mg/mL	15.59 ± 0.74 at 5 mg/mL			
		GPVGAAGPS	16.16 ± 1.95 at 5 mg/mL	15.20 ± 1.12 at 5 mg/mL			
		GQAGVMG	41.29 ± 0.84 at 5 mg/mL	47.51 ± 3.02 at 5 mg/mL			
Yak bone		GASGPMGPR	35.47 ± 1.81 at 5 mg/mL	32.34 ± 1.21 at 5 mg/mL	11.98 ± 0.55 at 5 mg/mL	43.95 ± 0.45 at 5 mg/mL	Wang et al. (2022)
		GLPGPM	25.05 ± 0.46 at 5 mg/mL	23.98 ± 1.11 at 5 mg/mL	14.74 ± 0.26 at 5 mg/mL	58.33 ± 0.72 at 5 mg/mL	
Skipjack tuna (*Katsuwonus pelamis*) bone	Pepsin-trypsin system	GPDGR	EC_{50} = 1.07 ± 0.07 mg/mL	EC_{50} = 2.49 ± 0.12 mg/mL	EC_{50} = 1.21 ± 0.08 mg/mL	EC_{50} = 1.48 ± 0.12 mg/mL	Yang et al. (2019)
		GADIVA	EC_{50} = 0.41 ± 0.03 mg/mL	EC_{50} = 0.57 ± 0.03 mg/mL	EC_{50} = 0.25 ± 0.02 mg/mL	EC_{50} = 0.52 ± 0.03 mg/mL	
		GAPGPEMV	EC_{50} = 0.85 ± 0.06 mg/mL	EC_{50} = 1.93 ± 0.11 mg/mL	EC_{50} = 0.64 ± 0.05 mg/mL	EC_{50} = 0.68 ± 0.05 mg/mL	
		AGPM	EC_{50} = 1.68 ± 0.11 mg/mL	EC_{50} = 1.66 ± 0.09 mg/mL	EC_{50} = 0.49 ± 0.03 mg/mL	EC_{50} = 1.22 ± 0.08 mg/mL	
		GAEGFIF	EC_{50} = 0.21 ± 0.03 mg/mL	EC_{50} = 0.30 ± 0.04 mg/mL	EC_{50} = 0.32 ± 0.03 mg/mL	EC_{50} = 0.48 ± 0.03 mg/mL	
Skipjack tuna (*Katsuwonus pelamis*) bone	Trypsin and chymotrypsin	SSGPPVPGPMGPMGPR	IC_{50} = 9.489 mM	IC_{50} = 3.149 mM		IC_{50} = 3.803 mM	Ding et al. (2019)
Tilapia (*Oreochromis nilotica* L.) skin	Alcalase	$GP_{(OH)}$		IC_{50} = 2.02 ± 0.08 g/mL			Ren, Wu, et al. (2020)
		AD		IC_{50} = 1.96 ± 0.05 g/mL			
		$DP_{(OH)}G$		IC_{50} = 10.23 ± 0.41 g/mL			
		APPF		IC_{50} = 6.62 ± 0.25 g/mL			
		KPFGSGAT		IC_{50} = 0.76 ± 0.03 g/mL			
Pacific cod (*Gadus macrocephalus*) skin	Papain	TCSP					Ngo et al. (2011)
		TGGGNV					
Salmon skin	Extracellular protease	PMRGGGYHY					Wu et al. (2018)
Spanish mackerel skin	Pepsin	GPY	EC_{50} = 2.12 ± 0.16 mg/mL	EC_{50} = 1.00 ± 0.09 mg/mL	EC_{50} = 3.22 ± 0.21 mg/mL	EC_{50} = 3.98 ± 0.26 mg/mL	Zhang et al. (2019)
		GPTGE	EC_{50} = 4.51 ± 0.24 mg/mL	EC_{50} = 1.46 ± 0.12 mg/mL	EC_{50} = 2.13 ± 0.15 mg/mL	EC_{50} = 2.96 ± 0.19 mg/mL	
		PFGPD	EC_{50} = 0.86 ± 0.05 mg/mL	EC_{50} = 0.80 ± 0.09 mg/mL	EC_{50} = 0.81 ± 0.05 mg/mL	EC_{50} = 0.91 ± 0.08 mg/mL	
		GPTGAKG	EC_{50} = 3.27 ± 0.27 mg/mL	EC_{50} = 4.63 ± 0.21 mg/mL	EC_{50} = 2.27 ± 0.14 mg/mL	EC_{50} = 1.73 ± 0.11 mg/mL	
		PYGAKG	EC_{50} = 1.07 ± 0.10 mg/mL	EC_{50} = 3.02 ± 0.19 mg/mL	EC_{50} = 0.66 ± 0.08 mg/mL	EC_{50} = 0.80 ± 0.06 mg/mL	
		GATGPQG	EC_{50} = 3.86 ± 0.19 mg/mL	EC_{50} = 3.65 ± 0.30 mg/mL	EC_{50} = 2.11 ± 0.16 mg/mL	EC_{50} = 7.21 ± 0.27 mg/mL	
		GPFGPM	EC_{50} = 8.54 ± 0.43 mg/mL	EC_{50} = 7.93 ± 0.52 mg/mL	EC_{50} = 5.24 ± 0.32 mg/mL	EC_{50} = 9.83 ± 0.35 mg/mL	
		YGPM	EC_{50} = 0.82 ± 0.04 mg/mL	EC_{50} = 0.72 ± 0.06 mg/mL	EC_{50} = 0.88 ± 0.09 mg/mL	EC_{50} = 0.73 ± 0.06 mg/mL	
Tilapia (*Oreochromis* sp.) scale	Pepsin and pancreatin	GYDEY					Shiao et al. (2021)
		EPGKSGEQGAPGEAGAP					
Skipjack tuna (*Katsuwonus pelamis*) scale	Alcalase	$HGPP_{(OH)}GE$	EC_{50} = 1.34 mg/mL		EC_{50} = 1.03 mg/mL	EC_{50} = 1.19 mg/mL	Qiu et al. (2019)
		DGPKGH	EC_{50} = 0.54 mg/mL		EC_{50} = 0.41 mg/mL	EC_{50} = 0.71 mg/mL	
		MLGPFGPS	EC_{50} = 0.67 mg/mL		EC_{50} = 0.74 mg/mL	EC_{50} = 1.59 mg/mL	
	Neutrase	DGPEGR					

(*continued on next page*)

Table 2 (*continued*)

Source	Enzyme used	Sequence[a]	ABTS radical scavenging activity (%)/IC_{50}/EC_{50}	DPPH radical scavenging activity (%)/IC_{50}/EC_{50}	Hydroxyl radical scavenging activity (%)/IC_{50}/EC_{50}	Superoxide anion radical scavenging activity (%)/IC_{50}/EC_{50}	Reference
Redlip croaker (*Pseudosciaena polyactis*) scale				EC_{50} = 4.24 ± 0.18 mg/mL	EC_{50} = 1.65 ± 0.11 mg/mL	EC_{50} = 7.98 ± 0.34 mg/mL	W.-Y. Wang, Zhao, et al. (2020)
		GPEGPMGLE		EC_{50} = 0.59 ± 0.06 mg/mL	EC_{50} = 0.45 ± 0.05 mg/mL	EC_{50} = 0.62 ± 0.07 mg/mL	
			EGPFGPEG		EC_{50} = 0.37 ± 0.05 mg/mL	EC_{50} = 0.33 ± 0.04 mg/mL	
			EC_{50} = 0.47 ± 0.05 mg/mL				
			YGPDGPTG		EC_{50} = 1.76 ± 0.12 mg/mL	EC_{50} = 1.95 ± 0.14 mg/mL	
			EC_{50} = 0.99 ± 0.10 mg/mL				
		GFIGPTE	EC_{50} = 0.45 ± 0.06 mg/mL	EC_{50} = 0.42 ± 0.05 mg/mL	EC_{50} = 0.74 ± 0.06 mg/mL		
		IGPLGA	EC_{50} = 4.47 ± 0.24 mg/mL	EC_{50} = 2.43 ± 0.13 mg/mL			
		EC_{50} = 2.96 ± 0.17 mg/mL					
Croceine croaker (*Pseudosciaena crocea*) scale	Pepsin and trypsin	GFRGTIGLVG	IC_{50} = 0.421 mg/mL	IC_{50} = 1.271 mg/mL	IC_{50} = 0.293 mg/mL	IC_{50} = 0.463 mg/mL	Wang et al. (2013)
		GPAGPAG	IC_{50} = 0.309 mg/mL	IC_{50} = 0.675 mg/mL	IC_{50} = 0.240 mg/mL	IC_{50} = 0.099 mg/mL	
		GFPSG	IC_{50} = 0.210 mg/mL	IC_{50} = 0.283 mg/mL	IC_{50} = 0.107 mg/mL	IC_{50} = 0.151 mg/mL	

ABTS: 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); DPPH: 1,1-diphenyl-2-picrylhydrazyl; IC_{50}: Half maximal inhibitory concentration; EC_{50}: Half maximal effective concentration.

[a] $P_{(OH)}$: hydroxyproline.

hydrophobic amino acid residues Ala, Ile, and Val in collagen peptides GADIVA and GAEGFIF could help the peptides contacted with target free radicals (Yang et al., 2019). Furthermore, when one Met residue in the peptide SSGPPVPGP**M**GPMGPR was replaced by Gly, the free radical scavenging ability of the new peptide (SSGPPVPGP**G**GPMGPR) decreased by ~31%, which suggested that the Met residue may provide an active site for scavenging DPPH radicals (Ding et al., 2019).

3.5.2. *ACE-I inhibitory activity*

Angiotensin I-converting enzyme (ACE-I) is a multifunctional zinc-containing enzyme and inhibiting its activity may help prevent and treat hypertension (S. Cao, Wang, Hao, et al., 2020). Synthetic ACE-I inhibitors used to treat hypertension, like captopril and temocapril, can cause adverse effects including coughing, skin rashes, and angioneurotic edema (Ngo et al., 2015). Alternatively, collagen peptides, which are biologically safer, have been found to show good ACE-I inhibitory activity (Fu et al., 2019; Ngo, Ryu, & Kim, 2014), and more information is shown in Table 3. The inhibition mechanism of the enzyme activity can be divided into competitive, non-competitive, or uncompetitive pattens and are generally shown using Lineweaver-Burk plot (Abdelhedi & Nasri, 2019). Fu et al. (2016) obtained Lineweaver-Burk plots for two collagen peptides (VGPV and GPRGF) and found that both plots showed that samples were non-competitive ACE-I inhibitors. J. Chen et al. (2020) suggested that the collagen peptide (LSGYGP) was a mixed non-competitive inhibitor.

The structures of collagen peptides determined their ACE-I inhibitory activity. The three amino acid residues at the C-terminal of collagen peptides had the most important in the specific binding to ACE-I (Fahmi et al., 2004), especially when these residues were hydrophobic amino acids like Pro, Trp, and Leu (Abdelhedi and Nasri, 2019). Collagen peptides with ACE-I inhibitory activity derived from thornback ray skin gelatin (Lassoued et al., 2015), squid skin collagen (Alemán, Gómez-Guillén, & Montero, 2013), Pacific cod skin gelatin (Himaya, Ngo, Ryu, & Kim, 2012), and tilapia skin gelatin (J. Chen et al., 2020)

Table 3
Collagen peptides with ACE-I inhibitory activity.

Source	Enzyme used	Sequence[a]	ACE-I inhibitory activity (IC_{50} (μM))	Reference
Bovine bone	Alcalase	$RGLP_{(OH)}GL$	1.44	S. Cao, Wang, Hao, et al. (2020)
		$RGMP_{(OH)}GF$	10.23	
Skate (*Okamejei kenojei*) skin	Alcalase and protease	LGPLGHQ	4.22	Ngo et al. (2015)
		MVGSAPGVL	3.09	
Bovine connective tissue	Alcalase	VGPV	405.12	Fu et al. (2016)
	Papain	GPRGF	200.91	
Tilapia (*Oreochromis niloticus*) skin	Properase E	LSGYGP	2.577	J. Chen et al. (2020)
Sea bream scales	Alkaline protease	GY	265	Fahmi et al. (2004)
		VY	16	
		GF	708	
		VIY	7.5	
Thornback ray (*R. clavata*) skin	Protease from *Bacillus subtilis*	APGAP	170	Lassoued et al. (2015)
	Protease from *Bacillus amyloliquefaciens*	GIPGAP	27.9	
Squid (*Dosidicus gigas*) skin	Pepsin-pancreatin	$DPVAPGGP_{(OH)}QP$	246 ± 36	Alemán et al. (2013)
		$GRGSVPAP_{(OH)}GP$	48 ± 2	
Pacific cod (*G. macrocephalus*) skin	Pepsin, trypsin and α-chymotrypsin	LLMLDNDLPP	35.7	Himaya et al. (2012)

IC_{50}: Half maximal inhibitory concentration.

[a] $P_{(OH)}$: hydroxyproline.

contained Pro at the C-terminal. Chen, Sun, Li, and Liu (2021) recently compared 270 types of collagen peptides released from tilapia skin collagen and concluded that the Pro residue at the penultimate position of the C-terminal of collagen peptides may contribute more to their ACE-I inhibitory activity than that at the third from the end.

3.5.3. *DPP-*Ⅳ *inhibitory activity*

Dipeptidyl peptidase-IV (DPP-IV) is a plasma membrane glycoprotein and one of the main functions of DPP-IV is breaking down incretins which can decrease blood glucose level by inhibiting glucagon production, stimulating insulin release, and decreasing gastric emptying (Ritian et al., 2021). Thus, elongating the half-life of incretins by inhibiting the activity of DPP-IV could be used for the treatment of type 2 mellitus (T2DM) (Deacon & Holst, 2006). Some peptides separated from dietary proteins hydrolysates have DPP-Ⅳ inhibitory activity (Acquah, Dzuvor, Tosh, & Agyei, 2020). Several collagen peptides with DPP-IV inhibitory activities have been identified and are shown in Table 4. Neves et al. (2017) separated four collagen peptides from salmon gelatin hydrolysates that have multifunctional bioactivities including inhibiting DPP-IV *in vitro*. Huang, Hung, Jao, Tung, and Hsu (2014) confirmed that collagen peptides have a hypoglycemic effect on diabetic rats by reducing the activity of DPP-IV in plasma. Jin et al. (2020) reported three collagen peptides separated from Atlantic salmon skin collagen hydrolysates with different DPP-IV inhibition patterns (LDKVFR: competitive inhibitor, VLATSGPG: non-competitive inhibitor, YYGYTGAFR: mixed-type).

The peptides with high DPP-IV inhibitory activity usually have 2–8 amino acid residues and have Pro or Ala at the second N-terminal residue (Huang et al., 2014). Collagen peptides sequenced in GPAE with the structural characteristics of preferred DPP-IV inhibitory peptides showed good DPP-IV inhibitory activity (IC_{50} = 49.6 μM) (Li-Chan, Hunag, Jao, Ho, & Hsu, 2012). However, six collagen peptides from halibut and tilapia skin gelatin hydrolysate were also found to show fine DPP-IV inhibitory activity and had Pro residues at the second site of N-terminal, but their sequences all exceeded 8 amino acid residues (T.-Y. Wang, Hsieh, et al., 2015). Moreover, two collagen peptides GPVA (Neves et al., 2017) and GPGA (Li-Chan et al., 2012) both identified from salmon gelatin hydrolysates and with the structural characteristics of the above preferred peptides showed significantly different DPP-IV inhibitory activities (IC_{50} = 264.74 and 41.9 μM, respectively). Therefore, the DPP-IV inhibitory activity of collagen peptides is not only related to the length of amino acids and the second amino acid of N-terminal, and the underlying mechanisms of activity-structure relation of collagen peptide with DPP-IV inhibitory activity need to be further investigated.

3.5.4. *Antifreeze activity*

The mechanical damage caused by the growth of ice crystals during freezing and frozen storage is an important factor for the quality loss of frozen food (Zhu, Zhou, & Sun, 2019). Antifreeze peptides have been shown to be incorporate with the ice and restrain its growth (Chen, Wu, Cai, & Wang, 2021). Some collagen-derived antifreeze peptides have been separated from the collagen/gelatin hydrolysates of pig skin (Cao et al., 2016; Wang, Chen, et al., 2015), carp skin (Damodaran & Wang, 2017), and chicken skin (Du & Betti, 2016). And the antifreezing mechanisms of these collagen peptides have been discussed. The collagen peptides could, on the one hand, influence the formation of ice crystals by non-colligative reduction of the freezing point (X. Chen, Wu, et al., 2021) and, on the other hand, significantly reduce the size of ice crystal aggregates formed during recrystallization (Cao et al., 2016). W. Wang, Hsieh, et al. (2015) found that collagen peptides showed good antifreeze activity by binding to the membrane phospholipids to protect the cell membranes.

The collagen peptides were reported to combine with ice crystals through electrostatic interactions and hydrogen bonding (Damodaran & Wang, 2017). Therefore, theoretically, the Pro, Hyp, and Ala residues in the collagen peptides might contribute to their antifreeze activities by creating a nonpolar environment to stabilize the hydrogen bonds between the peptides-ice crystal complex (X. Chen, Wu, et al., 2021). Damodaran and Wang (2017) suggested that collagen peptides from any source with molecular weights of 1000–2500 Da could inhibit the growth of ice crystals. This may be due to the collagen peptides within this molecular weight range dynamically changing their conformation to overcome the steric hindrances that may occur during binding to the ice nucleus surface (Damodaran, 2007; Damodaran & Wang, 2017). The difference in secondary structure may also explain the different antifreeze activity of collagen peptides. Du and Betti (2016) analyzed the secondary structures of collagen peptides from chicken skin collagen hydrolysates using far-UV circular dichroism and suggested that a lower level of unordered structures in the antifreeze peptides might have an important in their antifreeze activity.

3.5.5. *Other activities*

Collagen peptides have other bioactivities such as antibacterial, anti-aging, stimulating wound healing and cell proliferation, treating bone and joint diseases, and improving skin health (Ahmed, Verma, & Patel, 2020; Daneault, Prawitt, Fabien Soulé, Coxam, & Wittrant, 2017; Fu et al., 2019; Pal & Suresh, 2016; Zhao et al., 2021).

4. Applications of collagen and its derivatives in food industry

Collagen and its derivatives are edible and have various functional

Table 4
Collagen peptides with DPP-Ⅳ inhibitory activity.

Source	Enzyme used	Sequence	DPP-Ⅳ inhibitory activity (IC_{50} (μM))	Reference
Salmon (*Salmo salar*) skin	Pepsin	TKLPVAF	242.10 ± 3.40	Ritian et al. (2021)
		YLNF	146.90 ± 4.40	
Salmon trimmings	Alcalase and Corolase PP	PP	4343.48 ± 29.78	Neves et al. (2017)
		GF	1547.15 ± 34.15	
		GPVA	264.74 ± 1.59	
		GGPAGPAV	8139.11 ± 134.68	
Atlantic salmon (*Salmo salar*) skin	Trypsin	YYGYTGAFR	1102.8	Jin et al. (2020)
		LDKVFR	128.71	
		VLATSGPG	256.86	
Halibut skin	Flavourzyme	SPGSSGPQGFTG	101.6	T.-Y. Wang, Hsieh, et al. (2015)
		GPVGPAGNPGANGLN	81.3	
		PPGPTGPRGQPGNIGF	146.7	
Tilapia skin	Flavourzyme	IPGDPGPPGPPGP	65.4	
		LPGERGRPGAPGP	76.8	
		GPKGDRGLPGPPGRDGM	89.6	
Atlantic Salmon skin	Flavourzyme	GPAE	49.6	Li-Chan et al. (2012)
		GPGA	41.9	

IC_{50}: Half maximal inhibitory concentration.

properties and bioactivities (Gómez-Guillén et al., 2011). These properties endow collagen and its derivatives great potential in the applications of food additives, food packaging and preservation materials, and functional food ingredients.

4.1. Applications of collagen in food industry

4.1.1. Collagen used as food additives

Collagen can be used as food additives to improve food quality in food processing (Irastorza, Zarandona, Andonegi, Guerrero, & de la Caba, 2021). For example, the addition of collagen to frankfurters and hams as binders and extenders could improve the binding properties (purge and cooking losses) of products during cold storage and cooking (Prabhu, Doerscher, & Hull, 2004). Collagen could replace vegetable protein in the preparation of chicken hams, which could improve the texture properties, reduce the pressing and thawing loss of chicken hams, while maintaining good sensory characteristics (Prestes et al., 2013). The addition of pre-emulsion of wheat sprout and collagen to the chicken patties to replace pork back fat could not only help to reduce cooking loss, but also maintained the sensory properties of chicken patties in an appropriate substitution ratio (no more than 40%) (Kim et al., 2018). Collagen fibers are a good emulsifier in food industry, especially the acidic foods (Santana et al., 2011). Collagen can also function as for carriers for bioactive agents, for example, rosemary extract showed a better antioxidant activity in inhibiting lipid oxidation of sausages during storage after encapsulating in collagen carriers (Waszkowiak & Dolata, 2007).

4.1.2. Collagen used as food packaging and preservation materials

Collagen is a good film-forming material, which has the potential to substitute for non-biodegradable plastic packaging materials in food packaging and preservation (Ma et al., 2020). Generally, collagen is a good material for casings in sausage production, since that they can readily form stable networks that could shrink and stretch to adapt to the mechanical operation in continuous processing (Oechsle et al., 2016). The cooking characteristics and tenderness of sausage being stuffed in collagen casings are similar to those in natural casings (tough and transparent films processed from an animal's gastrointestinal tract) (Suurs & Barbut, 2020). Collagen casings could block the direct contact of oxygen and water vapor with sausages and reduced the exudation of gravy (Shi et al., 2019). Moreover, collagen films have been successfully utilized as edible wrappers in a variety of fudges because of their good barrier and mechanical properties (Xu et al., 2020). However, there may be some application problems, such as the collagen casings may rupture or separate from meat stuffing during filling or cooking (C. Chen et al., 2020) and the collagen films have a high swelling rate in water (X. Chen, Zhou, et al., 2019). Physical (dehydrothermal and aging treatment) (X. Chen, Zhou, et al., 2019; Shi et al., 2019), chemical (glutaraldehyde) (X. Chen, Zhou, et al., 2019), or enzymatic (transglutaminase) (Wu, Liu, Liu, & Wang, 2017) cross-linking can improves physicochemical and mechanical properties of collagen casings/films by promoting the covalent and/or non-covalent bonds between and/or within collagen molecules. Chemical or enzymatic cross-linking has the advantages of rapidity and good performance, but they also bring potential health problems (Amirdivani et al., 2018; Shi et al., 2019). In contrast, physical cross-linking is safer and greener, but it has low cross-linking effect and can lead to the degeneration of collagen (X. Chen, Zhou, et al., 2019). The combination of two or more cross-linking methods provides the prospect of overcoming the shortcomings of single cross-linking mentioned above. For example, C. Chen et al. (2020) studied the effects of glutaraldehyde cross-linking and drying temperature on collagen casings, and found that higher drying temperature improved the physicochemical and mechanical properties of casings crosslinked by glutaraldehyde, while the higher degree of cross-linking caused by higher drying temperature decreased the denaturation of collagen.

4.2. Applications of gelatin in food industry

4.2.1. Gelatin used as food additives

In the confectionery industry, gelatin is a commonly used gelling agent in many confectionery gel products such as gummy candies (Ge et al., 2021; Kurt, Bursa, & Toker, 2021). Besides participating in the formation of the texture of confectionery products (Almeida & Lannes, 2017), such as elasticity and chewiness, gelatin can also be used for foam formation and stabilization. For example, gelatin is used as a foaming agent in the production of marshmallows and can stabilize the foam by increasing the viscosity of the medium (Mardani et al., 2019; Tan & Lim, 2008). Due to its thermally reversible gelling and low gel-melting temperature (<37 °C), gelatin-containing products, such as jelly and ice cream, have different mouthfeel properties and controlled flavor release (Gómez-Guillén et al., 2011; Mariod & Fadul, 2014; Mutlu, Tontul, & Erbaş, 2018). During the processing of yogurt, gelatin is usually added as a food stabilizer to limit whey syneresis, and adding gelatin to dairy products could improve the emulsifying capacity of the final products (Baziwane & He, 2003; Mudgil, Jumah, Ahmad, Hamed, & Maqsood, 2018). Gelatin is also usually used in fruit juices and beverages as a clarifying agent (Bi, Li, & Wang, 2019; Duan et al., 2018; M.; Ren, Wu, et al., 2020), in meat products to improve water-binding capacity and texture properties (Essa & Elsebaie, 2022; Hernández-Briones, Velázquez, Vázquez, & Ramírez, 2009; Lee & Chin, 2016), in bakery products as a stabilizing, foaming, or setting agent (Yu et al., 2019). Examples of the application of gelatin as food additives are summarized in Table 5.

4.2.2. Gelatin used as food packaging and preservation materials

Gelatin films/coatings are used as barriers against external factors such as oxygen, carbon dioxide, ultraviolet, and moisture to improve the shelf-life of products. For example, gelatin-based edible films containing orange peel pectin could increase the microbial durability of cheese during 7 days of chilled storage, as well as its physicochemical and textural properties (Jridi et al., 2020). During a 10-day retail display period, edible chitosan-gelatin coatings were found to effectively reduce weight loss, lipid oxidation, microbial development, and discoloration of coated beef steaks (Cardoso et al., 2019). The gelatin-based bilayer films prepared by thermo-compression molding (i.e., packing bags) could delay the quality loss of bagged striped catfish fillets during a 7-day refrigerated period (Nilsuwan, Guerrero, de la Caba, Benjakul, & Prodpran, 2020). However, the applications of gelatin films/coatings in high moisture foods are limited because of their low water resistance. Liu et al. (2016) found that the water resistance of gelatin films modified by transglutaminase increased by ~65%, which may be due to the formation of more covalent crosslinks leading to tighter network structures of films. Various modification methods have been successfully used to improve the mechanical properties (Peng et al., 2022), thermal stabilities (Peng et al., 2021), ultraviolet (Guo, Qiang, Ma, Ren, & Zhu, 2021) and water vapor (Zhang, Simpson, & Dumont, 2018) barrier capacities of gelatin-based films/coatings. Moreover, gelatin-based films/coatings can be used as the carriers of bioactive substances (e.g., antimicrobial and/or antioxidant agents), which has the potential in constructing multi-functional films or coatings to provide active packaging of foods. The addition of (−)-Epigallocatechin gallate could enhance the ability of gelatin films in preventing the oxidation of fat and protein of tilapia fillets (J. Cao, Wang, Hao, et al., 2020). Different packaging forms can affect the preservation effect of gelatin-based active packaging films/coatings. For example, Nowzari, Shábanpour, and Ojagh (2013) found that chitosan-gelatin films and coatings showed significant antioxidant and antibacterial effects on refrigerated rainbow trout fillets, and the protective effects of coatings against lipid oxidation was better than films, which may be due to that chitosan tends to show its antioxidant effect in solution form. The use of different antimicrobial or antioxidant substances with more efficient activity and safer and their effects on the physicochemical, mechanical, structural, and functional properties of the resulting packaging films/coatings, and the controlled release of

Table 5
Examples of the application of gelatin as food additives.

Application	Source	Bloom strength (g)	Concentration (%)	Function/Effect	Reference
Gummy candy		240	5–10	With the increase of gelatin concentration, gummy candies had greater hardness, chewiness and resilience, and higher melting temperature.	Kurt et al. (2021)
Chocolate spread	Chicken feet		0.3–1.2	The addition of gelatin could improve the consistency of chocolate spread but decreased its brightness value.	Almeida and Lannes (2017)
Marshmallow	Bovine	200	2–2.4	With the increase of gelatin concentration, marshmallows had greater moisture loss by the end of 25-week storage. And the marshmallow with 2.2% gelatin had the biggest hardness.	Tan and Lim (2008)
Jelly	Bovine		15–25	With the increase of gelatin concentration, jelly candies had greater hardness, adhesiveness, chewiness and gumminess.	Mutlu et al. (2018)
Ice cream	Insect		0.5–1	Ice cream containing 0.5% insect gelatin had better taste and texture than that containing 1%.	Mariod and Fadul (2014)
Yogurt	Bovine	125	0–1.25	The addition of gelatin could improve the hardness, gumminess and viscosity of yogurt.	Mudgil et al. (2018)
Ice cream	Channel catfish (*Ictalurus punctatus*)		0.5	The addition of gelatin could make ice cream with a thicker and smoother texture.	Duan et al. (2018)
Beer	skin		0.02–0.06	When the addition concentration was <0.04%, gelatin could effectively clarify beer, otherwise it led to slow sedimentation and cloudiness in beer.	
Mulberry wine			0.2–2 g/L	The addition of gelatin could clarify mulberry wine, but had negative effects on the level of phenol content, antioxidant activity and color of wine.	M. Ren, Wu, et al. (2020)
Citrus wine			15–75 mg/L	The addition of gelatin could clarify citrus wine, and decreased the limonoid concentration.	Bi et al. (2019)
Grade A or FA surimi	Fish	275	0.5–1.5	With the increase of gelatin concentration, the mechanical properties of grade FA surimi decreased, but did not show changes in of grade A surimi.	Hernández-Briones et al. (2009)
Low fat sausage	Pig skin	209	0.5–1.5	The addition of gelatin could improve the textural properties and decrease the centrifugal loss, but increase the cooking loss of low fat sausage.	Lee and Chin (2016)
Regular fat sausage				The addition of gelatin could decrease the cooking loss of regular fat sausage, but the textural properties were reduced with increased of gelatin.	
Beef burger				The addition of mixed gel prepared by date seed soluble dietary fiber and type A gelatin could increase the moisture and protein content, and the springiness of beef burger.	Essa and Elsebaie (2022)
Bread	Pig skin		0–1.0	The addition of gelatin could decrease the hardness of breadcrumb, darken the appearance, and retarded the staling process of bread.	Yu et al. (2019)

these substances is being studied (Etxabide, Uranga, Guerrero, & de la Caba, 2017).

4.3. Applications of collagen hydrolysates/peptides in food industry

4.3.1. Collagen hydrolysates/peptides used as food additives

Collagen hydrolysates can be used as antioxidants in lipid foods, emulsifiers in emulsion-based foods, fat substitutes in low-fat meat products, clarifiers in beverages, and additives for improving milk quality, as shown in Table 6. The addition of commercial fish collagen hydrolysates to meatballs could inhibit lipid oxidation, and the fishy smell of collagen hydrolysates was masked by the spices in the formula (Palamutoglu & Kasnak, 2019). Collagen hydrolysates from fish skin and bones could extend the shelf life of two types of emulsion-based foods: butter (water-in-oil) and chocolate sauce (oil-in-water) *via* the dynamic quasifibrillar assembly of collagen hydrolysates into a dense network at

Table 6
The applications of collagen hydrolysates/peptides as food additives in different products.

Application	Commercially or experimentally	Source	Sequence	Concentration	Function	Reference
Meatball	Commercially	Fish skin		1–3% (w/w)	Antioxidant	Palamutoglu and Kasnak (2019)
Butter and chocolate sauce	Experimentally	Fish skin and bones		1:150 (w/w)	Emulsifier	Dey et al. (2021)
Frankfurters	Commercially			25–75% substitution ratio	Fat substitute	Sousa et al. (2017)
Chrysanthemum beverage	Commercially	Pig skin		0–1 g/L	Clarifier	Q.-X. Zhang, Simpson, and Dumont (2018)
Probiotic fermented milk	Commercially			3% (w/v)	Additive for improving milk quality	Znamirowska et al. (2020)
Frozen dough	Experimentally	Pig skin Pig skin		1% (w/w) 0–1.5% (w/w)	Antifreeze	Chen et al. (2017) Yu et al. (2020)
Surimi	Experimentally	Blacktip shark skin		8% (w/w)	Antifreeze	Kittiphattanabawon et al. (2012)
Ice cream	Experimentally	Carp fish skin Pig skin	 GLLGPLGPRGLL	4.0% (w/w) 0.05–0.5% (w/v)	Antifreeze	Damodaran and Wang (2017) Cao et al. (2016)
Lactobacillus bulgaricus	Experimentally	Shark skin	GAIGPAGPLGP	250 μg/mL	Antifreeze	Wang et al. (2014)
Streptococcus thermophiles	Experimentally	Tilapia scales Pig skin		1.0 mg/mL 0–6.0 mg/mL	Antifreeze	X. Chen et al. (2020) W. Wang, Hsieh, et al. (2015)

the emulsion interface (Dey et al., 2021). Partial replacement (25–75%) of pork backfat by commercial collagen hydrolysates could improve the physical and chemical qualities of frankfurters, and with the increase of substitution ratio, the water holding capacity, emulsion stability and texture properties of products were better (Sousa et al., 2017). Collagen hydrolysates from pigskin shavings as clarifier could increase the transmittance of chrysanthemum beverage, improve the sensory quality and storage stability, while slightly reduce the content of nutrients (Q.-X. Zhang, Simpson, & Dumont, 2018). The addition of commercial collagen hydrolysates to probiotic fermented milk could increase the hardness and adhesiveness of product, reduce syneresis, and be benefit to the survival of *Bifidobacterium* Bb-12 during 21-day storage (Znamirowska, Szajnar, & Pawlos, 2020).

Collagen hydrolysates/peptides are effective food cryoprotectants. Typical examples of the applications of collagen hydrolysates/peptides in different frozen products are listed in Table 6. Collagen hydrolysates from pig skin could improve fermenting (Chen, Wu, Li, & Wang, 2017) and baking properties (Yu et al., 2020) of frozen dough, and endow the dough with a softer texture, larger volume, softer crumb, and better appearance after baking. Collagen hydrolysates from shark skin gelatin could prevent protein denaturation by decreasing protein aggregation during the freezing and thawing process, and therefore contribute to surimi cryoprotection (Kittiphattanabawon, Benjakul, Visessanguan, & Shahidi, 2012). Collagen hydrolysates/peptides successfully inhibited the ice crystal growth of ice cream during frozen storage (Damodaran, 2007; Damodaran & Wang, 2017) and increased the melting resistance of ice cream (Cao et al., 2016) which helps keep the ice cream smooth and creamy. The cryoprotective effects of collagen hydrolysates/peptides could also be utilized in preserving cold-stressed probiotics. Wang, Zhao, Chen, Zhou, and Wu (2014) found that treatment with 250 μg/mL of collagen peptides (GAIGPAGPLGP) led to 90.28% of *Lactobacillus bulgaricus* surviving after cold treatment. The same protective effect was also observed with *Streptococcus thermophilus* after freezing (X. Chen et al., 2020; W. Wang, Hsieh, et al., 2015). The cryoprotective effect may be related to maintaining the integrity of cell membrane and the reduction of oxidative damage by collagen-derived antifreeze peptides with cold stress.

4.3.2. Applications of collagen hydrolysates/peptides in functional foods

Collagen hydrolysates/peptides can be used as dietary supplements to improve human skin health (e.g., wound healing and skin aging). Fish skin collagen hydrolysates could promote skin wound healing in rat *via* altering cutaneous microbiome colonization which could control the inflammatory reaction, and increase wound angiogenesis and collagen deposition (Mei et al., 2020). Bovine and porcine collagen hydrolysates could promote human skin wound healing by enhancing the proliferation of fibroblasts and keratinocytes (Mistry et al., 2021). Collagen hydrolysates from silver carp skin could repair photoaging skin, and collagen hydrolysates with low molecular weights had stronger repair effect than with high molecular weights (Song, Meng, Cheng, Li, & Wang, 2017). Z. Liu, et al., (2019) proposed that the mechanisms of collagen hydrolysates improving and repairing skin aging are: (1) to promote procollagen synthesis by activating TGF-β/Smad pathway, (2) to prevent collagen degradation by inhibiting the expression of activator protein-1, matrix metalloproteinase-1 and -3, and (3) to reduce oxidative damage by scavenging reactive oxygen species in skin cells and enhancing the activities of antioxidant enzymes in skin. However, Zhang, Zhang, Song, and Li (2020) suggested that the main mechanism of collagen hydrolysates improving skin condition is to promote the synthesis of type I collagen rather than to inhibit the degradation of type I collagen.

Collagen hydrolysates/peptides may be used as the functional ingredients in functional foods for patients suffering from cardiovascular disease (e.g., hypertension, T2DM, and hyperlipidemia). Collagen peptides RGL-(Hyp)-GL and RGM-(Hyp)-GF from bovine bone could decrease systolic blood pressure of spontaneously hypertensive rats (S. Cao, Wang, Hao, et al., 2020). And jellyfish collagen hydrolysates could reduce blood pressure of renovascular hypertension rats by decreasing the concentration of angiotensin II in kidney (Zhuang, Sun, Zhang, & Liu, 2012). Fish skin gelatin hydrolysates could improve the glycemic control in diabetic rats by inhibiting plasma DPP-IV activity and inducing glucagon-like peptide-1 secretion (T.-Y. Wang, Hsieh, et al., 2015). Saito, Kiyose, Higuchi, Uchida, and Suzuki (2009) studied the effects of fish skin collagen hydrolysates on blood lipids in rats, and found that collagen hydrolysates could inhibit the transient increase of plasma triglycerides by affecting lipid absorption and metabolism. Moreover, Tometsuka et al. (2021) found that a single oral administration of ginger protease-degraded collagen hydrolysates did not change the content of triglyceride and cholesterol in blood, but a long-term use (10 weeks) may decrease tissue and blood lipids by changing lipid metabolism.

Collagen hydrolysates/peptides have potential to be used in the field of sports food as they can strengthen lean muscle (Oertzen-Hagemann et al., 2019), alleviate activity-related knee joint discomfort (Zdzieblik, Oesser, Gollhofer, & König, 2017), and increase endurance performance (Jendricke, Kohl, Centner, Gollhofer, & König, 2020). Dietary gelatin which could be decomposed into peptides by endogenous enzymes *in vivo*, was found to regulate the systemic iron homeostasis in rats to enhance non-heme iron absorption and thus has the potential to be used as iron supplements (Wu et al., 2019). Collagen hydrolysates from cod skin could protect liver tissue against oxidative damage *via* increasing the activities of antioxidant enzymes and reducing the lipid peroxidation (Han et al., 2015). Collagen hydrolysates from bovine bone could protect mice from dexamethasone-induced immunosuppression by stimulating the T cell proliferation and increasing the interleukin-2 production (Si, Guo, Xu, Qin, & Song, 2021). Collagen hydrolysates/peptides have been increasingly used in the development of functional foods. For example, fermented milk containing collagen hydrolysates may help relieve joint pain (Walrand, Chiotelli, Noirt, Mwewa, & Lassel, 2008). The yogurts supplemented with collagen peptides GPLGAAGP, GRDGEP, or MTGTQGEAGR showed higher antioxidant activities, and ACE-I and DPP-IV inhibition activities without changing the physicochemical and sensory properties of the products (Ayati, Eun, Atoub, & Mirzapour-Kouhdasht, 2022). The oral nutritional supplements made from collagen hydrolysates and milk protein could supplement calories and protein for the elderly to mitigate muscle mass loss (Brook et al., 2021). The addition of collagen hydrolysates from fish skin enriched the health promotion characteristics (with higher protein content and antioxidant potential) of gluten-free noodles (Wangtueai, Phimolsiripol, Vichasilp, Regenstein, & Schöenlechner, 2020) and biscuits (A. Kumar, Elavarasan, et al., 2019), while the presence of dietary fiber was beneficial to the antioxidant activities of collagen hydrolysates (L. Wang, Zhao, Brennan, et al., 2020).

5. Conclusions and future outlook

Collagen and its derivatives from byproducts of food-producing animals represent a promising protein resource. They have shown excellent mechanical properties, functional properties, and biological activities. These special features, along with their bioavailability, edibility, and biodegradable characteristics, make them to be widely utilized in different fields of food industry. In this paper, the structural and bio- and physical-chemical properties of collagen and its derivatives and their applications in food industry have been reviewed. However, the species sources of collagen and its derivatives are still limited and there is a lack of standardized preparation procedures. And the methods of introducing collagen and its derivatives into different forms of food products as food additives and the possible reactions with other food components during food processing and storage need further research. In addition, collagen-based food packaging materials may not be able to adapt to the mechanical operation in continuous food processing, and the water-resistance property of gelatin-based film/coating is still poor.

The rich amino acid residues in the side chains of collagen and gelatin provide the physical, chemical and/or enzymatic modification possibilities, which may help to overcome the current application limitations of collagen/gelatin-based food packaging materials. The balance of function, physicochemical and mechanical properties of collagen based active food packaging materials, and the controlled release of these active substances need further research. Moreover, the molecular mechanisms and structure-activity relationships of bioactive collagen peptides are not completely clear. And the development of collagen peptides as functional food products is also facing problems of inadequate evidence of clinical bio-efficacy and the high cost of industrial-scale production. Yet, more efforts should be paid to meet the above challenges to promote better application of collagen and its derivatives in food industry.

CRediT authorship contribution statement

Cheng Tang: Conceptualization, Investigation, Visualization, Writing - Original Draft, Writing - Review and Editing. **Kai Zhou:** Conceptualization; Investigation, Writing - Review and Editing, Funding acquisition. **Yichen Zhu:** Conceptualization, Investigation. **Wendi Zhang:** Conceptualization, Investigation. **Yong Xie:** Investigation, Visualization. **Zhaoming Wang:** Investigation. **Hui Zhou:** Investigation, Funding acquisition. **Tingting Yang:** Investigation. **Qiang Zhang:** Investigation. **Baocai Xu:** Writing - Review and Editing, Supervision, Project administration, Funding acquisition.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This study was supported by the National Key R&D Program of China (2021YFD2100804), the Fundamental Research Funds for the Central Universities in China (No. PA2019GDZC0099 and JZ2020HGQA0152), the Major Science and Technology Project of Anhui Province (202003b06020023), and the Key Generic Technology R&D Project of Hefei (2021GJ079).

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