Extraction, Isolation and Characterization of Collagen Peptide from Fish and Recent Biological Activities of the Collagen Peptides

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Abstract:
Particularly in the form of collagen peptides, collagen, an important structural protein present in many animal tissues, has drawn much interest for its possible health advantages. In this study, we look at the methods for isolating, characterizing, and extracting collagen peptides from fish sources. Due to its great availability and sustainability, fish collagen is a possible replacement for conventional collagen sources. Fish collagen peptides must be extracted using a number of processes, including demineralization, deproteinization, and acid or enzymatic treatment. These procedures are necessary to produce collagen that is very pure and bioactive. For characterizing isolated collagen peptides, methods including SDS-PAGE, FTIR spectroscopy, and amino acid analysis are frequently used to evaluate their quality and make-up. The subject of contemporary research has been the biological functions of collagen peptides generated from fish. These peptides have demonstrated a range of health-promoting qualities, including as antioxidant, anti-inflammatory, and anti-aging activities. They have also shown promise in boosting joint health, skin health, and wound healing. Fish collagen peptides are useful additives in medications, cosmetics, and nutritional supplements due to their bioavailability and bioactivity. Additionally, new research has demonstrated the potential of fish collagen peptides to improve gastrointestinal, bone, and cardiovascular health. These results indicate that fish collagen peptides have several uses in the nutraceutical and functional food industries.

Keywords: Collagen, Acid Soluble Collagen (ASC), Pepsin Soluble Collagen (PSC), Extraction method.

Introduction:
The most prevalent protein in an animal's body is collagen. The Greek word "kola" meaning glue is where the term "collagen" originates. About 30% of the total protein in animal bodies is made up of collagen. The majority of collagens come from terrestrial animals, usually from the skin or bones of bovine and porcine animals. But it's also possible to extract collagen from the skin, bone, scales, and fins of creatures with marine origins (Jose *et al.*, 2014). Collagen is a vital protein that is present in large amounts in the bodies of both humans and animals. All connective tissues, including skin, bones, tendons, ligaments, and cartilage, rely on it as their primary structural element. Collagen plays a pivotal role due to its unique characteristics, serving as a fundamental component that provides crucial support, strength, and flexibility. This multifaceted attribute makes collagen indispensable across various sectors. Due to collagen's capacity to improve skin health and lessen indications of aging, it is widely employed in the cosmetics and skincare industries. It lessens the visibility of wrinkles and fine lines by maintaining the skin's suppleness, moisture, and firmness. For better skin texture and look, collagen is frequently included to creams, serums, masks, and other skincare products (Choi *et al.*, 2014). The food and beverage sector uses collagen as a functional component. Protein bars, drinks, and supplements employ it; it is taken from animal sources like fish, poultry, or beef. Collagen is thought to boost joint health, improve skin texture, and advance general wellbeing since it includes necessary amino acids(*Oral Administration of 14C Labeled Gelatin Hydrolysate Leads to an Accumulation of Radioactivity in Cartilage of Mice (C57/BL) - ScienceDirect*, no date) . Collagen is used in tissue engineering and regenerative medicine in the biomedical and pharmaceutical fields. It is the perfect scaffold for tissue repair and regeneration due to its bioactivity and biocompatibility. Wound dressings, skin fillers, bone transplants, and other medical equipment all employ collagen-based products(Bellis, 2011). In the textile business, collagen fibres are used to make textiles with distinctive qualities including moisture absorption, toughness, and antibacterial features. Sportswear, medical textiles, and cosmetic clothing all use these collagen-based fabrics(Cavallaro, Kemp and Kraus, 1994). Collagen has been a component in photographic film manufacturing in the entertainment sector. In the past, photographic films have been coated with gelatine made from collagen to create a light-sensitive emulsion that records pictures (Shi *et al.*, 2009). Due to their potentially beneficial health effects and adaptable qualities, collagen peptides have become more important in functional foods, nutraceuticals, and biomedical applications. Here are some crucial details emphasizing the significance of collagen peptides in various sectors.

Bioactive peptides, such as certain amino acid sequences that have been linked to a number of health advantages, are abundant in collagen peptides. They are known to boost bone density, support joint function, support skin health, and help the maintenance of healthy hair and nails. Collagen peptides are consequently utilized more frequently as useful components in food items and nutraceutical supplements (*The effect of oral collagen peptide supplementation on skin moisture and the dermal collagen network: evidence from an ex vivo model and randomized, placebo-controlled clinical trials - Asserin - 2015 - Journal of Cosmetic Dermatology - Wiley Online Library*, no date, p. 2015). In several biomedical domains, collagen peptides have found use, notably in tissue engineering and regenerative medicine. They promote wound healing and regeneration by acting as superior scaffolds for cell development and tissue restoration. Drug delivery methods, tissue grafts, and wound dressings all employ collagen-based biomaterials (Wahid *et al.*, 2018). Certain amino acids included in collagen peptides are advantageous for digestion and intestinal health. It has been demonstrated that glycine, in particular, supports the gut lining, assisting in the healing of damaged tissues and enhancing gut barrier function. Because of this, collagen peptides are an important component in improving digestive health (Nieuwdorp *et al.*, 2014). Due to its capacity to enhance skin suppleness, moisture, and minimize the appearance of wrinkles, collagen peptides have become more popular in the cosmetic and skincare industries. Collagen peptides promote the production of collagen in the skin, which helps to keep the skin looking young and beautiful (Aguilar-Toalá *et al.*, 2019). Due to their high availability, eco-friendly manufacturing, and possible health advantages, collagen peptides generated from fish have drawn interest as a sustainable and plentiful source. The relevance of collagen peptides obtained from fish as a sustainable resource is summarized below. Fish by-products including skin, scales, and bones—which are frequently thrown during fish processing—are used to make fish collagen. Fish collagen helps to reduce waste and encourages a more sustainable approach to the fishing industry by using these byproducts(Venkatesan *et al.*, 2017). Fish collagen peptides are more accessible and quickly absorbed by the human body than collagen from other sources due to their lower molecular weight. The body can effectively absorb the necessary amino acids found in fish collagen peptides thanks to this improved bioavailability(Nagai and Suzuki, 2000). Fish-derived collagen peptides have been linked to several health advantages, including as better bone density, joint mobility, and skin health. Fish collagen peptides have been demonstrated in studies to improve skin suppleness, hydration, and wrinkle reduction when consumed regularly (Subhan *et al.*, 2021). Fish-derived collagen peptides are acceptable for a wider variety of people, including those with dietary restrictions or allergies, as they are thought to be non-allergenic and safe for eating. Fish collagen peptides are less likely to result in adverse responses than certain other collagen sources (Rezvani Ghomi *et al.*, 2021). Fish collagen peptides are commonly used as a functional component in many food and beverage items, including protein bars, drinks, and supplements. Furthermore, they discover uses for regenerative medicine, tissue engineering, and dressings for wounds in the beauty and biomedical sectors (Mahboob, 2015).

Extraction and Isolation of Collagen Peptides from Fish:

The extraction and isolation of collagen peptides from fish have garnered significant attention due to the versatile applications of these bioactive compounds across various industries. Fish collagen, primarily sourced from fish skin and scales, offers a sustainable and valuable alternative to other collagen sources, with potential benefits in food, pharmaceuticals, cosmetics, and biomaterials(Coppola *et al.*, 2020).

There are several methods for extracting collagen from fish, each tailored to optimize the yield and quality of collagen peptides: Following are the most used methods for the extraction of collagen from the fish (Figure 1).

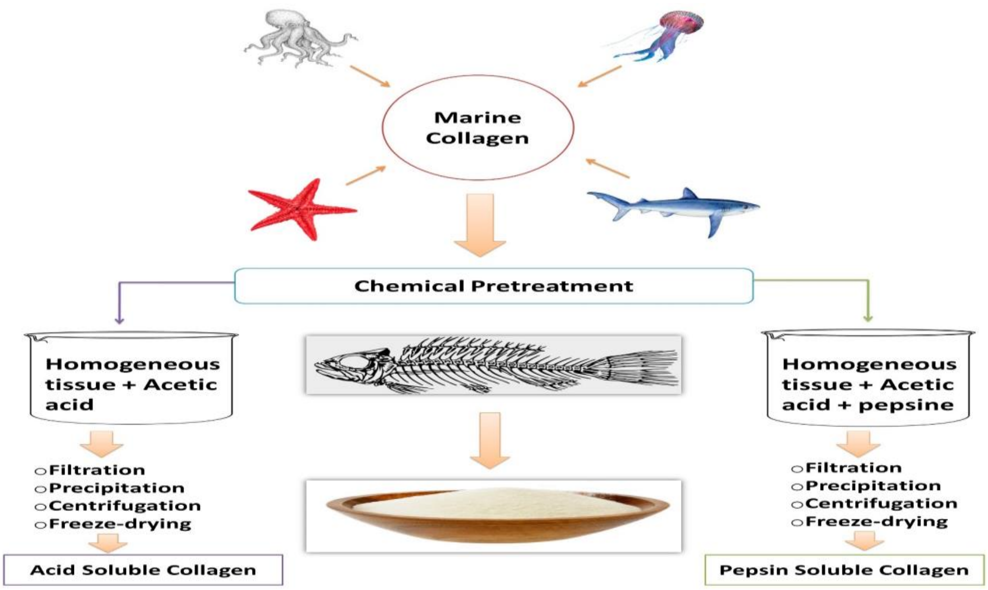

Figure 1: Methods for the extraction of collagen from the fish

In acid extraction Method technique, collagen is extracted from the fish tissues by dissolving them in acidic solutions. To dissolve the non-collagenous proteins, the fish skin or scales are normally washed, diced, and then treated with an acidic solution (such as acetic acid or hydrochloric acid). The final processing processes include filtering and other measures to clean up the produced collagen solution. This technique solubilizes collagen by treating the source material (such as fish skin, bones, or mammalian tissues) with acidic solutions like acetic acid or hydrochloric acid. Collagen from fish skin and scales is frequently extracted using acid(Nagai and Suzuki, 2000; Ranasinghe *et al.*, 2022) .In enzymatic extraction comparing's to acid extraction, enzyme extraction is a gentler technique. It entails the breakdown of non-collagenous proteins using enzymes called proteolytic enzymes like pepsin or trypsin, leaving the collagen intact. The collagen is isolated and purified following the digestion by enzymes of the fish tissues, which have been immersed in an enzyme solution (van Oort, 2009). This Alkaline extraction technique involves treating fish scales or skin with an alkaline solution (e.g., sodium hydroxide) to dissolve collagen and remove non-collagenous materials. The collagen fibrils enlarge during the alkaline treatment, which makes it simpler to remove. After being neutralized, the collagen solution undergoes additional purification steps (Gómez-Guillén *et al.*, 2011). High Pressure Processing at high hydrostatic pressure comprises putting the fish tissues to this type of processing. The collagen becomes solubilized under pressure, making it easier to remove from the fish. This procedure is renowned for retaining collagen's functioning and natural structure (Nazeer *et al.*, 2011). Fish tissues are frozen and then thawed repeatedly in the freeze-thaw extraction technique. The repeated freeze-thaw cycles aid in rupturing the fish's cell walls and releasing the collagen. The collagen solution is purified and concentrated after extraction (Wang *et al.*, 2008). Using a process called ultrafiltration; chemicals are separated according to their molecular sizes. The collagen solution can undergo ultrafiltration after an initial extraction to help concentrate and purify the collagen by eliminating smaller particles and contaminants(Alves *et al.*, 2017). Collagen from fish scales and bones may be extracted using chelating chemicals, such as EDTA (ethylenediaminetetraacetic acid). To solubilize and extract the collagen, the chelating agents aid to remove the calcium salts that are present in the fish tissues (Alemán *et al.*, 2011). It can be difficult to maximize collagen extraction yields since they rely on a number of variables, including the source material, extraction technique, and processing conditions. Researchers are always coming up with solutions to these problems and increasing the effectiveness of extraction(Coppola *et al.*, 2020). The following are some typical issues and solutions for raising collagen extraction yields: The amount and properties of collagen might vary between sources, for example different fish species or tissues from mammals. The extraction yield may be affected by this fluctuation. Collagen extraction can be challenging due to cross-linkages that prevent the solubilization of the collagen Fibers. In the extraction process, temperature, pH, and other environmental factors may have an impact on the yield and solubility of collagen(*Effect of extraction time on the physico-chemical characteristics of collagen from sin croaker (Johniecop sina) waste - ProQuest*, no date). The purity and output of collagen extraction can be impacted by the presence of non-collagenous proteins, lipids, and minerals in the source material. The effectiveness of extraction can be increased by carefully choosing the source material based on the features and collagen content (J. Wang *et al.*, 2018). Impure substances and cross-links in the raw material can be removed during pretreatment to improve collagen solubilization (See *et al.*, 2015). The amount of collagen produced may be greatly affected by adjusting the extraction parameters, including pH, temperature, and time (Abdelaal, 2021). The effectiveness of collagen extraction can be increased by selecting the right enzymes and their concentrations for enzymatic hydrolysis (Venkatesan *et al.*, 2017). Combining diverse extraction techniques can result in larger yields and better collagen characteristics(Silvipriya *et al.*, 2015). Creating scalable extraction methods can provide reliable, ample production of collagen with optimal yields(Ranasinghe *et al.*, 2022). Identifying Fish Collagen Peptides Three polypeptide chains, also referred to as alpha chains, make up collagen. These chains are twisted into a triple helical shape. A series of amino acids, predominantly glycine, proline, and hydroxyproline, make up each alpha chain. The hydrogen bonds formed between the amino acid residues help to sustain the creation of the triple helix (Bella *et al.*, 1994). Collagen peptides are smaller pieces of collagen that are generally produced by denaturation procedures or enzymatic hydrolysis of collagen. Collagen peptides lack the triple-helical structure found in whole collagen molecules because of their reduced size (Rajabimashhadi *et al.*, 2023). Collagen's triple helix features a distinctive helical repetition of around 2.9 nm, with roughly 10 amino acid residues each turn. Additionally, the molecules of collagen supercoil, creating a recognizable banding pattern known as the "D-periodicity"(Bella, Brodsky and Berman, 1995). Collagen's distinctive stability is attributed to hydroxyproline, a modified form of proline. Collagen's resistance to heat denaturation is increased by the creation of hydrogen bonds by hydroxyproline residues (Shoulders and Raines, 2009). Collagen triple helices must be folded and assembled in order to produce collagen fibrils, which are the building blocks of connective tissues. Collagen fibrils are distinguished by their parallel alignment and orderly packing (Kadler *et al.*, 2007). Collagen peptides still have bioactive qualities that support bone density, joint health, and the health of the skin. Their bioactivity is ascribed to the existence of certain amino acid combinations, such glycine-proline-hydroxyproline, which are essential to produce collagen and the preservation of connective tissue (Asserin *et al.*, 2015a). Collagen and collagen-like peptides' atomic-level 3-D structures can be discovered using the potent technique of X-ray crystallography. Collagen molecules are crystallized in this process, and once the crystal is exposed to X-rays, diffraction patterns are produced, from which the molecular structure may be deduced (Bella *et al.*, 1994). The local conformation and dynamics of collagen molecules in solution are revealed by NMR spectroscopy. Researchers can learn more about collagen's secondary structure and hydrogen-bonding patterns by examining its NMR spectra (Goldberga, Li and Duer, 2018). Collagen and collagen peptide secondary structures are frequently investigated using CD spectroscopy. It determines the helical composition of chiral compounds by measuring the differential absorption of left- and right-circularly polarized light by those molecules (Brodsky and Persikov, 2005). Collagen molecules' modes of vibration are examined using FTIR spectroscopy, which reveals information on the existence of certain functional groups and the secondary structure (Belbachir *et al.*, 2009). The collagen structure in the original tissue, where the collagen molecules are not fully hydrated, is investigated using solid-state NMR spectroscopy (Huster, 2008).

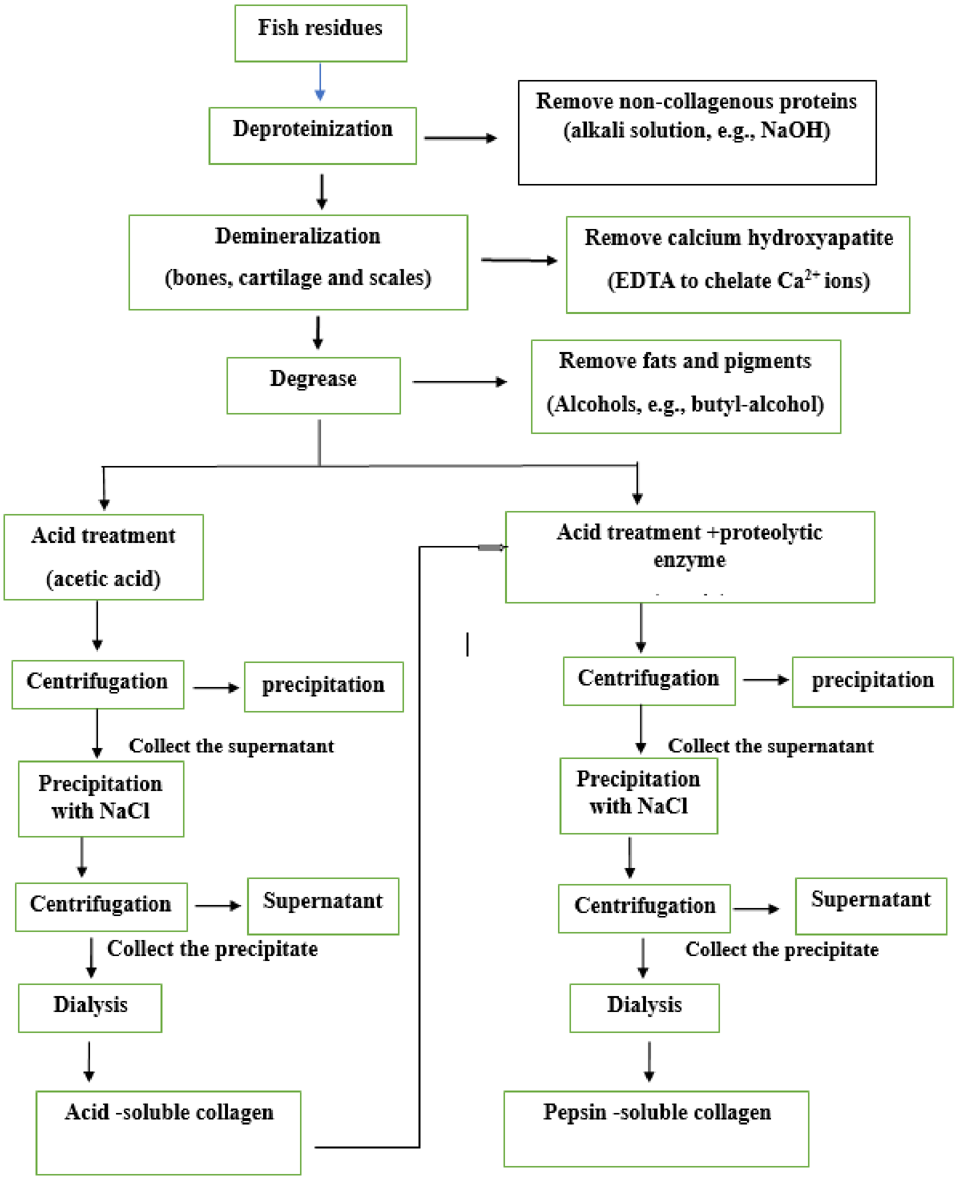

Figure 2: Methods for the extraction of ASC and PSC

Molecular Weight Determination:

Gel Permeation Chromatography (GPC) or Size Exclusion Chromatography (SEC): GPC/SEC is a chromatographic technique used to separate collagen peptides based on their molecular size. It provides information about the molecular weight distribution of collagen peptides (Gores, Radke and Held, 2021). The use of mass spectrometry using matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF MS): Collagen peptides' molecular weight may be determined using the mass spectrometry method known as MALDI-TOF MS. It offers precise measurements of mass for characterisation and identification (Karas and Hillenkamp, 2002). Each of the amino acids that occur in peptides of collagen are separated and quantified using high-performance liquid chromatography (HPLC). It offers details on the different types and proportional amounts of amino acids that are present (Abbas, Shakir and Walsh, 2022). This technique separates amino acids according to their charge and is used to analyse the composition of amino acids (Spackman, Stein and Moore, 2002). After hydrolysing collagen peptides, amino acid analysis is performed using GC-MS. It offers precise identification and measurement of amino acids(Larder *et al.*, 2022). Collagen's peptide sequences may be identified using the potent method of mass spectrometry. Collagen peptides are ionized and broken up, and the resultant mass spectra reveal the order of the amino acids (Ramirez *et al.*, 2007). Collagen peptides may be found in complicated mixtures using proteomics techniques, such as liquid chromatography-tandem mass spectrometry (LC-

MS/MS). The collagen modifications after translation and sequence are thoroughly explained by this method (Olsen, Ong and Mann, 2004). N-terminal sequencing is a technique for determining the amino acid composition of collagen peptides' N-terminal end. It sheds light on collagen's fundamental composition(Edman and Begg, 1967). To look for recognized collagen sequences and domains, you can utilize bioinformatics instruments and sequence databases like Uniports and NCBI. These sites offer insightful knowledge on the composition and use of collagen. Collagen peptides' secondary structures and helical composition may be examined using circular dichroism (CD) spectroscopy, revealing information about their structural domains (Ricard-Blum, 2011).

The three-dimensional arrangement of collagen domains has been clarified using sophisticated structural methods including X-ray crystallography, NMR spectroscopy, and electron microscopy (Bella, Brodsky and Berman, 1995). Quality of collagen is essential for bio compatibility and reducing the danger of negative responses when working with living tissues in biomedical and therapeutic applications including tissue engineering and wound healing (Rezvani Ghomi *et al.*, 2021). The improved tensile durability and adaptability of highly pure collagen make it appropriate for use in a variety of technical applications (Zhu *et al.*, 2022). Pure collagen maintains its natural bioactivity, which includes encouraging cell adhesion, proliferation, and the creation of extracellular matrix, all of which are essential for regeneration of tissue and repair (Asserin *et al.*, 2015a). Highly purified collagen reduces the risk of inducing an immune response, making it suitable for medical applications and reducing the chance of rejection (Ulery, Nair and Laurencin, 2011). Purification management maintains uniform quality for collagen preparations throughout batches, improving the repeatability of production and research procedures (Olsen *et al.*, 2003). The biological functions and mechanical characteristics of collagen can be impacted by residual non-collagenous proteins (Embery *et al.*, 2001). Lipid contamination may have an impact on the stability and solubility of collagen (Orgel *et al.*, 2006). Acids and alkalis, which were utilized in the extraction process, are possible contaminants that should be kept to a minimum in collagen preparations (Sampath Kumar, Nazeer and Jaiganesh, 2012).

Biological Activities of Fish Collagen Peptides:

Fish peptides made from collagen have been demonstrated to support skin hydration, firmness, and elasticity, which improves skin health and lessens the visibility of wrinkles (Evans *et al.*, 2021). By encouraging regeneration of cartilage and easing joint pain, fish collagen peptides are being demonstrated to enhance joint health(Benito-Ruiz *et al.*, 2009). Fish-derived collagen peptides may be advantageous for maintaining bone health and preventing osteoporosis since studies have shown that they increase bone density and boost the absorption of calcium (König *et al.*, 2018). By encouraging cell growth and collagen production, fish collagen peptides have been shown to hasten regeneration of tissue and healing from wounds(Raveendran *et al.*, 2017). Antioxidants and anti-inflammatory characteristics of fish collagen peptides may help explain why they are protective against oxidative stress and inflammation-related diseases (Karim and Bhat, 2009). Fish collagen peptides are being researched for their possible advantages on digestive health, including improving digestive health and boosting the function of the intestinal barrier (Jafari *et al.*, 2020). It has been demonstrated that the antioxidant abilities and radical-scavenging properties of fish collagen peptides are responsible for their potential health benefits (Nasri, 2019). Here are several research that emphasize the fish collagen peptides' beneficial antioxidant properties. Using the technique of electron spin resonance spectroscopy, this study assessed the antioxidant properties of fish-based protein hydrolysates, including collagen peptides. The outcomes showed that these peptides are capable of scavenging free radicals (Peng, Xiong and Kong, 2009). Collagen was recovered from fish waste materials in this study, and it was discovered to have antioxidant effects as a result of the presence of certain amino acids with anti-radical characteristics (Nagai and Suzuki, 2000). The bioactive substances produced from marine processes byproducts are highlighted in this study, particularly fish-derived collagen peptides with antioxidants and radical-scavenging properties (Kim and Mendis, 2006). This study proved the antioxidant activity potential of different substances, especially peptides of collagen from fish, and their ability to scavenge free radicals (Harnedy and Fitzgerald, 2013). This study proved the antioxidant activity potential of different substances, including peptides of collagen from fish, and the ability to scavenge free radicals (Karim and Bhat, 2009). This research showed that tilapia scale fish collagen peptides have anti-inflammatory properties via blocking the MAPK and NF-B signalling pathways in LPS-induced macrophages(Shang *et al.*, 2021). This study demonstrated that fish collagen hydrolysis products modulated the toll-like receptor 4 signalling pathway to decrease the production of genes that are pro-inflammatory in lipopolysaccharide-stimulated macrophages (Kemp and Kwon, 2021). The results of this study showed that feeding weaned pigs' protein-polysaccharide complex from black soldier fly larvae, which contain collagen peptides, altered the microbiota of the gut and enhanced nutritional absorption (Abachi *et al.*, 2023). This study demonstrated that fish peptides made from collagen prevented preadipocytes from differentiating into adipocytes and reduced obesity in mice fed a high-fat diet, indicating possible anti-inflammatory properties (Sheng *et al.*, 2023). Through the stimulation of the pathway mediated by PI3K/AKT, this study showed that fish peptides made from collagen encouraged the proliferation and differentiation of MC3T3-E1 cells, which are pre-osteoblasts involved in bone formation. Through the stimulation of the PI3K/AKT signalling pathway, this study showed that fish collagen peptides encouraged the growth and development of MC3T3-E1 cells, which are pre-osteoblasts responsible for bone formation (Jana *et al.*, 2024). This study demonstrated that peptides made from collagen shielded PC12 cells against apoptosis caused by oxidative stress and dysfunction of the mitochondria, suggesting potential advantages for skin health (Chotphruethipong *et al.*, 2021). By controlling the TGF-/Smad and MAPK pathways of signaling and shielding the skin from damaging UV radiation, this study showed that fish peptides containing collagen prevented UVB-induced premature aging of the skin (Fu *et al.*, 2022). According to this study, peptides made from collagen from Oreochromis aureus fish scales had beneficial effects on fibroblast and HaCaT cells, two types of cells crucial for healing wounds and regenerating skin (Hou *et al.*, 2020). In the present study, tilapia skin collagen peptides on the healing of wounds in rats were investigated. It was found that the peptides aided in repair of tissues and healing (Hu *et al.*, 2017). The primary protein in connective tissues' extracellular matrix, which is found including those of joints and bones, is collagen. The majority of the collagen in cartilage, which wraps the ends of bones in joints and offers flexibility and cushioning, is type II collagen. Collagen peptides taken orally have been demonstrated to promote the body's natural production of collagen, particularly collagen of type II, which is found in joint cartilage. This might assist and preserve joint health (Benito-Ruiz *et al.*, 2009). Peptides made from collagen are promising natural options for promoting joint health since they have been linked to a decrease in joint pain (Oesser *et al.*, 1999). Collagen peptide supplement has been found in studies to increase the density of bones and maintain bone health in postmenopausal women (König *et al.*, 2018). Collagen peptides have been investigated for their potential to promote bone regeneration and healing in cases of bone fractures and defects (Kołodziejska, Kaflak and Kolmas, 2020). Collagen peptides are being demonstrated to improve cartilage structure in along with collagen production, which is essential for flexibility in joints and functionality. Collagen peptides are being demonstrated to improve cartilage structure in along with collagen production, which is essential for flexibility in joints and functionality(Shigemura *et al.*, 2009). It is being proposed that peptides made from collagen have an inhibiting impact on the blood pressure-regulating enzyme that converts angiotensin (ACE). Blood arteries may expand as a result of ACE inhibition, which may decrease your blood pressure (Zhao *et al.*, 2017). Collagen peptides can improve endothelial function, which is the condition of the blood vessel's inner lining. Better vasodilation and blood flow control are linked to better function of endothelial cells, which supports the cardiovascular system. Collagen peptides may enhance endothelial function, which is the condition of the blood vessel's inner lining. Better vasodilation and blood flow control are linked to improved endothelial function, which supports the cardiovascular system (Cai *et al.*, 2021). Collagen peptide supplements may improve lipid profiles by lowering total cholesterol and low-density lipoprotein (LDL) cholesterol levels, which are risk factors for cardiovascular disease, according to certain research (Hwang, Park and Lee, 2023). Antioxidant characteristics of peptides made from collagen can aid in preventing oxidative stress and inflammation in blood vessels, promoting cardiovascular health. Antioxidant properties of collagen peptides can aid in preventing inflammatory processes and oxidative stress in blood vessels, promoting cardiovascular fitness (Pérez *et al.*, 2024). The walls of blood vessels require collagen since it provides structural support and integrity. The upkeep and repair of blood vessels, which is essential for heart wellness, may be facilitated by peptides of collagen (Venkatesan *et al.*, 2017). By maintaining the structure of the lining of the intestines, collagen peptides may help to preserve the integrity of the gut barrier. A good gut barrier lowers the risk of inflammation along with other digestive disorders by preventing the flow of toxic chemicals from the intestinal tract into the circulation (Hakuta *et al.*, 2017). Gut Microbiota Modulation Collagen peptides can act as scaffolds in tissue engineering, providing a three-dimensional environment for cell growth and tissue regeneration while delivering bioactive factors (L. Wang *et al.*, 2018). The gastrointestinal comfort and symptoms of digestive discomfort, such as bloating and indigestion, have been linked to peptides made from collagen (Nath *et al.*, 2018). Digestive Enzyme Support the function of the digestive enzymes may be supported by collagen peptides, assisting in the digestion and absorption of nutrients in the gastrointestinal system. The activity of digestive enzymes may be supported by collagen peptides, assisting in the absorption and digestion of nutrients in the gastrointestinal system(Li *et al.*, 2013). Biocompatibility and Biodegradability collagen peptides are derived from natural sources, making them biocompatible with human tissues. They have a low risk of inducing adverse reactions, making them suitable for various drug delivery applications (Lee, Singla and Lee, 2001). Sustained Drug Release it is possible to tailor peptides of collagen to deliver sustained medication release, guaranteeing a managed and lasting therapeutic impact (Furtado *et al.*, 2022). Targeted Drug Delivery functionalized collagen peptides can be designed to target specific tissues or cells, enhancing drug delivery efficiency and reducing off-target effects (An, Lin and Brodsky, 2016). Wound Healing Application in collagen-based drug delivery systems are used for wound healing applications, where the collagen carrier not only delivers therapeutic agents but also aids in tissue regeneration (Wang *et al.*, 2017). Stimulation of Collagen Synthesis collagen type I and type II may be synthesized in the body by oral collagen peptide dietary supplements, according to research. This keeps connective tissues, such as skin, cartilage, tendons, and bones, structurally sound (Oesser *et al.*, 1999). Anti-Oxidant Activity antioxidant capabilities in peptides made from collagen have been discovered to protect cells against oxidative injury and minimize free radical damage (Asserin *et al.*, 2015a). Anti-Inflammatory Effects as a result of collagen peptides' anti-inflammatory properties, which include the suppression of cytokines that are pro-inflammatory and enzymes, inflammation in many tissues may be reduced (Zhang *et al.*, 2024). Collagen peptides have been shown to promote cell proliferation and differentiation in various cell types, contributing to tissue repair and regeneration (Kołodziejska, Kaflak and Kolmas, 2020). The possible immunomodulatory agents effects of collagen peptides, which can affect the body's immunological responses and support the immune system, have been studied (Kim and Mendis, 2006). Peptides of collagen have the ability to connect with certain cell surface receptors and cause a variety of biological reactions, including encouraging cell adhesion, migration, and tissue healing (Elango *et al.*, 2022). When peptides made from collagen connect with integrin receptors that are on a cell's surface, the FAK pathway is activated, which is essential for adhesion to cells and migration (Huang *et al.*, 2022). The phosphatidylinositol 3-kinase (PI3K)/AKT pathway, that is important in encouraging proliferation of cells and differentiation, has been demonstrated to be activated by peptides made from collagen (Chen *et al.*, 2013). Toll-like receptors, also known as TLRs, on immune system cells can interact with collagen peptides, thereby regulating immunological responses and perhaps adding to their immunomodulatory effects (Federico *et al*., 2020). Collagen peptides can modulate immunological responses and perhaps contribute to their immunomodulatory effects by interacting with Toll-like receptors (TLRs) on immune cells (Huang *et al.*, 2022). The MAPK (mitogen-activated protein kinase) pathway may be triggered by peptides made from collagen, which increases collagen production in a variety of cell types (Kim and Mendis, 2006). Peptides made from collagen have been found to interact with the angiotensin-converting enzyme (ACE), which raises the possibility that they may play a part in the renin-angiotensin system's control of blood pressure levels (Zhao *et al.*, 2017). Type I and type II collagen, in specific, has been shown to have their gene expression upregulated by collagen peptides. This action may support collagen production and deposition in a variety of tissues, supporting tissue regeneration and healing (Oesser *et al.*, 1999). Peptides made from collagen have been demonstrated to promote osteoblast and fibroblast development and proliferation in a variety of cell types. These results may help in the regeneration of tissue and repair (Kumada and Zhang, 2010). According to research, collagen peptides can decrease inflammation in a variety of tissues by altering the gene expression of pro-inflammatory cytokines and enzymes (Sivaraman and Shanthi, 2021). Collagen peptides can influence the gene expression of immune-related factors, contributing to their immunomodulatory effects on the immune system (Kim and Mendis, 2006). The process of extracellular matrix remodelling and the balance of tissues may be impacted by collagen peptides' effects on the gene expression of matrix metalloproteinases, or MMPs, and tissue inhibitors of metalloproteinases (TIMPs) (Asserin *et al.*, 2015a). The expression of the genes of growth factors like transformed growth factor-beta (TGF-β), which is essential for tissue repair and healing from wounds, has been shown to be influenced by peptides made from collagen (Finnson *et al.*, 2013). The cells that produce collagen, known as fibroblasts, have been found to be stimulated by collagen peptides either ingested orally or applied topically. This enhanced collagen synthesis causes the ECM to deposit new collagen fibres, encouraging tissue healing and enhancing the structural strength of the tissue (Oesser *et al.*, 1999). It has been discovered that peptides made from collagen have an impact on the expression of genes and activity of tissue inhibitors of metalloproteinases (TIMPs) and matrix metalloproteinases, also known as (MMPs). TIMPs are MMPs' natural inhibitors, whereas MMPs are enzymes that degrade collagen and other ECM components during tissue remodelling. MMP and TIMP activity can be balanced by collagen peptides, ensuring regulated ECM deterioration and repair (Asserin *et al.*, 2015b). Peptides made from collagen have the ability to improve cell adhesion and migration, which encourages the recruitment of cells that are important for tissue healing, such fibroblasts and endothelial cells. Faster regeneration and repair of tissues are facilitated by improved adhesion of cells and migration (Chattopadhyay and Raines, 2014). Peptides made from collagen have the ability to improve cell adhesion and migration, which encourages the recruitment of cells that are important for tissue healing, such fibroblasts and endothelial cells. Faster regeneration and repair of tissues are made possible by improved adhesion of cells and migration (Chattopadhyay and Raines, 2014). Antioxidant and anti-inflammatory characteristics found in collagen peptides assist lower the level of inflammation and oxidative stress and speed up tissue healing procedures (Shang *et al.*, 2021). It has been demonstrated that collagen peptides can increase the creation of collagen by fibroblasts and other collagen-producing cells when taken orally or given topically. Type I and type II collagen, which make up the majority of skin, cartilage, tendons, and bones, are most affected by this action (Oesser *et al.*, 1999). The extracellular matrix (ECM) of tissues is where freshly generated collagen fibers are deposited, and collagen peptides encourage this process. This increased ECM deposition enhances tissue resilience, strength, and organization (Jo, Hwang and Jang, 2021). Matrix metalloproteinases, or MMPs, and tissue inhibitors of metalloproteinases (TIMPs) have their expression of genes and activity regulated by collagen peptides. TIMPs are MMPs' natural inhibitors, whereas MMPs are enzymes that break down collagen and other ECM components during tissue remodeling. The activity of MMPs and TIMPs can be balanced by collagen peptides, ensuring regulated ECM deterioration and repair (Asserin *et al.*, 2015a). It has been demonstrated that peptides made from collagen have anti-catabolic properties on collagen. By lowering the activity of enzymes that break down collagen and protecting the skeletal strength of collagen in the ECM, they can prevent collagen degradation (Yu, Li and Kim, 2011). These peptides can increase collagen fibrillogenic, causing the ECM to produce collagen Fibers that are better ordered and organize. By lowering the activity of enzymes that break down collagen and protecting the skeletal strength of collagen in the ECM, they can prevent collagen degradation (Rodrigues *et al.*, 2023). These peptides can increase collagen fibrillogenic, causing the ECM to produce collagen Fibers that are better ordered and organized (LIU *et al.*, 2009).

Recent Advances in Collagen Peptide Research:

One of the most used techniques for obtaining collagen peptides is hydrolysis by en It entails the breakdown of collagen fibers into smaller peptides using certain enzymes, such as collagenase. To produce greater yields and particular peptide profiles, cutting-edge methods optimize the enzymatic conditions, including temperature, pH, and concentration of the enzyme (Nagai and Suzuki, 2000). Using high-frequency ultrasound waves to extract collagen-rich raw materials is known as ultrasound-assisted extraction. The collagen structure is damaged by this mechanical action, which makes it easier for collagen peptides to be released into the solvent. It has been demonstrated that ultrasound may speed up the extraction procedure and increase the effectiveness of extraction (Lu *et al.*, 2023).It has been demonstrated that ultrasound may speed up the extraction procedure and increase the effectiveness of extraction (Lu *et al.*, 2023). Collagen peptides are extracted from raw materials using supercritical fluid extraction (SFE), which uses supercritical carbon dioxide as the solvent. This technique may be used to extract thermally labile bioactive chemicals and is thought to be ecologically benign. SFE may have benefits in terms of selectivity and little solvent residue left in the finished product (Jafari *et al.*, 2020). In microwave-assisted extraction, the collagen-rich source materials are heated to speed up the extraction process. The method can speed up collagen peptide extraction and increase collagen peptide yield (Song *et al.*, 2017). This novel strategy combines methods for membrane separation with enzymatic hydrolysis. Membrane separation is used to separate and purify the collagen peptides from the enzymatic reaction mixture after enzymatic hydrolysis converts collagen into peptides. The extraction and purification of collagen peptides may be more effective overall thanks to this hybrid approach (Xiong *et al.*, 2009). Collagen peptides can be crosslinked to increase their mechanical strength, stability, and resistance to enzymatic deterioration. This can be accomplished using a variety of techniques, such as physical cross linking using UV irradiation or heat treatment, or chemical crosslinking, which is done using substances like glutaraldehyde or Geni pin (Madaghiele *et al.*, 2014). To generate materials with multiple uses for targeted delivery and tissue engineering applications, peptides of collagen can be bio-conjugated with other bioactive compounds, such as growth factors, peptides, or medications (Lee *et al.*, 2011). To bestow new capabilities, such as antibacterial qualities or controlled release of drugs, peptides made from collagen can be changed to contain nanoparticles, such as nanoparticles of metal or drug-loaded nanoparticles (Girija, Balasubramanian and Cowin, 2022). Immobilization on solid substrates which is for enhance their mechanical characteristics and develop materials appropriate for tissue engineering and regenerative medicine, collagen peptides can be adsorbed onto solid substrates, such as membranes or scaffolds (Klimek and Ginalska, 2020). In order to encourage cell adhesion, tissue integrating, and wound healing, collagen peptides can be employed to form beneficial coatings on surfaces, such as medical implants or wound dressings (Kołodziejska, Kaflak and Kolmas, 2020).The method can speed up collagen peptide extraction and increase collagen peptide yield (Song *et al.*, 2017). This novel strategy combines methods for membrane separation with enzymatic hydrolysis. 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Peptides of collagen may be micro-encapsulated to shield them from the elements, keep them stable, and regulate their release by utilizing methods like freeze drying or spray drying (Suja Rani and Latha, 2024). To increase the transport and penetration of collagen peptides into the skin or other target tissues, liposomes, which are tiny lipid vesicles, can be used to wrap the peptides (Zhong *et al.*, 2023). Peptides of collagen can be incorporated in nano emulsions, improving their bioavailability and stability for use in food items and cosmetic products(McClements, 2012).Peptides of collagen may be micro-encapsulated to shield them from the elements, keep them stable, and regulate their release by utilizing methods like freeze drying or spray drying (Suja Rani and Latha, 2024). To increase the transport and penetration of collagen peptides into the skin or other target tissues, liposomes, which are tiny lipid vesicles, can be used to wrap the peptides (Zhong *et al.*, 2023). Peptides of collagen can be incorporated in nano emulsions, improving their bioavailability and stability for use in food items and cosmetic products(McClements, 2012). Numerous biological uses for collagen peptides have been discovered, including tissue engineering and wound treatments. Due to their special qualities, they can promote numerous biological therapies and encourage tissue regeneration and wound healing. The following are some important biomedical uses for collagen peptides. For the construction of three-dimensional tissue engineering scaffolds, collagen peptides are frequently employed(Lu, Li and Chen, 2013). These scaffolds assist the adhesion, proliferation, and differentiation of cells, promoting tissue regeneration. Scaffolds made of collagen are especially well suited for use in connective tissues including cartilage, skin, cartilage, and bone(Burdick and Vunjak-Novakovic, 2009)**.**For the construction of three-dimensional tissue engineering scaffolds, collagen peptides are frequently employed(Lu, Li and Chen, 2013). These scaffolds assist the adhesion, proliferation, and differentiation of cells, promoting tissue regeneration. Scaffolds made of collagen are especially well suited for use in connective tissues including cartilage, skin, cartilage, and bone(Burdick and Vunjak-Novakovic, 2009)**.** Due to its capacity to facilitate wound healing and tissue repair, collagen peptides are added to wound dressings. Collagen-based dressing contribute to better wound closure and less scarring by promoting cell migration, accelerating the regeneration of tissue, and maintaining an environment that is moist(Parenteau-Bareil, Gauvin and Berthod, 2010). Collagen peptides have haemostatic qualities, which make them important ingredients in haemostatic treatments used to stop bleeding during operations or in cases of serious accidents (Scherer *et al.*, 2008). For a variety of uses, including tissue enhancement, healing wounds, and targeted medication administration, collagen peptides can be created into injectable biomaterials

(Seliktar, 2012). For the purpose of to encourage cartilage and bone healing, collagen peptides have been studied, particularly those originating from certain sources like fish collagen. They can be included in biomaterials for bone transplants and the regeneration of cartilage in joints(Aleman and Martinez-Alvarez, 2013). Collagen peptides can be used as medicinal agents' drug delivery systems, allowing for controlled administration of medications or growth factors at the desired location for better therapeutic results (M and I, 2020).(Parenteau-Bareil, Gauvin and Berthod, 2010). Collagen peptides have haemostatic qualities, which make them important ingredients in haemostatic treatments used to stop bleeding during operations or in cases of serious accidents (Scherer *et al.*, 2008). For a variety of uses, including tissue enhancement, healing wounds, and targeted medication administration, collagen peptides can be created into injectable biomaterials (Seliktar, 2012).For the purpose of to encourage cartilage and bone healing, collagen peptides have been studied, particularly those originating from certain sources like fish collagen. They can be included in biomaterials for bone transplants and the regeneration of cartilage in joints(Aleman and Martinez-Alvarez, 2013). Collagen peptides can be used as medicinal agents' drug delivery systems, allowing for controlled administration of medications or growth factors at the desired location for better therapeutic results (M and I, 2020). Due to its distinctive nutritional and bioactive characteristics, collagen peptides are growing increasingly popular in customized nutrition and functional foods. They provide a wealth of advantages that may be customized to address specific nutritional and health requirements. Here are several applications for collagen peptides in functional meals and individualized nutrition. Collagen peptides are a great source of protein, especially for people who have specialized nutritional needs, including athletes, the elderly, or people on restrictive diets (such vegetarians or vegans). To satisfy certain protein requirements, collagen peptides can be incorporated to customized protein drinks or smoothies (van Vliet, Burd and van Loon, 2015). Collagen peptides can be found in function meals like collagen-fortified snacks or drinks for those who have joint problems or bone health difficulties. These goods may promote bone density and flexibility in joints (McAlindon *et al.*, 2011).To satisfy certain protein requirements, collagen peptides can be incorporated to customized protein drinks or smoothies (van Vliet, Burd and van Loon, 2015). Collagen peptides can be found in function meals like collagen-fortified snacks or drinks for those who have joint problems or bone health difficulties. These goods may promote bone density and flexibility in joints (McAlindon *et al.*, 2011). Because of its advantages for skin health, collagen peptides are frequently employed in customized nutrition. To promote moisture in the skin, elasticity, and general attractiveness, they can be added to functional meals or beauty-enhancing items like collagen-enriched medications or drinks (Asserin *et al.*, 2015a). Improving digestive health through tailored diet, collagen peptides may also be employed. They may be included into functional meals to assist digestive processes and promote a healthy gut flora, such as stomach-friendly meals or probiotic-rich compositions (Chakrabarti, Guha and Majumder, 2018). It has been investigated if collagen peptides can help in weight loss attempts. They can be incorporated into specialized dietary regimens to help with satiety and control of appetite, such as collagen-fortified meal replacement drinks or a low-calorie snack (Hochstenbach-Waelen *et al.*, 2009). Personalized formulations based on dietary requirements and personal preferences might include collagen peptides. Based on variables including age, gender, lifestyle, and health objectives, collagen peptide supplements may be specially designed by companies in the personalized nutrition sector. They may be included into functional meals to assist digestive processes and promote a healthy gut flora, such as stomach-friendly meals or probiotic-rich compositions (Chakrabarti, Guha and Majumder, 2018). It has been investigated if collagen peptides can help in weight loss attempts. They can be incorporated into specialized dietary regimens to help with satiety and control of appetite, such as collagen-fortified meal replacement drinks or a low-calorie snack (Hochstenbach-Waelen *et al.*, 2009). Personalized formulations based on dietary requirements and personal preferences might include collagen peptides. Based on variables including age, gender, lifestyle, and health objectives, collagen peptide supplements may be specially designed by companies in the personalized nutrition sector.

Aspects of Safety and Regulation:

Before being widely used in several applications, such as food, cosmetics, and biomedical items, safety and toxicity evaluation of fish collagen peptides is of utmost relevance. The safety profile of fish collagen peptides has been the subject of several research and the general agreement is that both oral and topical use of these compounds is safe. The safety assessment of fish collagen peptides includes the following major elements. The biocompatibility of fish collagen peptides with human cells and tissues has been well demonstrated. When tested on different cell lines, in vitro tests have shown that they do not cause cytotoxic or unfavourable cellular reactions (Qin *et al.*, 2022). For people who are allergic to fish, collagen from fish peptides may be potentially allergenic. Fish-based collagen peptides, on the other hand, are often made from fish scales or skins, which are less likely to cause allergies than other fish-derived proteins like fish muscle or gelatine. To make sure the finished product complies with safety regulations, manufacturers frequently conduct allergenicity testing (Wan *et al.*, 2023). The oral toxicity of collagen from fish peptides has been examined in several research using animal models. These investigations have often shown no major side effects, even at large dosages, which is suggestive of minimal oral toxicity (Li *et al.*, 2013). Dermal irritation risk has been evaluated for topical application of fish collagen peptides. According to research, fish collagen peptides are non-irritating and secure for topical use (Kalin *et al.*, 2015). Testing for metals and possible pollutants in fish collagen peptides is another aspect of safety evaluations. Strict quality control procedures are used to make sure that the finished product is devoid of any dangerous materials (Cutajar *et al.*, 2022). Before being widely used in several applications, such as food, cosmetics, and biomedical items, safety and toxicity evaluation of fish collagen peptides is of utmost relevance. The safety profile of fish collagen peptides has been the subject of several research, and the general agreement is that both oral and topical use of these compounds is safe. The safety assessment of fish collagen peptides includes the following major elements. The biocompatibility of fish collagen peptides with human cells and tissues has been well demonstrated. When tested on different cell lines, in vitro tests have shown that they do not cause cytotoxic or unfavourable cellular reactions (Qin *et al.*, 2022). For people who are allergic to fish, collagen from fish peptides may be potentially allergenic. Fish-based collagen peptides, on the other hand, are often made from fish scales or skins, which are less likely to cause allergies than other fish-derived proteins like fish muscle or gelatine. To make sure the finished product complies with safety regulations, manufacturers frequently conduct allergenicity testing (Wan *et al.*, 2023). The oral toxicity of collagen from fish peptides has been examined in several research using animal models. These investigations have often shown no major side effects, even at large dosages, which is suggestive of minimal oral toxicity (Li *et al.*, 2013). Dermal irritation risk has been evaluated for topical application of fish collagen peptides. According to research, fish collagen peptides are non-irritating and secure for topical use (Kalin *et al.*, 2015). Testing for metals and possible pollutants in fish collagen peptides is another aspect of safety evaluations. Strict quality control procedures are used to make sure that the finished product is devoid of any dangerous materials (Cutajar *et al.*, 2022).

Conclusion:

In conclusion, significant research on the safety and toxicity of fish collagen peptides has shown that both application and eating are safe. However, before utilizing goods containing fish collagen peptides, anyone with known sensitivities to fish or marine-derived products should use caution and speak with a healthcare provider. To guarantee safe usage in varied applications, it is crucial to follow specified dose requirements and abide by safety laws, just as with any new chemical or product. Collagen peptides may cause stomach pain, including bloating, particularly if the person is not accustomed to taking high-protein supplements. Before utilizing collagen peptide products, those who are taking particular drugs or who have pre-existing medical issues should speak with their doctor to rule out any possible interactions or contraindications. Some people, especially those with sensitive or allergic skin problems, may experience skin sensitivity or irritation from external application of collagen peptides in cosmetics or wound dressings. To detect possible hazards and guarantee the safety of their goods, collagen peptide product producers must carry out exhaustive allergenicity testing and safety evaluations. Additionally, it is essential to clearly disclose possible allergies and negative effects on product packaging to inform customers and enable them to make educated decisions. Consumers should carefully read product labels, particularly if they are aware of any allergies or sensitivities to certain substances. People ought to consult a healthcare provider before using collagen peptide products if there is any doubt regarding their appropriateness or safety. Fish collagen peptides have the potential to be useful bioactive ingredients in a variety of applications, according to research. Fish collagen peptides offer outstanding biocompatibility, biodegradability, and safety characteristics, according to studies. Their impact on bone and joint wellness, skin health, healing of wounds, and other medicinal uses has all been studied. Additionally, the antioxidant, anti-inflammatory, and immune-modulating qualities of fish collagen peptides have been studied. Their potential advantages in customized nutrition, functional foods, tissue engineering, and medication delivery systems have been emphasized by the research. Fish peptides made from collagen have a bright future ahead of them, and further study is anticipated to provide new uses and advantages. A few intriguing future avenues include examining their function in tailored nutrition for specific health outcomes, optimizing extraction and purification processes to increase yield and purity, and developing innovative encapsulating strategies for controlled release in drug delivery systems. Additionally, the use of fish collagen peptides into tissues engineering and regenerative medical methodologies may result in ground-breaking treatments for tissue repair and regeneration. Prioritizing eco-friendly procedures and ethical procurement in collagen manufacturing is essential given the rising demand for collagen peptides. Fish collagen peptides provide a plentiful and sustainable source, however ethical fishing and procurement practices are crucial to safeguarding marine ecosystems Collagen peptides present opportunity for the food business to create functional meals and individualized nutrition solutions that support healthy skin, joints, and general wellness. Collagen peptides have potential for pharmaceutical companies as delivery systems for drug vehicles and therapeutic substances for regeneration of tissue and wound repair. Their bioactivity and biocompatibility in the biomedical sector make them appealing for use in tissue engineering and regenerative medicine. The sector will gain more value if it emphasizes sustainable processes in collagen manufacturing, which are in line with the increasing demand from customers for green products and ethical sourcing.

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