REVIEW

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Progress in the extraction and application of collagen peptides

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Author contributions

Meng-Han Yang conceived the structure of this article and wrote the paper. Zi-Meng Yuan collected data and analyzed relevant studies. Chun-Ming Dong directed the drawing and critically reviewed the article. All authors read and approved the final manuscript.

Competing interests

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Abstract

Collagen peptide is the product of complete hydrolysis of collagen, which has a relatively small molecular weight and is more easily absorbed than proteins and amino acids.Collagen peptide not only has unique nutritional value, but also has certain physiological functions, which makes it has great potential value in various fields, so it has set off a wave of research on collagen peptide in the biological world.This paper describes the sources and extraction methods of collagen peptides, and describes the research progress and application of collagen peptides in the medical, food, material and skin care industries according to their physiological functions, which will provide new ideas for the future research of collagen peptides.

Keywords: collagen peptide; extraction method; physiologic function; application field

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Introduction

One of the most common and abundant proteins in mammals is collagen, accounting for about one-third of the total protein content [1]. Collagen is a polymer compound with a relatively large number of types, 29 types have been identified [2]. Collagen has a variety of biological functions such as protecting the skin [3], increasing skin elasticity [4], improving skin photoaging [5], slowing down skin aging [6], improving bone condition [7], preventing osteoporosis [8], improving intestinal condition [9], promoting wound healing [10], and enhancing immunity [11]. Collagen is made of three left-handed helical peptide chains intertwined with each other (Figure 1), and the unique triple helical structure and the presence of hydrogen bonding and disulfide bonding increase the stability of the structure, which improves the mechanical strength and toughness of collagen; however, due to the strong stability of the collagen structure, it is not easy to be dissolved in hot water and cold water, and it is difficult for ordinary proteolytic enzymes to degrade it, which is difficult for mammals to digest and absorb, and difficult to perform itsbiological functions [12–15].

Two or more amino acids form a peptide chain through dehydration condensation, and multiple peptide chains are intertwined and folded to form a protein molecule [16]; based on the number of amino acids, peptides can be classified into short peptides and long peptides, which constitute the active structure of proteins, thus affecting the structure of proteins as well as the corresponding physiological functions, and even affecting the conduct of normal life activities in mammals [17].

Collagen peptides, often referred to as collagen polypeptides, are a mixture of small molecular weight peptides formed after collagen undergoes enzymatic hydrolysis by specific proteases or other treatments [18]. Most contain short sequences of 2 to 20 amino acids [19]. Like collagen, they are trimeric peptides composed of three α-chain peptides that form a triple helix structure. Each α-chain is a left-handed helix, and three left-handed helices intertwine to form a right-handed superhelix, enhancing the stability and bioactivity of the collagen peptides [20]. The primary structure still contains the repeating sequence glycine-X-Y, where X and Y can be any amino acid, but are most commonly hydroxyproline and proline, with minor amounts of tryptophan and cysteine [21]. This sequence composition facilitates the assembly of collagen peptides into fibril structures, enhancing the stability of the extracellular matrix of connective tissues. Collagen peptides possess unique hydroxylysine residues, allowing for qualitative detection based on their amino acid composition [22]. Quantitative detection can also be achieved by measuring the content of hydroxyproline, which helps calculate the yield of collagen peptides. Compared to collagen and other peptides, as shown in Table 1, collagen peptides are small molecular compounds with lower molecular weights; they are soluble in both hot and cold water, as well as in acidic and alkaline solutions; the viscosity of their aqueous solutions is relatively low, and even at high concentrations, they do not coagulate, maintaining good fluidity; they are more easily absorbed by mammalian intestinal wall cells, thereby exerting their effects in the body [23, 24]. With a smaller molecular weight, typically below 5 kDa, and higher bioactivity, collagen peptides are easier to modify biologically and synthesize chemically. They are absorbed more rapidly than collagen and faster than small molecule amino acids. Mammals can directly absorb and utilize collagen peptides, which circulate in the bloodstream in their intact peptide form. The unique structure of collagen peptides endows them with diverse biological activities, such as antioxidation, antibiosis, antifreeze, and anti-inflammatory properties. They can carry certain genetic information, thus regulating various physiological activities and biochemical reactions in the body. Collagen peptides fully exhibit their functional characteristics in the body, such as promoting bone and joint health, enhancing skin lubricity, improving mental state and sleep quality, alleviating anxiety and insomnia, strengthening the immune system, accelerating cell proliferation, and protecting organs [25]. Therefore, exploring the preparation of collagen peptides and understanding their functions in different tissues is of great significance for the subsequent development and utilization of collagen peptides.

In recent years, research on collagen peptides has made breakthroughs, especially in the skin care, medical, materials, and food industries. For example, recombinant collagen peptides produced by genetic engineering technology are used in the skin care industry [26]. Natural collagen peptides serve as food additives to improve the nutritional value of food [27]. Additionally, the development of collagen peptide-related pharmaceuticals aims to improve the health of organisms and enhance the immune system [28]. Collagen peptides can also be added to corresponding materials as stabilizers to enhance their solidity [29]. Furthermore, collagen peptides have a wide range of applications in the animal husbandry industry, such as feeding breeder chickens. Adding an appropriate amount of collagen peptide supplements can improve the intestinal health of the breeder's offspring [30].

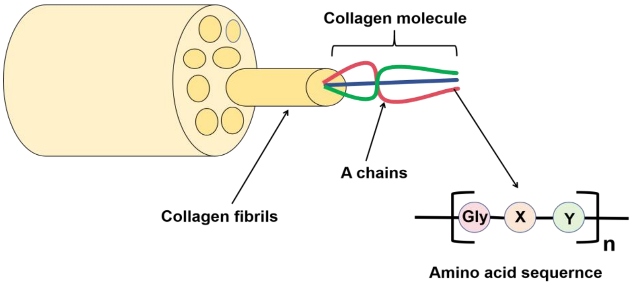

Figure 1 The molecular structure of the collagen protein

Table 1 Comparison of peptides, collagen, and collagen peptides

	Peptide	Collagen	Collagen peptide
Structure	Something between amino acids and proteins	Structural protein	Low molecular weight collagen peptide mixture
Relative molecular mass	The molecular weight was between 180 and 5000 Da	The molecular weight is approximately 300 kDa	The molecular weight is approximately 10 kDa
Constitute	18 Amins	18 amino acids, small amounts of glucose and galactose	Less than 18 amino acids, small amounts of glucose and galactose

Source and preparation

There are many ways to prepare collagen peptides, mainly divided into three types: direct extraction from natural organisms, artificial synthesis, and hydrolysis of collagen in vitro.

When the extraction amount of collagen peptides requiring specific structure and function for scientific research or the required collagen peptide synthesis is more complex, it can be directly extracted from natural organisms. Elango et al. extracted natural collagen peptides from salmon bone and thus studied collagen peptides with excellent osteogenic potential [31]. Li Shuang et al. extracted natural collagen peptides from Atlantic cod bone to study their antioxidant activity and stability, providing guidance for the development of antioxidant polypeptide products [32]. However, the peptide content of collagen in natural organisms is relatively small, and most of it is used for scientific research. Large-scale development and industrial production are relatively difficult, with relatively low utilization and economic benefits.

The synthesis of collagen peptides can be carried out through chemical synthesis, enzymatic synthesis, and DNA recombinant technology, but the capital and time costs of synthetic collagen peptides are relatively high, the technical requirements are demanding, and the actual utilization value and output are not high, generally limiting their use to drug research and development. Gomez-Guillen et al. used triple helix-prone self-assembly technology to simulate the natural collagen peptide structure and thermal behavior to produce fibrils, controlling the stability and self-assembly length of the collagen peptide by regulating the amino acid composition, temperature, and solvent [33]. Falk et al. added Fe^{2+} to the solution of triple helical collagen peptides to trigger the self-assembly process and form morphologically diverse fibrils to synthesize the target collagen peptide [34]. Siyi Song et al. used solid-phase synthesis technology to chemically synthesize the Harpadon nehereus collagen peptide LR-7 and subsequently investigated its synergistic effect with taurine in preventing cardiovascular damage in hypertensive mice induced by high salt intake [35]. Currently, the main method for obtaining collagen peptides is through graded enzymatic hydrolysis or chemical hydrolysis of collagen in vitro [36].

Raw material source

Natural collagen peptides are predominantly sourced from by-products of terrestrial and aquatic organisms and leather waste (Figure 2). Terrestrial organisms primarily refer to creatures living on land, including livestock raised by humans and various economic animals, such as duck skin, rabbit bones [37], sheep bones [38], mutton bones [39], duck bones, cattle bones [40], yak bones [41], pig skin [42], pig bones [43], chicken skin [44], donkey, etc. Aquatic organisms are those that live in various bodies of water, including economically important animals raised through aquaculture, such as the scales of silver carp [45], sturgeon skin [46], tilapia skin [47], squid cartilage [48], freshwater fish scales [49], Atlantic salmon bones [50], sea bass skin [51], salmon skin [52], white carp skin [53], cod skin [54], tuna bones [55], kelp, turbot skin [56], seaweed, jellyfish, sea cucumber skin, sea cucumber flesh, aquatic plants [57], and so forth. If we analyze the current market share of collagen peptides based on the richness of different raw materials, collagen peptides from terrestrial organisms dominate, followed by those from aquatic organisms, while collagen derived from leather waste ranks the lowest. However, with advancements in science and technology, as well as increasing public awareness of food safety, people have become more aware of the various disease risks associated with collagen peptides derived from terrestrial organisms, which can easily trigger allergic stress reactions [58]. Meanwhile, collagen peptides extracted from leather waste contain heavy metals like Cr^{3+}. The removal process for heavy metals is complex, though many researchers have proposed optimization schemes [59–62], such as using compound extraction methods to reduce Cr^{3+} content. These methods include acid-base compound extraction, alkaline enzyme compound extraction, ultrasonic and alkaline extraction combined, as well as acid extraction, alkaline extraction, and oxidation extraction methods. However, in terms of cost, policy, sales channels, and benefits, these methods are not widely accessible. On the one hand, aquatic organisms are less related to humans, significantly reducing the risk of disease transmission; on the other hand, their living environments are relatively less polluted and contain higher concentrations of collagen peptides, making them a safer raw material source. Considering recent market trends, the market share of collagen peptides extracted from terrestrial organisms and leather waste is steadily decreasing, while the market share of collagen peptides derived from aquatic organisms is on the rise, even surpassing that from terrestrial sources [63], particularly the best fish by-products [64]. Although some researchers have noted that a small number of individuals may experience allergic reactions, such as red-brown spots or rashes on the skin [65], collagen peptides extracted from aquatic organisms still hold significant development potential overall.

The collagen peptide extraction methods

The in vitro collagen hydrolysis method is mainly divided into three steps [66]: The first step is to pretreatment the raw material, remove the lipids, pigments, miscellaneous proteins and other non-collagen protein substances in the raw material, and destroy the quaternary spatial structure of collagen, so as to facilitate the extraction of collagen. The common method is to pretreatment with sodium hydroxide [67]. The second step is to use physical, chemical and biological methods to treat collagen, mainly the purpose is to destroy the fibrous organization between collagen, weaken the intermolecular interaction force and hydrogen bonding, and destroy the peptide bonds of some linker protein molecules, so as to improve the sensitivity and purity of collagen proteolysis. Finally, the resulting collagen was further processed enzymatically and hydrolysis, so as to obtain the desired collagen peptide. The common method for extracting collagen peptides [68], as shown in Table 2, the most common methods are enzyme formulation and compound extraction.

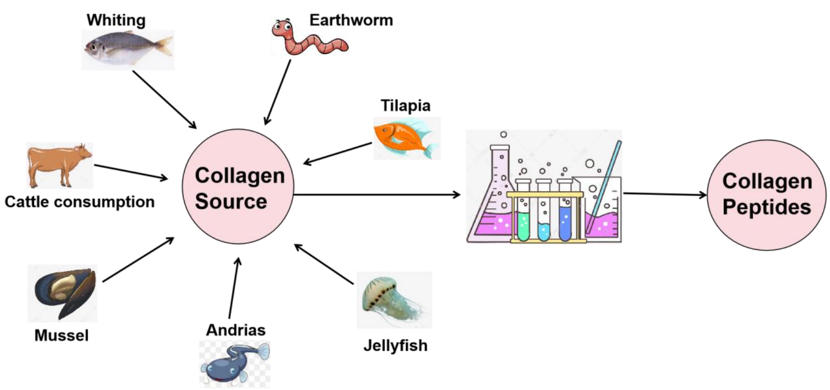

Figure 2 Source of the collagen peptide

Table 2 Comparison of the collagen peptide extraction methods

Extraction method	Condition	Advantage	Weakness
Chemical extraction method	Acid or alkaline solution as a medium	Short time, low cost, simple operation	Affect the biological activity of the peptide and disrupt its original structure and function
The enzyme formulation	Specific proteases undergo enzymatic digestion	The structure remains relatively intact and more purposeful	Low immune properties and produce complex byproducts
Hot water extraction	With pure water as the medium, strictly control the temperature	Environmental-friendly, non-toxic, and simple to operate	Excessive temperature can disrupt the structure of the peptide
Heat pressure immersion method	With pure water as the medium, the temperature and pressure are strictly controlled	Environmental friendly, economical, exposing more hydrophobic groups and amino acid residues	High-pressure control is more difficult, and the energy consumption is larger
Salt formulation	A certain concentration of the salt solution serves as the medium	The response was mild	To breaking the stability of the peptide structure is complex
Ultrasonic-assisted extraction method	The ultrasound of certain power for a period of time after adding protease	Thermal stability and antioxidant properties enhancement, effectively shorten the time	The cost of ultrasound equipment is high, and the time and frequency of excess births can affect the peptide yield
Microbial fermentation and extraction method	Using microbial growth metabolism to produce extracellular proteases	Improve the nutritional value, with high biological safety	Culture the strains for a long time
Composite extraction method		Overcoming the limitations and harmfulness of a single extraction method	Complex operation

Chemical extraction method. The chemical extraction method primarily refers to the process of using acidic or alkaline solutions to extensively break down the primary and secondary structures of collagen molecules, disrupting the collagen fiber matrix and weakening the bonding between molecules, thereby obtaining collagen peptides [69]. This method can be further divided into acid extraction and alkali extraction processes. The entire procedure is simple to operate, takes a short time, and has a high extraction efficiency; however, the reagents used are highly acidic or alkaline, leading to rapid and intense reactions. While this process breaks the peptide bonds within the collagen structure, it also impacts the biological activity of the collagen peptides, potentially damaging their original structure and function. As a result, both the yield and quality of the obtained collagen peptides may decrease, and there is even a risk of generating toxic substances that could be detrimental to human health [70]. This approach is widely used due to its operational simplicity and efficiency, but the potential drawbacks related to the degradation of bioactivity and the possibility of creating harmful by-products must be carefully considered when choosing an extraction method for collagen peptides intended for use in health-related applications.

Acid extraction method refers to the use of acidic solution as an extraction medium [71], the first use of acidic solution to soak raw materials for pretreatment, to destroy the amide bond of collagen peptide chain, to get the amino acid and collagen peptide short chain, and then after centrifugation, pumping filtration and other processes to get the target collagen peptide method, which is suitable for the raw materials that have a lower degree of fibre and are relatively easy to break. The most commonly used acidic reagents are hydrochloric acid, acetic acid, acetic acid, citric acid, oxalic acid, lactic acid and so on. The type, concentration, soaking time and temperature of the acidic solution need to be controlled strictly according to the characteristics of the raw material, so as to avoid affecting the final peptide yield of the acid extraction method, as well as the structure and function of collagen peptides. The triple helix structure of collagen peptides extracted by acid extraction remains unchanged and is loose and porous, which has better moisturising effect. However, the whole hydrolysis process is difficult to control, and acidic reagents will destroy the structure of tryptophan, serine and tyrosine, and even destroy the nutritional value of collagen peptides to a certain extent. The application of acid extraction method in industrial production is generally higher temperature requirements, the corrosion resistance of the equipment has higher requirements, and caused by equipment and environmental pollution is relatively large, the later removal of a certain degree of difficulty, to a certain extent, increase the cost, so the use of acid extraction method is not high.

Alkaline extraction, which is more similar to acid extraction, is a process that involves the use of an alkaline solution to soak pretreated raw materials to break the amide bonds between collagen peptide chains, obtaining the amino acids and collagen peptide chains, and subsequently preparing the target collagen peptides by centrifugation and other operations. The principle of alkaline extraction is based on the saponification of alkaline reagents with collagen-bound fats [72], which destroys the amide bond between the amino and carboxyl groups, thus destroying the amino acids containing sulfhydryl and hydroxyl groups to produce a racemisation, which ultimately results in the removal of non-helical peptide segments, exposing collagen fibres, and obtaining collagen peptides of different molecular weights. Generally rough and hard raw materials will use alkaline extraction method, need to choose the appropriate alkaline drugs, the concentration of alkaline solution and soaking time according to the thickness and hardness of the raw materials; commonly used alkaline drugs are sodium hydroxide, calcium carbonate and potassium hydroxide. Under alkaline conditions, non-collagenous components can be effectively removed [73], increasing the protein yield and the corresponding peptide yield, but the whole hydrolysis process of alkaline extraction is difficult to control, and the peptide bond connecting collagen molecules is easy to break, which will destroy the superhelical structure and the stability of collagen peptides, and also produce substances harmful to human body such as racemic compounds [74]. Some alkaline reagents also have a modifying effect on the protein, and when the protein changes, the peptide also changes accordingly, and the whole process is difficult to control, which makes it less used in the laboratory and industry.

Enzyme formulation. Enzymatic extraction refers to the preparation of target collagen peptides by selecting specific proteases to break the peptide bonds of peptide segments in the non-helical region of collagen [75], so that they can be decomposed into smaller peptide fragments. The cleavage sites of proteases are specific, and specific peptide bonds can be broken by the specific selectivity of proteases to produce biologically active peptides of different lengths, so different proteases should be selected according to the structural and functional properties of the target collagen peptides [76]. According to the different catalytic mechanism of proteases, common proteases can be divided into alkaline protease [77] (trypsin), acid protease [78] (pepsin) and neutral protease [79] (papain); according to the different structure of the enzyme, it can be divided into glutamine, seramide, cysteine protease and metalloprotease. The optimal reaction conditions of each enzyme are different, and the appropriate reaction conditions [80] should be selected according to the characteristics of the protease and the target collagen peptide, such as the pH value of the solution, temperature, protein concentration, enzyme concentration, liquid ratio and enzyme hydrolysis time. The collagen peptide will not destroy its triple helix structure, the broken peptide bond is targeted, and the network structure of the collagen peptide is more complete, the fibrosis is more obvious, and has a high biological safety [81]. Different proteases have different enzymatic sites and degrees of digestion (Table 3). The whole process of enzymatic extraction is more targeted, and the yield and purity of the target collagen peptides will be increased accordingly; the extraction process can be carried out under relatively mild conditions, which is less hazardous to the environment and consumes less energy [82]; it is usually used in the industries such as biomedical materials and food. However, the enzymatic degradation produces different by-products, theand the immunological properties of the target collagen peptides are low.

Shanshan Su et al. prepared collagen peptides by enzymatically digesting type I collagen from tilapia fish skin using alkaline protease [83]. The specific experimental procedure involved immersing the extracted tilapia fish skin collagen in a 0.1 mmol/L phosphate buffer solution of pH 8.0 overnight at 4 °C. The next day, the samples were treated in a boiling water bath for 5 minutes, cooled under running water for 10 minutes, and incubated at 55 °C for 15 minutes. After mixing thoroughly with alkaline protease at a 2:100 (w/w) ratio, the samples were fully enzymatically digested. The temperature was then raised to above 95 °C for enzyme inactivation, and the samples were cooled in an ice bath for 20 minutes before centrifuging at 11,000 g for 20 minutes. The supernatant was collected, filtered through a 0.45 μm PES membrane to obtain collagen peptides with relatively high purity, and stored frozen at −25 °C. The release kinetics of collagen peptides were later explored to provide insights for future developments in the food industry.

Due to the strong specificity of protease cleavage sites, single enzymatic extraction methods only break peptide bonds at specific positions on the collagen peptide chain, resulting in large molecular weights and limited collagen peptide types. This limits their specific bioactivities and functions. To address this, some researchers have proposed composite enzymatic methods that increase the variety of proteases and cleavage sites, reducing the molecular weight of collagen peptides and overcoming the limitations of single-enzyme extraction. Jiaohan Lu et al. used alkaline protease and trypsin to extract collagen peptides from cod skin through a hybrid enzyme extraction method [84]. After adjusting the pH of the treated cod skin gelatin solution to 7.5 using 1M NaOH, the temperature was controlled at 50 °C. Alkaline protease was then added to extract gelatin, followed by the addition of trypsin to fully digest the collagen. After the reaction, the temperature was raised to 100 °C to terminate the enzymatic process. The solution was filtered through a 0.45 μm PES membrane, followed by dialysis and desalination to obtain high-purity cod skin collagen peptides, which were stored at −20°C. This method improved enzymatic efficiency and peptide yield compared to single-enzyme extraction.

While composite enzymatic extraction methods can leverage the advantages of different proteases under certain conditions, proteases may also inhibit each other under certain circumstances. To address this issue, researchers have developed stepwise enzyme extraction methods, which allow for more convenient control of enzyme reaction conditions and enzyme addition, maximizing the efficiency of enzyme reactions. However, this method is more time-consuming and complex [85]. Jiajia Gao et al. used flavor protease and trypsin in a stepwise manner on pre-treated jellyfish samples, producing four different types of jellyfish collagen peptides with varying molecular weights [86].

Therefore, different protease preparations and methods should be selected based on the characteristics of the collagen and target peptides. A rational enzymatic solution should be designed to efficiently prepare collagen peptides with different structures, physiological activities, and functions.

Table 3 Common proteases and their restriction sites

Protease	The restriction site
Trypsin	Alanine, Lysine carboxy-terminal peptide bond
Pepsin	Phenylalanine, Leucine carboxy-terminal peptide bond
Papain	Hydrophobic side chain amino acid peptide bond
Alkaline protease	Aromatic amino acid, hydrophobic amino acid carboxyl terminal peptide bond
Bromelain	Carboxyl terminal peptide bond of basic amino acid and aromatic amino acid
Sarre peptidase	Hydrophobic amino acid amino terminal peptide bond

Hot water extraction formulation. Hot water extraction refers to the extraction of collagen peptides using ultrapure water as a medium [87], which usually requires strict temperature control, based on high temperatures to destroy the hydrophobic interaction and hydrogen bonding forces between the amino acids that make up the collagen molecule, so as to hydrolyse collagen to obtain peptides. Compared with chemical and enzymatic methods, the hot water extraction method is simpler, environmentally friendly, economical, non-toxic and even safe for consumption, which is an economic and safe extraction process. However, the high temperature is difficult to maintain and the energy consumption is large, and the peptide chain of collagen molecules is prone to break under high temperature for a long period of time to produce large molecules of gelatin, which leads to relatively low peptide yield, and the gelatin obtained has a relatively large molecular weight, which is not easy to be absorbed by the human body, and is not easy to be used.It is not easy to be absorbed and utilised by human body, so the hot water extraction method is rarely used to prepare collagen peptide in industrial production.

MIN S et al used a laboratory scale intermittent static hydrothermal treatment reactor, which was filled with pre-treated distilled water at 95 °C [88]. Subsequently, samples with treated pig skin were placed into the reaction vessel to explore the effect of temperature on the degree of protein hydrolysis through temperature settings, and the results showed that at temperatures between 150 °C and 190 °C, the higher the temperature, the greater the degree of hydrolysis of proteins, and the number of free amino acidsincreased, and the peptide yield of collagen increased, but when the temperature was between 190 °C and 240 °C, the protein hydrolysis was relatively complete, and the products mainly existed in the form of small peptides and free amino acids, and the collagen peptide content was very small.

Thermal pressure extraction method. The essence and process flow of hot-pressure extraction are almost the same as that of hot-water extraction [89–91], with the difference being the different conditions imposed. Hot-pressure extraction involves dissolving the raw material with water as the medium, and the raw material is subjected to a pressure of 100,000 to 1,000,000 Pa in a confined space, so as to make use of high temperatures and high pressures to destroy the hydrophobic interactions between the amino acids in the primary structure of collagen and the hydrogen-bonding forces, and to damage the collagen. Sung Hee Park et al. used a laboratory-scale high-temperature and medium-pressure treatment reactor to extract collagen peptides from tuna fish skin by hot-pressure leaching to investigate the antioxidant and anti-aging properties of collagen peptides [92], and the temperature in the reactor was controlled to be between 150 °C and 250 °C, and the pressure was controlled to be between 350-3900 kPa during the hydrolysis of collagen, and the target collagen peptides were obtained after a period of reaction.The target collagen peptides were obtained after a period of reaction.The hot press extraction method is more environmentally friendly, economical, non-toxic, and the collagen peptides obtained are more functional and have higher utilisation value, but it is more difficult to control the high pressure, the time is longer, and the energy consumption is larger, so few scholars have used this method to extract collagen peptides.

Salt formulation. Salt extraction involves the use of a certain concentration of salt solution as an extraction medium to dissolve collagen to obtain salt-soluble collagen [93], followed by hydrolysis to obtain salt-soluble collagen peptides, and finally dialysis desalting to obtain target collagen peptides.Commonly used salt media include NaCl, KCl, CH_3COONa, phosphate, citrate, etc. The reaction conditions are mild and the operation is relatively simple, but the type and concentration of salt have an effect on the extraction rate and the stability of the structure of collagen peptides, which makes the practical operation more difficult, and collagen peptides are seldom extracted by the salt extraction method alone.

Microbial fermentation and extraction method. Microorganisms can grow and metabolically in a suitable environment to produce extracellular protease [94], which decomposes the processed raw material and transforms it into target collagen peptides. To select appropriate microbial species, common microbial species and their proteases as Table 4, different kinds of microbial species fermentation produces different kinds of protease, to affect the extraction of collagen peptide; microbial species metabolism enzyme line is more complex, endonuclease can enzymatically release macromolecular collagen into small molecular peptide, modify enzyme modification exposed hydrophobic bond bitter groups, to improve the purpose of collagen peptide flavor [95]. Compared with other extraction methods, microbial fermentation extraction method will not cause damage to amino acids, mild reaction conditions, process is relatively simple, add microbial bacteria fermentation can remove miscellaneous protein and fat can also complete collagen and collagen peptide extraction, do not need to use of chemical reagents and enzyme preparation, will not produce harmful substances, will not bring pressure to protect the environment, greatly save the production cost, improve the production efficiency. In addition, microbial fermentation extraction can process collagen peptides to improve their sensory quality and nutritional value, but microbial fermentation is a long process, and it is difficult to select the right species, including the species, extracellular proteases and the conditions for fermentation.

Jeevithan et al. extracted low molecular weight collagen peptides by microbial fermentation and extraction method [96], selecting Bacillus sphaericus as the fermenting strain and whale shark cartilage as the extracting raw material, both of them were fully mixed, and the control conditions were in the optimal growth environment of the strain, so that the strain produces heat-resistant proteases during growth and metabolism to enzymatically digest raw materials for preparing collagen peptides of whale shark cartilage, and the results of protein electrophoresis. The results of protein electrophoresis (SPE) showed that three kinds of collagen peptides were obtained.

Ultrasonic-assisted extraction method. Ultrasonic-assisted extraction method uses the huge pressure generated by ultrasonic cavitation to separate the uncrosslinked collagen molecules and improve the extraction rate of collagen peptides [97]; ultrasonic treatment can also open the collagen fibres, destroy the structure of collagen, increase the contact area between the enzyme and the raw material, and promote the effect of subsequent proteases. Yuejing Hao et al. used ultrasonic-assisted extraction to extract pig boneCollagen peptides were extracted by ultrasonic-assisted extraction [98]. Firstly, the obtained pig bone collagen was dissolved in ultrapure water, and the concentration was controlled to be 30 mg/mL, and the samples were processed by using ultrasonic cell crusher to control the ultrasonic power and ultrasonic time. After ultrasonic treatment, the solution was treated in a water bath at 40 °C for 10min, and the pH was adjusted to 10.5 using NaOH solution, alkaline protease was added for enzymatic treatment, and the enzyme was inactivated using a boiling water bath after enzymatic treatment, and the solution was cooled down and then HCl solution was added to adjust the pH to 7.0, and finally the solution was centrifuged at 12,000 g for 10 min under the condition of 25 °C, and the supernatant was lyophilised to get the pork bone collagen peptides, so as toexplore the anti-inflammatory activity of pig bone collagen peptide. Ultrasound-assisted extraction method can obtain high-quality collagen peptides with enhanced thermal stability and antioxidant properties to a certain extent, as well as the traditional enzyme extraction method [99]. The difference with the traditional enzyme extraction method is that it can improve the enzymatic efficiency, effectively shorten the extraction time, reduce the contamination, and the operation is simple and cost-effective. The peptide yield of collagen peptides often depends on the time and frequency of ultrasound, high-frequency and high-power ultrasonic treatment can effectively shorten the extraction time and increase the yield, but the larger ultrasonic frequency will affect the stability of the collagen structure, and even the structure of the enzyme, so that the enzyme loses its activity, etc.. Therefore, in the industrial production of low-frequency and high-power ultrasonic extraction of collagen peptides is often aided by the use of low-frequency and high-power ultrasonic extraction of collagen peptides, a certain frequency and time of ultrasonic treatment will increase the enzymatic efficiency. A certain frequency and time of ultrasonic treatment will increase the activity of the enzyme, improve the efficiency of enzymatic digestion.

Compound extraction method. Compound extraction method refers to the random combination of two or more different extraction methods to overcome the limitations and hazards of a single extraction method, which greatly improves the extraction rate of collagen peptides and maintains the stability of peptide structure and function. Usually the enzymatic extraction method is mixed with acid extraction, alkaline extraction, hot water extraction and other methods [100].

(1) Acidase compound extraction: Acid-enzyme complex extraction method refers to the hydrolysis of collagen using an acidic solution as a medium and the use of enzymes to destroy the structure of collagen to obtain collagen peptides [101]. Zamorano-Apodaca et al. conducted a study to explore the biofunctional properties of collagen peptides derived from the by-products of processing different fish mixtures [102]. In this study, an acetic acid solution was selected as the extraction medium, and papain was used as the extraction enzyme. The collagen peptides were extracted using an acid-enzyme complex extraction method for subsequent experiments. Compared to the simple acid extraction method, this approach increased the extraction rate of collagen peptides, employed milder reaction conditions, reduced environmental pollution, and improved reaction speed, thereby saving time and costs. Most importantly, the collagen peptide structure remained relatively intact, and the resulting peptides had higher purity. Furthermore, the extraction efficiency was higher compared to other methods, making the extracted peptides suitable for the development of new drugs, health products, and beverages, offering promising prospects for future applications.

(2) Alkali thermal complex enzyme extraction method: Alkaline-thermal composite enzyme extraction method means that the raw materials are first soaked and treated with alkaline reagent, and then heat-treated after cleaning, and then enzymatically digested with composite enzyme, so as to obtain the required collagen peptide. After the raw materials are soaked in alkaline reagent, the excess oil and protein can be removed, and the concentration of collagen increases; after heat treatment, the structure becomes looser, and part of collagen will be dissolved first, meanwhile, the enzyme preparation can play a better role, and the enzymolysis efficiency improves, so as to increase the rate of peptide yield. Single enzymatic digestion can only be carried out from a few specific amino acid sites, while the enzyme extraction method is a mixture of different enzyme preparations, thus increasing the number of cleavage sites, multi-directional enzymatic cleavage of raw materials, the synergistic effect between the various enzymes, to improve the hydrolysis degree of collagen and peptide extraction efficiency.

Physiologic function

Based on the special structure, collagen peptides have unique bioactivities such as biocompatibility, haemostasis, plasticity, functionality, etc., and some of these bioactivities have been verified by in vivo animal models and even human clinical trials. Collagen peptides have a variety of physiological functions, including prevention and treatment of osteoporosis, facilitating the formation of collagen in the skin, beauty and anti-aging, improving immunity [103], antiulcer, treatment of rheumatoid arthritis, lowering blood pressure [104], regulating endocrine balance, promoting wound healing, enhancing the stability of the collagen structure of the bone, promoting bone healing [105], promoting the absorption of calcium and other minerals, promoting the growth of hair, anti-thrombosis, and promoting the growth of hair.hair growth, antithrombotic [106], antioxidant [107], antibacterial [108], anti-allergic, anti-fatigue [109], alleviate hypercholesterolemia, inhibit atherosclerosis [110], protect the gastric mucous membrane, reduce uric acid content in the kidneys [111], and reduce fat [112]. With the continuous development and progress of science and technology, the research on collagen peptides is becoming more and more in-depth, so that its application can be further expanded to better meet the needs of the market or clinical diagnosis.

Application

Collagen peptides are a kind of natural proteins, compared with other natural proteins containing special hydroxyproline and hydroxylysine, tertiary helical structure is easier to be enzymatically cleaved, lower molecular weight, strong antioxidant and good water solubility is easier to be absorbed by the human body to play its biological functions, superior cellular regulation and immune function and other characteristics [113], so that collagen peptides have been in many fields ofwide range of applications (Figure 3).

Table 4 Common microbial species and their proteases produced by fermentation

Microbial species	Protease produced by fermentation
Mould	Acid protease
Saccharomyces	Acid protease
Bacillus	Thermoprotease
Bacillus licheniformis	Alkaline protease

Figure 3 Application of the collagen peptide

Medical industry

With the rapid development of economy and science and technology, people's demand for health is getting higher and higher, health care consciousness is getting stronger and stronger, collagen peptide has a wide range of applications in medical treatment due to its unique structural characteristics. For example, the relatively small molecular weight of collagen peptide from giant salamander, which is easy to be absorbed by the human body and at the same time enhances a certain degree of antioxidant properties, has a wide range of applications in health care products [114]; collagen peptide extracted from earthworms and tilapia fish skin has a good antiplatelet activity, and it can replace the related medications in preventing thrombosis and wound healing [115–117]; collagen peptide extracted from yak, tilapia and cod can promote bone cell mineralisation, and can also promote bone mineralisation in bone cells, and can help to improve bone health. Collagen peptides can promote bone cell mineralisation, improve intestinal health, and alleviate acute gastric ulcers [118–120]. Collagen peptides offer several health benefits, including the improvement of liver health, reduction of liver damage, and inhibition of colitis progression [121]. Low-molecular-weight collagen peptides have been shown to alleviate inflammation associated with osteoarthritis and exhibit anti-inflammatory effects [122]. Additionally, specific collagen peptides derived from animal sources can enhance muscle mass in athletes, regulate uric acid levels without imposing additional stress on the kidneys, and mitigate fatigue resulting from overexertion [123, 124]. Furthermore, collagen peptides possess anti-hair loss properties and can be formulated into oral liquid products [125]. Their application in nutritional supplements not only alleviates symptoms in patients with chronic pain [126] but also contributes to an improved psychological state, fostering a more positive outlook on life. Studies also suggest that collagen peptides may reduce cancer incidence [127], promote wound healing [128], accelerate bone healing [129], and enhance mineral absorption [130]. Consequently, the inclusion of collagen peptides in pharmaceuticals, health products, and functional beverages presents promising development opportunities.

Food industry

As people's living standards improve, factors such as taste, color, and nutritional value are becoming increasingly important alongside basic satiety. Collagen peptides contain essential nutrients, including calcium, phosphorus, and various trace elements, which are easily absorbed by the body. Primarily used as food additives in the food industry, collagen peptides enhance flavor, color, and nutritional value, while also extending shelf life [131, 132]. Research by Seda Ersus Bilek et al. demonstrated that hydrolyzed collagen peptides can be utilized to create 100% natural fruit-flavored beverages, increasing protein content and potentially alleviating joint pain, improving skin health, reducing blood clot risk, and mitigating post-exercise fatigue [133]. Additionally, beverages made from tilapia skin collagen peptides co-fermented with pineapple nectar showed benefits for immune protection, skin photo-aging prevention, and intestinal flora improvement [134]. A drink combining collagen peptides and apple juice was found to enhance skin smoothness, firmness, and moisture levels over time, while increasing dermal collagen content [135]. Furthermore, a novel ice-bound collagen peptide derived from pig skin demonstrated high anti-freezing properties, making it suitable for improving ice cream texture and prolonging storage stability at room temperature [136]. New beverages made from tilapia collagen peptides and passion fruit combine vibrant colors, flavors, and nutrients, including vitamins, while bolstering the immune system [137]. Collagen peptides can also enhance the adhesion and water-holding capacity of dairy products [138]. Overall, the versatile applications of collagen peptides in the food industry signal a promising future for new product development.

Skin care industry

Skin, as the largest organ of the human body, and collagen peptide, its main component, play a supportive role in influencing the state of the skin. Subject to external and internal influences, collagen peptide is easy to lose, and its structure is prone to change. Oral, injected, or topical applications can improve the state of the skin and can be developed into skincare products with corresponding effects [139]. Fish-derived collagen peptides combined with ionic liquids can be developed into skincare products with antioxidant properties, which can eliminate hydroxyl radicals produced in the body to help slow down the aging process, alleviate the aging of dermal cells, and improve skin diseases caused by Staphylococcus aureus [140]. Additionally, the combination of certain marine-derived collagen peptides and dissolving microneedles can address the problem of androgenetic alopecia caused by androgenic hormones [141]. Peptides can improve skin photoaging caused by ultraviolet rays, alleviate dullness produced by light radiation, have a certain brightening effect, and improve skin condition [142]. Collagen peptide contains polar amino acids and hydrophilic groups, which can combine with water molecules to increase skin hydration, thus alleviating dryness [143]. Furthermore, collagen peptides can inhibit the tyrosine kinase that generates melanin, thereby inhibiting melanin production with a whitening effect [144]. Collagen peptide from tilapia skin has anti-inflammatory and bactericidal effects, which can treat mouth ulcers and improve scalp and skin health [145]. Collagen peptides can be added in appropriate amounts to skincare products to enhance skin condition [146]. They can also be utilized in the medical aesthetic industry, with effects such as scar removal and anti-wrinkle properties [147], among others.

Materials industry

The collagen peptide structure is better compared to other proteins in terms of stability, ductility, and hydrophilicity, which can be used in the material development industry to develop new materials [148]. Collagen peptides are non-toxic natural proteins, which can be developed into certain materials for application in the medical and aesthetic industry, such as the production of facial mask diaphragms [149]. Collagen peptides in composites can reduce the stability of composites and improve their hydrophilicity [150]. Sturgeon skin collagen peptides can inhibit the denaturation of related proteins, and collagen peptides can be added to the preparation of shrimp paste to prolong the preservation time [151]. Collagen peptides based on the development of hydrogels can be made into wound dressings, which not only help with wound healing but also possess certain antimicrobial effects to prevent fungal and bacterial infections [152–154]. Salmon collagen peptides can be developed as a new cryoprotectant for protein storage, which maintains the structural stability of proteins and reduces oxidative damage [155]. The use of tilapia collagen peptides can enhance the effectiveness of blood microcapsules compared to other materials [156]. The collagen peptide has superior degradability, which can be used to develop food packaging bags that delay food spoilage and replace plastic bags to protect the ecological environment [157–160]. Collagen peptide can be added to silicone rubber to prepare collagen peptide/silicone rubber composites, which can control structural stability, strengthen the hardness of the composite material, and delay the vulcanization of the composite material [161]. Additionally, collagen peptides can be used to make bone regeneration scaffolds [162], inks [163], 3D scaffolds [164], and more.

Conclusion

As a natural product with various biological activities, collagen peptide has made remarkable progress in its extraction and application research in recent years. With the rapid development of science and technology, economy and the gradual enhancement of people's awareness of health, the prospect of its research and application is full of expectations. The main raw material of collagen peptide has gradually shifted from terrestrial organisms to aquatic organisms with higher safety, including fresh fish skin, fish scales, pig skin, etc. After enzymatic or chemical hydrolysis and other methods, it is decomposed into small molecule peptide segments, and then after the process of refining, separating, concentrating, sterilising and drying, collagen peptide products are produced. At present, the most commonly used methods for extracting collagen peptides are: chemical extraction, enzyme extraction, composite extraction, etc. However, the extraction efficiency and purity of these methods have certain limitations, so in the subsequent research we have to choose a reasonable method to improve the extraction efficiency and purity of collagen peptides as much as possible. Collagen peptides have a variety of physiological functions, including antioxidant, anti-tumour, anti-aging, blood pressure-lowering and other properties, and for their special physiological functions and biological activities, we have used them in a wide range of applications in the materials, food, medical and skin care industries. In the material industry, collagen peptide is used in the production of materials such as mask film cloth and wound auxiliary materials to increase the stability and hydrophilicity of the materials. In the food industry, collagen peptide can be used as functional food additives, develop new types of beverages, etc. to enhance the taste and nutritional value of food. In the medical industry, collagen peptide can be used as raw material to be added into medicines, to exert its anti-inflammatory, antioxidant, cholesterol lowering, improve immunity and other health functions.In the skin care industry, collagen peptide is widely used in skin care products to exert its moisturising and anti-aging properties, improve skin elasticity, gloss and moisture, and reduce the appearance of wrinkles and fine lines.

For the future research and development of collagen, we should be committed to exploring new collagen extraction methods, improving the extraction efficiency, purity and safety of collagen peptides, removing the fishy smell of collagen peptides extracted from fish by-products, solving the allergy phenomenon of some human beings to collagen peptide-related products, clarifying the mechanism of the functioning of collagen peptides in the human body, reducing theenvironmental pollution, set up a relevant system to solve the ethical problem of using animals to develop products, and explore how the development and research process of collagen peptides can be combined with advanced Internet technology to expand the application scope of collagen peptides. With the solution of related problems, more and more collagen peptide products will appear in the market and play more and more important roles in people's lives, bringing great social impact and economic benefits.

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