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REVIEW ARTICLE OPEN ACCESS

A REVIEW OF EXTRACTION METHODS AND APPLICATION OF MARINE COLLAGEN

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ABSTRACT

Marine collagen, sourced primarily from fish by-products, presents an increasingly significant and versatile bio-resource with diverse applications across healthcare sectors. This comprehensive review examines the multifaceted roles of marine collagen and its derivatives, underscoring their contribution to sustainable healthcare solutions.This review explores the potential impact of marine collagen-based drug delivery systems on improving treatment outcomes and patient well-being. Marine collagen's remarkable biocompatibility extends to the cosmetics and skincare industry. Collagen-based products have garnered significant attention due to their capacity to enhance skin elasticity and hydration, addressing aging-related concerns and promoting overall skin health. The cosmetic industry continues to benefit from the properties of marine collagen, offering consumers a sustainable and effective approach to enhancing their appearance and self-esteem. Importantly, the sustainability aspect of marine collagen sourcing cannot be overstated. Utilizing by-products from the fishing industry not only mitigates waste but also aligns with global efforts toward more environmentally responsible practices. This review examines the implications of such sustainable sourcing on environmental conservation and responsible resource utilization.Marine collagen and its derivatives offer versatile and sustainable bio-resources for healthcare applications. Their diverse applications in regenerative medicine, pharmaceuticals, and cosmetics, along with their eco-friendly sourcing, position them as pivotal components in shaping the future of healthcare. The potential for marine collagen to transform healthcare and environmental practices is vast, making it a valuable focus for ongoing research and development efforts. As we delve deeper into the capabilities of this remarkable resource, we can anticipate a future healthcare landscape that is not only more effective but also more sustainable and environmentally conscious.

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INTRODUCTION

Fish collagen, derived from the piscine sources of our planet's aquatic ecosystems, has garnered increasing attention in recent years due to its versatile applications and numerous advances in both research and industrial utilization. Moreover, fish collagen exhibits excellent wound-healing properties, driving its use in the development of advanced wound dressings and drug delivery systems. Collagen has a molecular weight of around 300 kDa, a diameter of about 14–15 Å, and an approximate length of 2800 Å. Till now,28 different types of collagen have been identified (Felician *et al*., 2018). Collagen as a multifunctional protein has high water absorption capacity, superior biocompatibility, low immunogenicity, bio-degradability, high porosity, easy processing, ability to penetrate a lipid-free interface, native ability to combine with other materials (synthetic polymers), less or no religious and ethical issues and the possibilities for large-scale extraction. All these properties make collagen a key protein that is used in food, cosmetics, pharmaceutical, and biomedical industries (Tylingo *et al*., 2016). The primary uses of collagen derived from mammalian sources are in drug delivery systems such as protein-delivery mini pellets and tablets, controlling materials for transdermal and gene delivery, and other uses include collagen-based wound sponges and basic matrices for cell culture systems (Subhan *et al*., 2015). It also has uses in tissue engineering like skin replacement, bone substitutes, and artificial blood vessels and valves. In the realm of food technology, fish collagen is emerging as a versatile ingredient with multifaceted applications. As consumers increasingly demand natural and sustainable food products, the incorporation of fish collagen in various food formulations has gained momentum. Its unique gelling and emulsifying properties improve texture and stability in processed foods, while its nutritional benefits, such as promoting joint and skin health, cater to health-conscious consumers. Recent studies, including the work of Smith *et al*., (2023), have explored the utilization of fish collagen in novel food products, demonstrating its potential to transform the industry. Moreover, the fishing industries may utilize fish processingwastes to obtain cheap collagen. The processing industries utilizeabout 25% of the total fish weight, while the remaining75% is considered as waste (Srikanya *et al*., 2017). Skin, bone, and scale, which make up around 30% of this waste and have high collagen contents, could be used to make collagen. The production of value-added goods that boost the financial performance of the fish processing industry may help to reduce environmental issues associated with fish waste. Compared to pig and bovine collagen, fish collagen has a higher bioavailability and is absorbed into the body up to 1.5 times more effectively(Sripriya and Kumar2015). Due to its ability to improve skin health and lessen indications of aging, fish collagen is now being used more frequently in cosmetics and personal care products. Formulations containing fish collagen are being enhanced for better skin penetration and absorption as research improves. This trend fits in with the broader shift towards eco-friendly and natural skincare products that have consumers' interest.

Present status: The global marine collagen powder market size is expected to expand from US$ 254.8 million in 2023 to US$ 401.4 million by 2033. Over the next ten years (2023 to 2033), global marine collagen powder sales are likely to soar at 4.6% CAGR. (Salvatore *et al*., 2020). Marine vertebrates, especially fish and marine mammals (ex: whales) too, are used for collagen extraction (Felician *et al*., 2018). It is impossible to ignore the fact that many nations employ waste from the processing of fish to extract collagen as a way to both meet the market's rising collagen demand and reduce environmental damage (Coelho *et al*., 2017).

Structure of Collagen: Types I, II, III, V, and XI of collagen combine to make collagen fibers. The collagen molecule is made up of three chains, which together make up its molecular structure. There are 1,000 amino acids with the -Gly-XY sequence in each of these chains. The third amino acid that serves as an attachment to the three chains in the tropocollagen molecule, proline, and 4-hydroxyproline, which are primarily located in the X and Y sequence, is positioned by the presence of glycine in these chains. Type I collagen is the current major standard in tissue engineering. The following table 1 gives information about the types and tissue distribution of collagen (Zata *et al*., 2020). Collagen is a complex molecule, the structure of which has been revised over the years. Type IV collagen with a more flexible triple helix (Figure 1) is combined in meshes confined to basic membranes [D'souza *et al*., 2020]. Collagen types VIII and X form hexagonal networks while others (XIII and XVII) encompass cell membranes. These can be formed by three identical chains (homotrimers) as in collagen types II, III, VII, VIII, X, and others, or by two or more different chains (heterotrimers) such as collagen types I, IV, and V, VI, IX-XI (Shigemura *et al*., 2011).

Table 1. Types, forms, and distribution of collagen (Source: Yamamoto et al., 2015)

	Type	Molecular formula	Polymerized form	Tissue distribution
Fibril- Forming (fibrillar)	I	$[\alpha1(I)]_2\alpha2(I)$	Fibril	Bone, skin, tendons, ligaments, cornea (represents 90% of total collagen of the human body)
	II	$[\alpha1(II)]_3$	Fibril	Cartilage, invertebrate disc, notochord, vitreous humor in the eye
	III	$[\alpha1(III)]_3$	Fibril	The blood vessels
	V	$[\alpha1(V)]_2\alpha2(V)$ and $\alpha1(V)\alpha2(V)\alpha3(V)$	Fibril (assemble with type I)	*Idem* as type I
	XI	$\alpha1(XI)\alpha2(XI)3\alpha(XI)$	Fibril (assemble with type II)	*Idem* as type II
Fibril- associated	IX	$\alpha1(IX)\alpha2(IX)\alpha3(IX)$	Lateral association with type II fibril	Cartilage
	XII	$[\alpha1(XII)]_3$	Lateral association with type I fibril	Tendons, ligaments
Network- forming	IV	$[\alpha1(IV)]_2\alpha2(IV)$	Sheet-like network	Basal lamina
	VII	$[\alpha1(VII)]_3$	Anchoring fibrils	Beneath stratified squamous epithelia

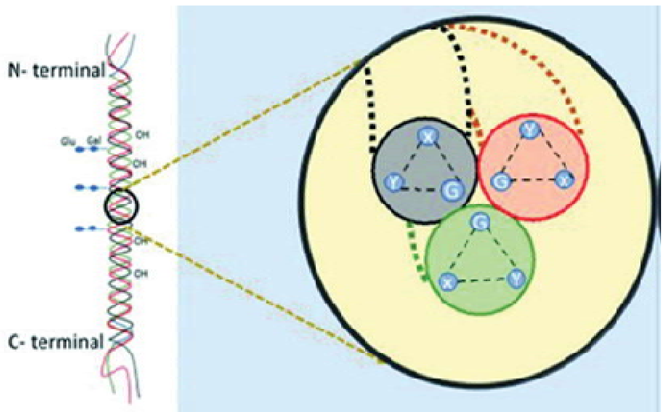


Figure 1. The triple helical structure of collagen (Source: D'souza *et al*., 2020)

How marine collagen is better than terrestrial collagen?

Marine-based collagen is identified as a safe and attractive alternative to terrestrial collagen with weak immunogenicity, high biocompatibility, and low risk of transmissible diseases (Felician *et al*., 2018). Marine invertebrates and vertebrates have grown in popularity because they can be used to extract collagen more easily than their terrestrial equivalents. Collagen is frequently extracted from marine invertebrates such as cuttlefish, prawns, sea anemones, starfish, jellyfish, sea urchins, sponges, octopus, mollusks, and squids

Different types of Collagen: Nearly 28 types of collagen have been identified so far which is composed of 46 distinct polypeptide chains. All of them have a characteristic triple helix but the length of the helix and the size and nature of the non-helical portion vary from one to another type (Miller, 1984). Among these, the 5 most common ones are:

Collagen I: Skin, bone, teeth, tendon, ligament, vascular ligature, organs (the main constituent of the organic part of the bone)
Collagen II: Eyes and cartilage (main constituent of cartilage).

Collagen III: Reticulate (the main constituent of reticular fibers), skin, muscle, and blood vessels.

Collagen IV: Forms the epithelium-secreted layer of the basement membrane and the basal lamina.

Collagen V: Hair, cell surfaces, and placenta. 90% of the collagen in the body is of type I followed by type II and III. The reason for the abundance of Type I collagen is due to its wide prevalence in almost all connective tissues (Cheah, 1985).

Natural availability (raw material): The marine source is found to be the safest source for obtaining collagen presently. Another reason for approving this source is due to the belief that "life originated from marine". Animal sources of collagen need difficult, time-consuming, and expensive extraction processes. In comparison to other sources, the yield obtained is also less (about 12 g of collagen per kg of the raw material utilized (Perumal, 2013)

Marine sources: To date, collagen has been found in a varied range of marine organisms. Marine sources of collagen are presented in Table 2.Figure 2 presents a technical function flowsheet for sourcing and producing soluble collagen. A significant number of commercial and aquaculture fish species, as well as non-fish species, are used as a source of marine collagen. Among them, the following can be noted (Han *et al*., 2021):

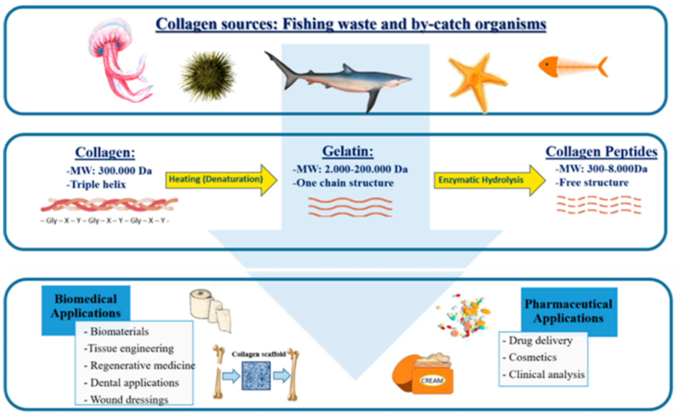


Figure 2. The classical structure and applications of marine collagen, gelatin, and collagen peptides are extracted from sustainable marine sources. (Source: Ferreira *et al*., 2012)

Table 2. Marine collagen sources

Sr.No	Organism	Partsfromwhichcollagen is derived
1	*Thunnusalbacares*	Swimbladder
2	*Cynoscionothonopterus*	Swimbladder
3	*Nibeacoibor*	Skin,waste
4	*Protonibeadiacanthus*	Swimbladder
5	*Priacanthustayenus*	Skin,muscletissue
6	*Sauridatumbil*	Scales
7	*Theragrachalcogramma*	Muscletissueandinternalorgans
8	*Pangasiussp.*	Skin
9	*Odonusniger*	Skin,bones,muscles
10	*Magalaspiscordyla*	Skin,scales

Other sources

Bovine: It makes use of the skin and bone of a cow. It is one of the major industrial sources of collagen. Due to the outbreak of diseases such as BSE, TSE, and FMD especially mad cow disease, which pose a threat to humans, researchers are in search of an alternative safer source of collagen. Nearly 3% of the population has an allergy to bovine collagen, which hinders its use and is one of its main drawbacks. Type I collagen is produced industrially using bovine Achilles tendon. Type II comes from cartilage in the nose or joints, while type IV comes from the placental villi (Ahuja *et al.,* 2012).

Porcine: Pig skin and bones are used for various purposes. Collagen for industrial usage is frequently obtained from this source. Since pig collagen is essentially identical to human collagen, using it rarely results in significant adverse reactions. Pigs are prohibited due to religious restrictions, but just like the bovine source, the setback of zoonosis provides a risk of contamination. For tendon reinforcement, hernia repair, skin and wound healing, and plastic and reconstructive surgery, adult porcine dermis and small intestine mucosa have been used (Cortial *et al.,* 2006).

Other animal sources: It includes chicken, kangaroo tails, rat tail tendons, duck feet, equine tendon (horse), alligator bone and skin, bird feet, sheep skin (ovine source), frog skin, and sometimes even from humans (Wood *et al*., 2008). Since recombinant human collagen has a lower immunogenicity than collagen from other sources, it is employed. The equine adult pericardium is utilized for hernia repair, skin and wound healing, and tendon reinforcement. Equine skin, articular cartilage, and flexor tendon are isolated sources of type I and type II collagen. From the chicken neck, collagen of types I, II, III, and V were extracted, with type I predominating. Collagen can be found in great abundance in chicken feet. The chicken embryo's sternal cartilage contains type IX as well as types I, III, and IV from the animal's epidermis and muscle tissues, respectively. Additionally, type I collagen was extracted from a bullfrog's fallopian tube (Wang *et al.,* 2011). From invertebrate tissue of *Archaeogastropod*, *Neritacrepidularia, gastropod* collagen was characterized.

Properties: Different methods for collagen extraction from marine organisms result in varying yields and physiochemical properties of the extracted collagens. Two common methods are acid-soluble collagen (ASC) extraction and pepsin-solubilized (PSC) extraction (Chen *et al*., 2022). The acid-collagen reaction utilized in ASC extraction increases collagen extraction efficiency by breaking crosslinks in the collagen helix and increasing repulsion among tropocollagen molecules (Niu *et al*., 2016). PSC, also known as atelo-collagen, shows increased purity and reduced antigenicity compared to ASC due to pepsin treatment that removes telopeptide regions and related non-collagenous proteins. Enzymatic treatment using pepsin in combination with acids has been shown by researchers to improve the yield of extracted collagen in multiple studies (Hadfi and Sarbon, 2019).

Structural Properties: Marine collagen shares structural similarities with mammalian collagen but exhibits certain distinctions. Recent research (Smith *et al*., 2023) has elucidated the fine structural differences in the amino acid composition and cross-linking patterns of marine collagen. These differences have significant implications for its use in tissue engineering and regenerative medicine, as they can influence cell adhesion, proliferation, and matrix formation.

Biological Activity: Marine collagen is known for its unique biological activities, including anti-inflammatory and antioxidant properties. A recent study by Chen and Li (2023) highlighted the potential of marine collagen in wound healing, attributing its bioactive peptides to the acceleration of the wound repair process and reduced inflammation. Such findings open new avenues for the development of advanced wound dressings and skincare products.

Extraction methods: Chemical hydrolysis and enzymatic hydrolysis can be used obtaining for collagen. Recently chemical extraction method for collagen is mostly used in addition the use of enzymes is considered more nutritional but still, there is a requirement for an alternate procedure to extract collagen (Sakib *et al*., 2021).Additionally, the enzymatic procedure produces less waste and takes less time, but it is quite expensive. Collagen may be extracted using an acidic or basic technique, depending on the origin of the raw material, as part of the chemical procedure, which also includes pretreatment. Pretreatment methods can be used to remove non-collagenous components and to increase yields (Schmidt *et al.*, 2016). The most widely used techniques for collagen extraction are based on collagen's solubility in neutral saline solutions, acidic solutions, and acidic solutions with additional enzymes (Schmidt *et al*., 2016). There are numerous methods for extracting collagen, each with its drawbacks. Many efforts are made to obtain collagen that is a high purity, high yield, reserved structurally intact, and has special features such as the capacity to form gels, retain water, and be thermally stable. Collagen extraction was made simpler by the acid-base approach.

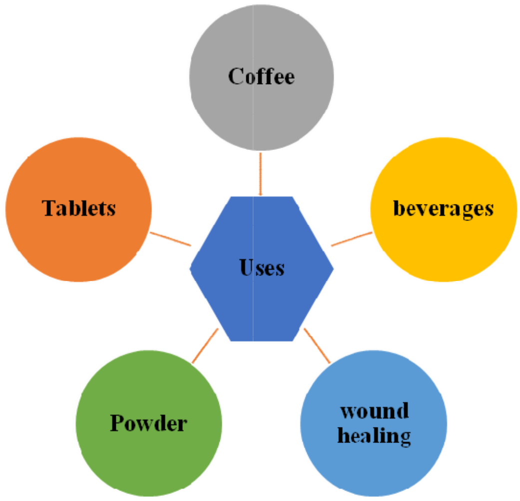
Pre-Treatment: Because of natural cross-linking collagen in the connective tissues of animals dissolves very slowly, even in hot water. A small amount of chemical treatment is also needed to break crosslinks before extraction (Schrieber and Gareis, 2007). In the end, the bases and diluted acids that were used were combined with the semi-hydrolyzed collagen to maintain the collagen chains intact while the crosslinks were broken. The waste materials are submerged in an acidic solution during the pretreatment process until the substance enters the solution. When a solution is introduced into the skin structure at a controlled temperature, it expands to two or three times its original size and breaks non-covalent intra- and intermolecular connections. The acidic process is moresuitable for more fragile raw materials with less intertwined collagen fibers, for example, fish skinsand porcine (Fernandes de Almeida *et al.*, 2012). Sodium hydroxide and calcium hydroxide are commonly utilized for pre-treatment, however, sodium hydroxide is more suitable for pre-treatment of the skin because it causes significant swelling, which promotes collagen extraction by increasing the exchange rate of the mass in the tissue matrix (Liu *et al.*, 2015).

Chemical hydrolysis: Organic acids like citric acid, lactic acid, and acetic acid and inorganic acids like hydrochloric acidare used for acid hydrolysis. However, organic acids have been observed more effective compared to inorganic acids (Liu *et al.*, 2015). The non-cross-linked can bedissolved by organic acids and also the inter-strand cross-liked in collagen can be broken by it; which is the very high solubility of collagen at the time of the extraction process (Liu *et al.*, 2015). Hence for the extraction of collagen acid solution, particularly acetic acid is used commonly. The pre-treatment materials have to be added to the acid solution to extract acid-soluble collagen, which could be 0.5 M acetic acid and should be held under continuous stirring at 4C° for 24-72 hours depending on the type of raw material (Liu *et al.*, 2015; Filtering process is needed to isolate supernatant from the collagen after the extraction process, which has state of liquid. After that, the filtrate is precipitated with NaCl to get the collagen powder. Centrifugation has to be used to collect the precipitate and later on, it could be re-dissolve in a minimum volume of 0.5M acetic acid and then dialyzed in 0.1 acetic acid for 48 hours, and then distilled water is applied for 2 days, with replacement of the solution on average every 12 hours(Schmidt *et al.*, 2016).

Enzymatic hydrolysis: Collagen has a strong intermolecular covalent bond in the telopeptide region of its triple helix structure, making it impossible to cut with just acetic acid alone. Instead, enzymes like pepsin from fish, mammalian trypsin, papain, alkaline protease, bromelain collagenase, etc., which increase collagen solubility, are added to cut away non-helical structures. Pepsin is the most popular enzyme for obtaining marine collagen out of all of these (Ehrlich *et al.*, 2010; Silva *et al.*, 2014). Whole isolated collagen, especially collagen type I with the same shape and amino acid arrangement, maintains the triple helix structure. All extracted collagen retains the triple helix structure, along with the same amino acid composition and shape as type I collagen. In comparison to spectral analysis of enzymatic analysis, chemical analysis reveals fewer interesting aspects, such as specificity, degree of hydrolysis control, low level of activities, and lower salt levels in the final hydrolysate. Enzymes are also very rarely used, thus the medium doesn't need to be depleted of them.

Acid extraction of collagen: Acid extraction collagen was carried out according to the methodology of Hwang *et al.*, (2007) with slight modifications. The skin of the fish was cut into small pieces. About 10 g of this material was weighed and mixed with 10 volumes of 0.1 M NaOH and stirred in a cold room (3–5ºC) for 24 h. The liquid was removed, and the residue was washed with distilled water (three times). The washed residue was stirred overnight with 10 volumes of 0.5 M acetic acid. After this, the extract was centrifuged at 10,000 × g for 20 min at 10ºC. The supernatant was dialyzed against distilled water for 2 days in a cold room, at 3–5ºC. The volume of dialyzed collagen extract was measured and freeze-dried. Freeze-dried collagen was referred to as wet weight or freeze-dried skin.

Uses of marine collagen



Additives: Collagens are added to food as food additives to increase the rheological characteristics of sausages and frankfurters and to make sure that there are enough animal nutritious fibers present. Meat that has collagen or its components added to the basic material may have improved technological and rheological properties. When collagen is added to liverwurst or paste, the smoothness of the goods improves and the frequency of fat caps is reduced. The collagen fiber that has been heated has a lot of promise for use as an emulsifier in food, especially in acidic products (Yuswan *et al.*, 2020).

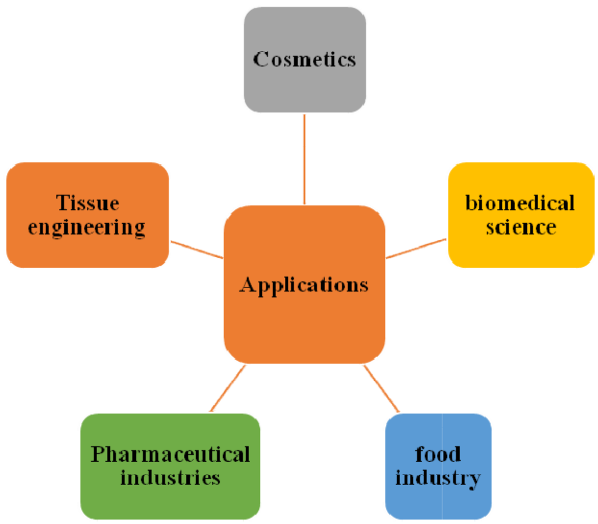
Coffee: With the growing popularity of collagen supplements has come a slew of new trends, such as the addition of collagen peptides to coffee. Many people believe that this is an excellent method to get extra collagen into their diets. Because of its neutral flavor, the unflavored form may be simply added to meals and beverages without dramatically altering their flavor. This is significant because collagen peptides are often produced by exposing animal skins to an acidic or alkaline solution to release the collagen. The hides are then boiled in water at temperatures as high as 190oF (88oC) to extract more collagen peptides [Meyer 2019]. Even so, if collagen proteins are subjected to even greater temperatures, a process known as degradation can occur, further degrading the protein. At this time, the protein may no longer work properly, rendering the supplement ineffective. One research found that when collagen proteins were exposed to temperatures ranging from 302–788oF (150–420oC), their initial breakdown occurred at 302oF (150oC) (Bozec *et al*., 2011). Coffee, on the other hand, is normally brewed at 195– 205oF (90–96oC) - a far lower temperature range. As a result, as long as your coffee is below 302oF (150oC) when you add your collagen supplement, the powder's quality should be unaffected.

Beverages: Collagen-infused beverages are another global market development nowadays. Many goods, such as soy collagen, cocoa collagen, cappuccino collagen, collagen juice, and bird nest drinks with collagen, are published by producers. Proposed a collagen-infused energy drink to help promote the natural capacity of the body to produce fatty tissues (Hashim *et al*., 2015). The collagen drink typically makes claims that it will stimulate the body's collagen-producing process, which will benefit the body's tissues and lessen wrinkles and skin drooping. As a result, the beverage "Vitagen Collagen" was created to encourage the growth of advantageous gut flora and to profoundly radiate beauty from the outside in. Avon has also created the ground-breaking Avon Life Marine Fish Peptide Collagen Drink, which is manufactured from salmon fish skin, vitamin C, and fructooligosaccharides made from pure and premium fish peptide collagen (Yuswan*et al*., 2020).

Wound healing: Collagen is a central element in the composition of the dermis comprising about 70–80% of skin, so it could have an essential role in skin wound repair. It provides an ideal environment as an extracellular matrix for fibroblast cells to proliferate which helps in the wound healing process (Velnar *et al*., 2009). Collagen plays a significant role in all phases of wound healing including hemostasis, inflammation, proliferation, and remodeling. Keeping in view promising wound healing potential, several collagen-based skin substitutes obtained from allogeneic or xenogeneic sources are commercially available, including IntegraTM, AllodermTM, MatridermTM, BiobraneTM, and PermacolTM (Shevchenko 2009). However, due to related issues and immunological reactions, an effort to substitute marine sources of material is started. Much research has recently demonstrated the biological uses of fish collagen, particularly for wound healing. Due to their highly porous and interconnected pore structure, high-density cell seeding, ability to allow passage of nutrients and oxygen across the membrane, high biostability, and least immune response compared to other naturally derived biomaterials, fish collagen membranes have demonstrated high potential in clinical applications (Chandika, 2015). A recent study showed the potentiality of fish collagen as a skin substitute for full-thickness wound healing (Pal *et al*., 2016). The collagen sponge demonstrated effective fibroblast and keratinocyte cell growth and proliferation. Additionally, the collagen sponge was found to hasten the healing of wounds in the rat model according to this study (Pal *et al*. 2016). All these studies highlighted the importance of fish collagen for potential applications in wound healing.

Powder: Collagen supplements, which are in powder form, are absorbed from the moment they enter the body before they reach the digestive system organs such as the stomach and intestines. In this way, higher efficiency is obtained. Collagen supplements in powder form are easier to use, they can be easily drunk by adding them to coffee, water, or the liquid you will consume. One research discovered that using oral collagen supplements improved skin elasticity, hydration, and collagen density (Choi *et al*., 2019).

Tablets: Collagen tablets contain less hydrolyzed collagen than liquid and powder forms. It also takes longer to break down and absorb than other forms (Musayeva *et al*., 2022).



Cosmetics: Collagen is a popular ingredient in cosmetics; to increase skin hydration and prevent skin aging. It can be applied to the mouth, mucous membranes, or hair. Additionally, collagen cross-linking and/or collagen blending with other proteins and polysaccharides can be employed to alter collagen films used in the cosmetic sector. According to current research directions, the application of collagen for cosmetic reasons is concentrated on raising the denaturation temperature of various types of fish-derived collagens. Additionally, as collagen has a direct impact on people's psychological and social well-being, it will undoubtedly be used for efficient rejuvenation treatments in the aging population. Due to customers' high acceptance rate, marine collagen has grown in popularity as a result. However, sourcing of marine collagen should take several aspects into account such as sustainable sourcing, use of fishery and aquaculture by-products, legislative requirements efficient and environmentally friendly processes (Coelho *et al*., 2017). Salmon and codfish skin collagen is utilized as a concentrated element in cosmetic compositions. This application also demonstrates that it has a high water-holding capacity, making it suitable for application to the skin as a moisturizer. Additionally, molecular markers for irritation and inflammation as well as topical collagen exposure in a human dermis reconstruction did not indicate any irritating potential. Therefore, the separation of collagen from fish skins may be a component of environmentally friendly and reasonably priced cosmeceutical products (Alves *et al*., 2017).

Biomedical science: The use of marine collagen protein (MCP) in various food industries has been practiced in the Asia Pacific region for many years. According to (Kumar *et al*., 2019) MCP has the potential to develop into a dietary supplement. In this study, MCP has been added (0–10%) in the biscuit flour and its physical, textural, and sensorial, functional effects of MCP-flour mix. Sensorial preference was noted for nutritionally improved collagen peptide biscuits and it can serve as a potential geriatric nutrition option (Kumar *et al*., 2019). Moreover, composed paneer has been widely recognized and has good texture and sensorial qualities (Jeevithan *et al*., 2014). The potential of blue shark skin collagen (Prionace glauca) to induce chondrogenic differentiation of human adipose stem cells was recently investigated, and this work highlighted the importance of using blue shark collagen biopolymer as a building block to produce highly effective temporary matrices for cartilage applications (Diogo *et al*., 2022). Due to its widespread availability and simplicity of use, jellyfish collagen has been highlighted as a potential material. Jellyfish collagen structural variations are a promising characteristic that affects integrin-mediated adhesion mechanisms in vertebrate cells. From R. esculentum, jellyfish collagen has been isolated as a potential component for cartilage tissue engineering (Sewing *et al*., 2017).

Food industry: The use of marine collagen protein (MCP) in various food industries has been practiced in the Asia Pacific region for many years. According to (Kumar *et al*., 2019) MCP has the potential to develop into a dietary supplement. The inclusion of MCP considerably reduced the water-holding capacity and gelatinization viscosity, two characteristics that show promise. When biscuits were supplemented, it was discovered that they have antioxidant effects and slightly fewer calories. Collagen peptide cookies with better nutrition were found to have a sensory preference, making them a possible geriatric nutrition choice (Kumar *et al*., 2019).

Pharmaceutical industries: Pharmaceutical companies use collagen as a drug delivery system, in injectable dispersions, as shields in ophthalmology sponges, and as microparticles. Due to qualities including mild antigenicity, cell attachment capability, biodegradability, and biocompatibility, it is used in the pharmaceutical and biomedical fields (Leitinger and Hohenester, 2007).

Tissue engineering: Due to its high biocompatibility, collagen type I is regarded as the most effective material in this area. It serves as the fundamental matrix in systems for cell culture. Collagen-based biomaterials, such as injectable matrices and scaffolds for bone regeneration, are frequently utilized in tissue engineering. These biomaterials are mostly made of the collagen that forms fibrils, which comprise types I, II, III, V, and XI. Due to its outstanding biocompatibility, low immunogenicity, high biodegradability, and superior mechanical, hemostatic, and cell-binding qualities, collagen is the perfect material for tissue engineering applications (Dong and Lv 2016). Fish collagen-based scaffolds have recently attracted a lot of attention due to their simple extraction from fish skin waste and bones and good biocompatibility, which eliminates the risk associated with bovine collagen. Fish collagen scaffolds have been used in numerous research to try and use them for prospective tissue engineering applications that have shown promise for their usage in regenerative medicine (Yamada *et al*., 2014).

Metabolism

Mechanism of Action: As a result of its capacity to stop bleeding, it to used as a hemostat or coagulation element. Animal-derived (natural) collagen is used in many clinical applications, but there is some concern about its role in inflammation, group-to-group variability, and possible disease transfection. Some synthetic nanomaterials that can mimic their properties have been developed to avoid immune problems. Accordingly, collagen with the trade name KODTM was developed. KOD collagen, anticoagulant fractions, can increase platelet activation and adhesion. It also binds the platelets the form clots, activates them, and promotes healing without promoting inflammation (Kumar *et al*., 2014). Collagen peptides are digested and spread across the body after ingestion. Watanabe-Kamiyama *et al*., 2010 examined the delivery of collagen peptides to the skin and other tissues through an in vivo experiment in which 14C-labelled proline or collagen peptides were administered to Wistar rats. Radioactivity was assessed in various tissues 0–6 hours after ingestion of collagen peptides and 14 days afterward. The findings were very positive in terms of time spent in the skin and showed that radioactivity stayed elevated in the skin tissue for up to 14 days. This shows the capacity of collagen peptides to penetrate the skin of the dermis where their key advantage is observed [Watanabe *et al*., 2010].

***Absorption, distribution, metabolization, and elimination*:** The first effect that is illustrated after absorption of collagen hydrolyzes has been shown by experimental studies to be an antioxidant and the second to be a biological activity (Tanaka *et al*.,2009). Studies show that CH is detected in the portal vein and blood after oral administration, and the peptides are absorbed from the gut as larger peptides in vivo. Some studies show that the peptide derived from CH is absorbed from the gut after oral administration of CH and many tissues can be reached with systemic administration. Some research has been done on the absorption of collagen-derived substances in their whole structure. Since the collagen tripeptide's average molecular weight is much lower than that of the traditional collagen peptide, investigations have shown that collagen tripeptide is quickly absorbed into the circulation and transported to tissues with ease. The research's findings have led to the suggestion that using collagen as tripeptides facilitates the absorption of functional peptides (Yamamoto *et al*., 2015).

Absorption and Distribution: Although collagen has been used medicinally for a long time, the process of absorption is not fully understood. Until absorption, peptides are normally processed proteolytically in the gastrointestinal system. However, Oesser *et al*. 1999 hypothesized that mice may absorb collagen hydrolysate taken orally from the bowels and deposit it preferably in cartilage tissue (Oesser *et al*. 1999). We have previously stated that after oral ingestion of collagen hydrolysates, many peptides derived from collagen can be detected in human serum and plasma (Iwai *et al*., 2005).

Metabolization and Elimination: Unfortunately, little is known about the regulation of collagen synthesis, secretion, deposition, and turnover in connective tissues. Changes in the cell environment are known to lead to changes in collagen forms, and it is recognized that simple changes such as an increase in ions of K+ will lead to an increase in cell proliferation and extracellular matrix synthesis (Lash *et al*., 1973). Changes in the surroundings of mesenchymal cells or immature fibroblasts cause or trigger regulatory changes in the ways that collagen production occurs in all of these processes. Similar variations can be seen in the development of a callus on a cartilaginous fracture, ectopic bone growth, and numerous healing procedures. It has also been demonstrated that several factors can impact the amount of collagen synthesized. For instance, it has been demonstrated that ascorbate increases collagen production both with and without increasing prolyl hydroxylase activity (Kao *et al*., 1975). Prostaglandins El and Fl induce collagen synthesis in the skin and bone of chick embryos, and activated macrophages release a soluble factor that stimulates the synthesis of collagen and other proteins in granulation tissues. Since these prostaglandins are increased in inflammatory lesions, these findings may help to explain why inflammation stimulates collagen synthesis. Prostaglandin E2 is a relatively specific inhibitor of collagen synthesis by osteoblasts, according to numerous reports, and other connective tissues produce one or more small basic proteins that mimic hyaluronate production but inhibit collagen production. Nonetheless, these findings are all preliminary, and many more good basic studies of the control of collagen transcription, translation, and posttranslational modifications, as well as the extracellular enzymes necessary for collagen deposition, stabilization, and degradation in all connective tissues, are urgently needed [Minor 1980]. There are few studies on the metabolism and elimination of collagen.

CONCLUSION

Marine collagen and its byproducts have gained recognition as adaptable and sustainable bioresources with enormous potential for use in the healthcare industry. This review has emphasized marine collagen's broad range of applications and its sustainability features, emphasizing its essential function in determining the direction of healthcare in the future. Fish scales, skins, and other marine byproducts are the main sources of marine collagen, which has become known for its remarkable biocompatibility and bioavailability. Its low allergenicity and likeness to human collagen make it an important tool in tissue engineering, regenerative medicine, and wound healing. Those looking for natural, long-lasting strategies to improve their beauty and well-being may find this to be of considerable significance. It is also impossible to underestimate the sustainability of marine collagen. This is vital in terms of environmental preservation and ethical sourcing, and it supports the global movement towards eco-friendly behavior. A versatile option for medical applications is provided by marine collagen and its derivatives. They are major actors in the fields of regenerative medicine, pharmaceuticals, cosmetics, and skincare thanks to their amazing adaptability, biocompatibility, and sustainable supply. The potential for innovative medical applications is still huge as our knowledge of marine collagen deepens and research and development advances. The sustainable procurement of marine collagen also highlights its contribution to waste reduction in the fishing sector and environmentally sound practices. Marine collagen will have a huge impact on how healthcare is provided in the future by providing long-lasting and potent remedies for a variety of health and well-being issues.

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