Review

Microbial Biosystems 9(2) (2024) 2024.1157
10.21608/mb.2024.314924.1157

Contents lists available at Egyptian Knowledge Bank
Microbial Biosystems
Journal homepage: http://mb.journals.ekb.eg/

MICROBIAL BIOSYSTEMS
INTERNATIONAL SCIENTIFIC JOURNAL OF MICROBIAL BIOLOGY

Marine collagen in advanced wound dressing technologies: Innovations and applications for healing

Indexed by Scopus

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ARTICLE INFO

Article history
Received 24 August 2024
Received revised 19 October 2024
Accepted 11 November 2024
Available online 19 December 2024

Corresponding Editors:
El-Maradny Y.
Mahdy D.

Keywords
Collagen,
Marine collagen,
Scaffold,
Wound dressing,
Wound healing

ABSTRACT

Collagen is a fibrous, triple-helical structure protein that plays a crucial role in our bodies. It is considered the most common protein in vertebrates and is found in various types distributed across different organs. Collagen offers numerous advantages, including ease of processing, biodegradability, hydrophilicity, and anti-ageing properties. It is also known to enhance tissue regeneration. Although synthetic collagen can be obtained, it is often not used due to its high cost and associated disadvantages. Instead, collagen is sourced from natural origins such as porcine, bovine, rodent, and marine sources. Among these, marine collagen is widely favored for its safety and non-toxic nature. This review focuses on the application of collagen in wound healing, specifically its use as a wound dressing to accelerate the four stages of the healing process by promoting cell migration and skin regeneration, particularly in chronic wounds. We will emphasize marine collagen due to its advantages as being safe, biodegradable, abundant, and low cost, that has been used in the manufacturing of scaffolds and their role in increasing wound healing rates. The manufacturing of scaffolds from various marine sources has demonstrated a significant effect on wound healing acceleration than normal wound dressings. Different types of scaffolds, including surgically applied scaffolds, sponges, and hydrogel scaffolds loaded with drugs, have also been explored for their effectiveness. The scaffolds loaded with the drug have the highest wound-healing acceleration rate.

Published by Arab Society for Fungal Conservation

Introduction

What is the collagen?

Collagen derives its name from the Greek word where "kola" means gum and "gen" means producing (Silvipriya et al., 2015). It is the most abundant and essential protein in vertebrates, comprising approximately 25-30% of total animal proteins (Subhan et al., 2021a). This fibrous protein has a molecular weight of about 300 kDa, a diameter of approximately 14–15 Å, and a length of roughly 2800 Å. Due to its unique properties, collagen is widely utilized as a biomaterial in various applications (Felician, 2018; Subhan et al., 2021a).

As illustrated in **Figure 1**, collagen consists of three polypeptide chains that are rich in hydroxyproline amino acids and are coiled into a triple-helical structure (Hochstein, 2014). The key amino acids in collagen are glycine, proline, and hydroxyproline (Bhaskar Bhadra et al., 2021). The repeating sequence of (Gly-X-Y)n features glycine at every third position, with proline located at positions X and Y, where X and Y can be any amino acids (Szpak, 2011; Silvipriya et al., 2015; Felician, 2018; Subhan et al., 2021a).

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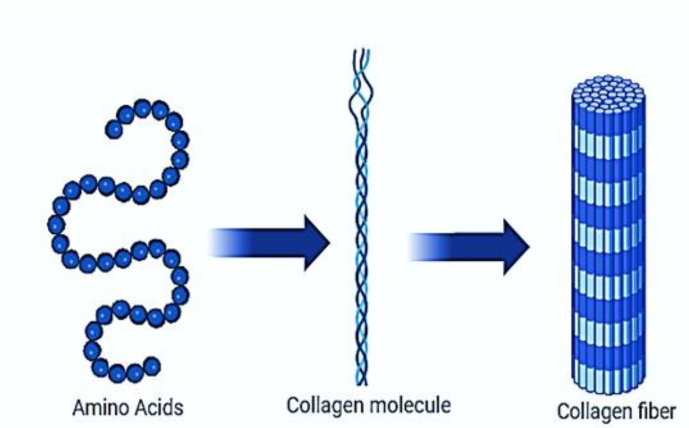

Fig 1. Diagrammatic presentation of the collagen molecular structure.

Collagen history

Collagen has been discovered in fossilized bones of a Tyrannosaurus rex aged more than 68 million years (Rezvani Ghomi et al., 2021). The development of collagen as a biomaterial began in 1881 when surgeons Joseph Lister and William Macewen utilized sutures made from collagen derived from the intestines of sheep (Chattopadhyay and Raines, 2014; Rezvani Ghomi et al., 2021). Subsequently, in 1956, the use of collagen as a cell culture matrix emerged, facilitating cell growth (Rezvani Ghomi et al., 2021). Ultimately, the first collagen-based bone implant received FDA approval in 1993 (Rezvani Ghomi et al., 2021).

Collagen function and properties

Collagen offers numerous advantages, including superior biocompatibility, low immunogenicity, ease of processing, biodegradability, high water absorption capacity, the ability to penetrate a lipid-free interface, high porosity, and compatibility with other materials such as synthetic polymers (Subhan et al., 2021a). Additionally, collagen exhibits hydrophilicity, supports cell growth, differentiation, and migration, enhances tissue regeneration, and possesses low antigenicity (Rezvani Ghomi et al., 2021).

Moreover, collagen is essential for providing strength, elasticity, and protection to the skin by preventing the absorption of toxins and pathogens, facilitating tissue development, and giving structural support to cells. As a robust protein, it is also present in bones, fascia, cartilage, and tendons, etc. (Silvipriya et al., 2015).

Given these properties, collagen has emerged as a vital protein with diverse applications (Subhan et al., 2021a), significantly influencing skin health and protection against aging.

Collagen effect as a supplement for anti-aging

Skin beauty and health are primary indicators of overall human well-being (Reilly and Lozano, 2021). Various methods, such as oral supplements known as nutricosmeceuticals, topical treatments, and surgical aesthetic procedures, can enhance collagen production and prevent its degradation (Reilly and Lozano, 2021). To improve skin hydration and address visible signs of fine lines, wrinkles, and loss of elasticity, supplements containing hydrolyzed bioactive collagen peptides, often combined with botanical antioxidants, minerals, and vitamins, are utilized (Asserin et al., 2015; Reilly and Lozano, 2021).

Oral supplements typically consist of hydrolyzed collagen (HC) combined with vitamins E, A, C, and zinc. HC can also be sourced from tilapia fish, as illustrated in **Figure 2** (León-López et al., 2019; Maia Campos et al., 2019). Upon ingestion, HC peptides are digested in the gut due to the presence of acids and enzymes in the stomach, leading to the degradation of collagen peptides into smaller molecules that can be absorbed into the bloodstream (Kiela and Ghishan, 2016; Reilly and Lozano, 2021). Once broken down, these components pass through the intestines, producing free amino acids and small peptides (Miner-Williams et al., 2014; Reilly and Lozano, 2021). The delivery of nutrients from the lumen to the bloodstream occurs through enzymatic processing, which facilitates cellular uptake via transporters. Approximately 20 minutes after ingestion, the components begin to enter circulation (Reilly and Lozano, 2021).

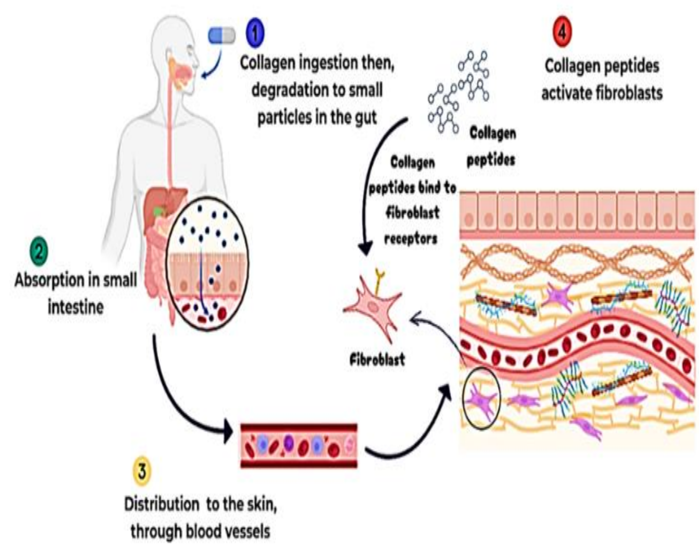

Fig 2. Mechanisms of collagen hydrolysis in the gut after ingestion.

Collagen age and durability

Collagen is essential for maintaining healthy skin, and preserving its firmness and elasticity (Sibilla et al., 2015; Reilly and Lozano, 2021). It is synthesized by fibroblasts (Reilly and Lozano, 2021), which also produce elastin, a protein that provides the skin with flexibility and the ability to stretch (Weihermann et al., 2017; Reilly and Lozano, 2021). Additionally, fibroblasts produce glycosaminoglycans (GAGs), which are long unbranched heteropolysaccharides (Reilly and Lozano, 2021). The activation of these cells leads to increased production of elastin and collagen, as well as enhanced GAG yield (Tracy et al., 2016; Reilly and Lozano, 2021).

The enzymatic activity responsible for collagen synthesis varies with age, as illustrated in **Figure 3**. Collagen production peaks between the ages of 20 and 30; thereafter, it begins to decrease by approximately 1.0–1.5% per year, becoming more fragile and brittle. This decline also affects other extracellular matrix (ECM) components, such as elastin and GAGs (Tobin, 2017; Reilly and Lozano, 2021).

Furthermore, the decrease in collagen is influenced by both internal and external factors. Internally, an individual's lifestyle choices—including smoking (Reilly and Lozano, 2021), alcoholism, unhealthy diet, and certain diseases (L. Wang et al., 2018; Rajabimashhadi et al., 2023)—play a significant role. Externally, factors such as sun exposure and pollution can lead to visible changes in skin appearance, including wrinkles and fine lines (Reilly and Lozano, 2021).

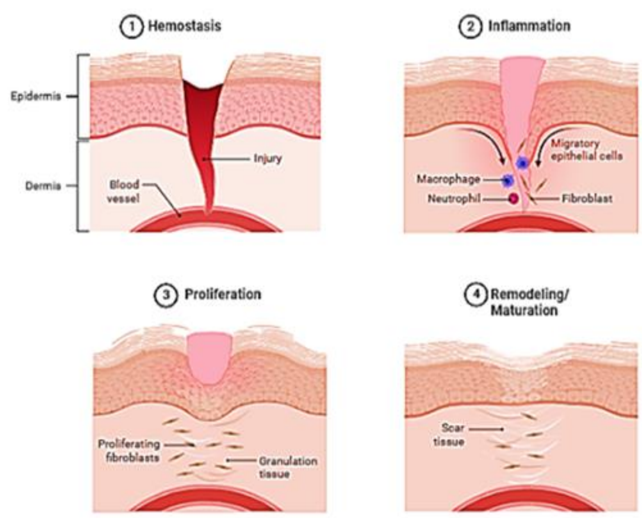

Fig 3. Illustrates the four stages of the wound healing process.

Types of collagens

Besides its role in beauty, collagen primarily functions to strengthen vertebrate connective tissues, protect organs, bind specialized cells together, and help maintain the shape of tissues and organs during movement (Bhaskar Bhadra et al., 2021).

Approximately 28 different types of collagen have been identified in humans (Subhan et al., 2021a; Felician, 2018). Although all collagen types share common characteristics, they differ in size, length, and the nature of their non-helical portions (Silvipriya et al., 2015).

Types I, II, and III are the dominant forms, collectively representing about 80% of the total collagen in the body. Types I and III play significant roles in wound healing (Hochstein, 2014), while type I is the most abundant collagen type in animals (Rezvani Ghomi et al., 2021). Each type of collagen has specific functions and varying amounts present in different tissues (Bhaskar Bhadra et al., 2021).

Type I collagen

Type I collagen is the primary member of the collagen family and the most studied type in the body. Its structure and location reflect its function in various tissues. Type I collagen is present in several body parts, including teeth, bones, tendons, ligaments, cornea, and skin (Bhaskar Bhadra et al., 2021). In the skin, collagen is produced by fibroblasts located in the dermal layer. Following type I, collagen types III and V rank next in terms of abundance (Shin et al., 2019; Bhaskar Bhadra et al., 2021; Reilly and Lozano, 2021).

Type II collagen

Type II collagen is a major constituent of mammalian cartilage, playing a crucial role in connective tissue synthesis. It is particularly abundant in the vitreous humor and cartilage (Deng et al., 2016; Bhaskar Bhadra et al., 2021). Additionally, type II collagen is found in non-cartilaginous tissues such as the eye, brain during embryonic development, heart, and notochord (Kuivaniemi and Tromp, 2019; Bhadra, 2021).

Structurally, type II collagen is a heterotrimer composed of three α1(II) chains, which are encoded by the COL2A1 gene (Bhaskar Bhadra et al., 2021). Notably, it exhibits greater glycosylation of hydroxylysine residues compared to type I collagen (Bhaskar Bhadra et al., 2021).

Type III collagen

Moreover, all collagen types are absorbed and incorporated into pharmaceuticals and cosmetics (Sadasivuni et al., 2020; Bhaskar Bhadra et al., 2021). Specifically, type III marine collagen plays a significant role in promoting healthier nails and hair, as well as improving skin hydration and elasticity (Lupu et al., 2020; Bhaskar Bhadra et al., 2021). Additionally, types I and III collagen are essential for the heart's fibrous meshwork, providing the necessary scaffold (Bhaskar Bhadra et al., 2021).

The primary aim of this review is to explore the use of marine collagen and its advantages, which include safety, availability, low cost, and eco-friendliness. These attributes make marine collagen an important source of natural collagen for various applications, such as the manufacturing of advanced wound dressings that accelerate the wound healing process, given that collagen is a key component of the skin.

Collagen sources

Natural collagen

Natural collagen, derived from various sources, is widely used across all fields and applications involving collagen. Examples of collagen extraction include bovine, porcine, marine, and poultry sources. Additionally, other land animal sources include chicken, kangaroo tail, sheepskin, rat tail tendons, alligator bone/skin, frog skin, bird feet, duck feet, and equine tendon (Browne et al., 2013; Rezvani Ghomi et al., 2021). Despite the benefits of natural collagen, it also presents certain disadvantages, such as potential allergies in humans, disease transmission, and denaturation at high temperatures. As a result, synthetic collagen has been developed.

Nonetheless, natural collagen, particularly from marine sources, is commercially utilized due to its advantages over other natural sources, allowing for a wide range of applications. **Table 1** illustrates different collagen sources along with their advantages and disadvantages. Each type is employed in various applications, as detailed in **Table 2**.

Table 1. Comparison between different collagen sources, advantages, and disadvantages

Collagen sources	Advantages	Disadvantages
Bovine collagen (use of cow's skin and bone)	• Biocompatible • Low immunogenicity • Well well-known industrial source of collagen (Davison-Kotler et al., 2019; Bhaskar Bhadra et al., 2021).	• It causes many diseases that threaten humans as: • TSE (Transmissible spongiform encephalopathies) • BSE (Bovine spongiform encephalopathy) • FMD (Fibromuscular dysplasia) • Causes allergy to nearly 3% of the population so it is rarely used (Silvipriya et al., 2015)
Porcine collagen The use of pig's bones and skin (Silvipriya et al., 2015)	• Low antigenicity • Like human collagen it is common in industry (Silvipriya et al., 2015; Bhaskar Bhadra et al., 2021).	• contamination • diseases • forbidden due to religious constraints (Silvipriya et al., 2015).
Rodent collagen	• Type I collagen the rat-tail tendon (RTT) is highly used in research. • It has high production of type I collagen about 90-95% (Davison-Kotler et al., 2019; Bhaskar Bhadra et al., 2021).	Not commonly used. The tests on type I-RTT collagen show that there are various mechanical and chemical changes in collagen as the rat gets older. It gets harder and less elastic (Bhaskar Bhadra et al., 2021).

Table 1. (Contd.)

Collagen sources	Advantages	Disadvantages
Marine collagen	• Safest collagen discovered (Silvipriya et al., 2015*)* • Produced in high amounts (Yang et al., 2015; Felician et al., 2018). • Low cost (Yang et al., 2015; Felician et al., 2018). • Halal for Muslims (Srikanya et al., 2017; Subhan et al., 2021a). • Does not cause any diseases (Subhan et al., 2021a) • Available as it is a waste product • Recyclable • Decrease environmental problems (Salvatore et al., 2020; Mathew-Steiner et al., 2021). • High content of collagen • greater absorption • Low molecular weight • The presence of biological contaminants and toxins is almost negligible • Metabolically compatible (Silvipriya et al., 2015) • Low viscosity • Excellent homeostatic properties • Minimal inflammatory response (Nirmal et al., 2022; Lu et al., 2022; Rajabimashhadi et al., 2023). physicochemical properties are similar to mammalian collagen and can be extracted and purified (Rajabimashhadi et al., 2023).	• Low melting point • Low amino acid contents • Low mechanical properties • Rapid rate of biodegradation • Biomechanical stiffness (Raftery et al., 2016; Subhan et al., 2021a;) • Denatured at temperatures lower than normal human temperature (37°C) (Felician et al., 2018) which decreases its medical applications (Tihăuan et al., 2022; Rajabimashhadi et al., 2023).

Table 2. Collagen different sources and their uses

Sources	Their uses and applications
Bovine collagen	- The bovine dermis is utilized for tendon reinforcement, as well as for skin and wound healing. Additionally, it is employed in hernia repair, plastic, and reconstructive surgery. The adult bovine pericardium is also used for hernia repair and muscle flap reinforcement (Silvipriya et al., 2015).
Porcine collagen	- Adult porcine dermis and small intestinal mucosa are used for tendon reinforcement, hernia repair, skin, and wound healing, as well as in plastic and reconstructive surgery (Silvipriya et al., 2015).
Marine collagen	- Marine collagen is used in various applications across the food industry, cosmetics, and pharmaceuticals (Venkatesan et al., 2017; Felician et al., 2018). Specifically, purified marine collagen can be utilized in the manufacturing of many biomaterials, serving as scaffolds, gels, composites, membranes for tissue engineering, and sponges (Felician et al., 2018).

Marine collagen

Marine collagen is derived from the marine environment and can be divided into two types based on the source. The first type is collagen isolated from marine invertebrate animals, which include sea anemones, cuttlefish, starfish, jellyfish (Khong et al., 2016; Felician et al., 2018), sea urchins, octopuses, sponges (Langasco, 2017; Felician et al., 2018), and squid (Felician et al., 2018), as well as prawns. The second category encompasses marine vertebrate animals, such as fish and marine mammals (Felician et al., 2018).

Fish are the most abundant vertebrates on the planet (Siaghi et al., 2024), and their waste products, including bones, skulls, scales, swim bladders, and remaining viscera, are utilized as sources of collagen. However, the skin is recognized as the best source of fish collagen. Extraction methods have also been explored for all other sources (Nakchum and Kim, 2016; Rajabimashhadi et al., 2023).

Marine collagen components

Fish collagen has a comparatively low denaturation temperature due to its low levels of proline, glycine, and hydroxyproline (Subhan et al., 2015; Subhan et al., 2021a). However, it contains a higher concentration of threonine and serine amino acids than mammalian collagen (Hashim et al., 2015; Subhan et al., 2021a).

Modifications in marine collagen

Marine collagen has several disadvantages, as previously mentioned. One solution to these challenges is the modification and combination of fish collagen with other natural or synthetic polymers and bioactive molecules (Raftery et al., 2016; Subhan et al., 2021a). Examples of such substances include elastin, polyethylene oxide, chitosan, hyaluronic acid, silk fibroin, alginate, and poly (L-lactic acid) (Ramadass et al., 2019; Geanaliu-Nicolae and Andronescu, 2020; Mathew-Steiner et al., 2021; Hernández-Rangel and Martin-Martinez, 2021).
Additionally, the thermostability of collagen can be improved through chemical crosslinking with compounds such as carbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC), glycosaminoglycans (GAGs), and glutaraldehyde (Felician et al., 2018).

Synthetic collagen

There are several methods for producing synthetic collagen to address health problems associated with natural collagen, such as disease transmission (Felician et al., 2018; Rezvani Ghomi et al., 2021). One approach involves the use of genetically engineered bacteria, such as E. coli (Bhaskar Bhadra et al., 2021). A commercially available example of this type of synthetic collagen is called KOD. This synthetic protein, consisting of 36 amino acids, self-assembles into hydrogels and triple-helix nanofibers (Kumar et al., 2014; Rezvani Ghomi et al., 2021).

However, KOD has some disadvantages, including a lack of enzymes and cofactors, as well as a high cost (Rezvani Ghomi et al., 2021). Additionally, this method yields low production rates and incurs high costs (An et al., 2014; Subhan et al., 2021a).

Collagen Applications

The properties of collagen discussed above make it suitable for a wide range of applications, as illustrated in **Figure 4**. These applications include pharmaceuticals, tissue engineering, the food industry, cosmetics, wound healing, and supplements, among others. Therefore, this review will primarily focus on the application of collagen, with a particular emphasis on marine collagen in wound healing and wound dressings.

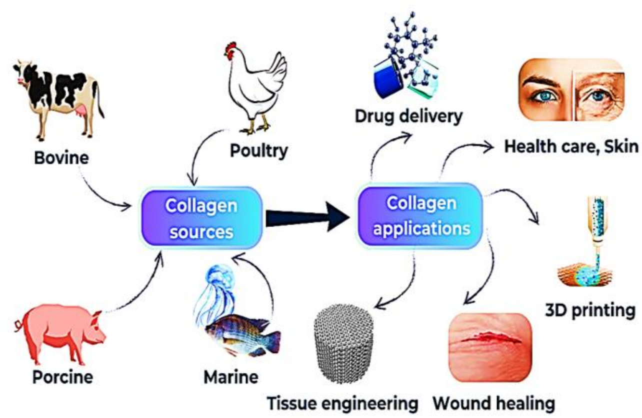

Fig 4. Schematic diagram illustrating various natural sources of collagen and their applications.

Food industry

In the past, collagen was used in the production of various food items, including drinks, meat products, and soups (Hashim, 2015; J. Wang et al., 2018; Rajabimashhadi et al., 2023). It plays a role in maintaining the chemical, physical, and sensory qualities of food (Pal and Suresh, 2016; Rajabimashhadi et al., 2023). In acidic products, collagen fibers, after being treated with heat, function as emulsifiers (Yuswan et al., 2021; Musayeva, 2022).
Foods prepared from marine collagen offer a higher protein percentage and lower fat content, along with comparable sensory acceptance and improved texture. Furthermore, collagen can replace half of the pork fat

content, resulting in better hardness, chewiness, and stability after cooking. Due to the high protein content of marine collagen, it is also added to beverages, such as natural fruit juice, to enhance functional and nutritional quality (Pal and Suresh, 2016; Rajabimashhadi et al., 2023).

Food packaging

Food packaging plays a crucial role in food preservation, primarily by protecting against oxidative and microbial degradation (Wang et al., 2017; Kozłowicz et al., 2019; Rajabimashhadi et al., 2023). Fish collagen has been widely utilized in this area, particularly after the incorporation of active functions into conventional packaging. Active packaging can prevent the transmission of H_2O, O_2, CO_2, odors, and fats, while also incorporating bioactive compounds such as antioxidants, antimicrobials, and flavoring agents to extend the shelf life of products (Listrat et al., 2016; Lim et al., 2019; Gokoglu, 2020; Rajabimashhadi et al., 2023).

Biopolymers used in food packaging must meet several criteria, including biodegradability, low water vapor permeability, effective oxygen barriers, appropriate thickness, transparency, edibility, and elasticity (Paolucci and Volpe, 2021; Kang et al., 2021; Rajabimashhadi et al., 2023). However, the use of fish collagen films in the packaging industry remains limited due to certain disadvantages, such as poor mechanical properties, low thermal stability, excessive water solubility, and high-water vapor permeability (Ahmad et al., 2016; Rajabimashhadi et al., 2023).

Tissue engineering

Establishing tissue engineering relies on the combination of scaffolding, cells, and signaling. A scaffold is defined as a temporary substitute that structurally supports tissue formation and provides an environment conducive to repair activities, cell migration, proliferation, and differentiation. Given its presence in human tissues, collagen is a preferred raw material for manufacturing transplantable devices used in tissue engineering. Its applications include bone, vascular tissue, skin, cartilage, corneal tissue, oral mucosa, and dental regeneration (Coppola et al., 2020; Salvatore et al., 2020; Rajabimashhadi et al., 2023).

The bioactivity of collagen makes this biopolymer highly effective in skin tissue repair, thanks to its healing, antigenic, new-tissue-thickening, and adhesion properties (Allan et al., 2021; Binlateh et al., 2022; Rajabimashhadi et al., 2023). Scaffolds must possess specific features, such as the ability to release drugs, maintain bioactivity, avoid triggering chronic inflammation, and ensure non-toxicity during degradation. Collagen scaffolds serve as alternatives to hydroxyapatite (HA) scaffolds, which are known to be brittle (Rezvani Ghomi et al., 2021).

The final physical properties of scaffolds, including structure, optical properties, biocompatibility, and other characteristics, depend on the source of collagen extraction and its age (Chae et al., 2015; Bhaskar Bhadra et al., 2021). While various tissue types are used in corneal tissue engineering, collagen stands out as the most promising major component (Xiong et al., 2019; Bhaskar Bhadra et al., 2021).

Fish collagen is particularly valuable for creating biocompatible scaffolds that support the growth of limbal stem cells, effectively replicating the human amniotic membrane. This is crucial for compensating for the lack of limbal stem cells, which can lead to vision problems due to corneal damage (Allan et al., 2021; Binlateh et al., 2022; Rajabimashhadi et al., 2023).

Collagen also plays an important role in tooth tissue repair. Tooth damage and loss are common problems, and widely used therapies to address these issues include dental implants, tooth transplantation, and artificial dentition (Bhaskar Bhadra et al., 2021). Different types of collagen have demonstrated the ability to promote the regeneration of dental tissue, making them essential for tooth regeneration (Allan et al., 2021; Binlateh et al., 2022; Rajabimashhadi et al., 2023).

Furthermore, synthetic bone scaffolds can be designed to facilitate bone healing by providing osteoinduction and osteointegration, along with mechanical integrity and enhanced cellular activity (Rezvani Ghomi et al., 2021).

3D printing

3D bioprinting has gained significant popularity in recent years, particularly for the manufacturing of vascular-like networks, implantable scaffolds, microphysiological devices, and biological tissues (Rezvani Ghomi et al., 2021; Ghomi et al., 2021a; Ghomi et al., 2021b). Initially, designs must be created computationally, utilizing advanced computed tomography or magnetic resonance imaging prior to the application of 3D bioprinting.

However, printing collagen presents challenges due to its viscosity. To address these issues, several solutions have been proposed, including the use of high-viscosity collagen solutions, hybrid inks, and cryogenic printing techniques (Nocera et al., 2018; Lee et al., 2019; Rezvani Ghomi et al., 2021). Moreover, 3D printing for tissue engineering applications has facilitated the production of high-cell-activity, low-cost fibrillary collagen scaffolds that exhibit non-cytotoxic properties (Eshkalak et al., 2020; Rezvani Ghomi et al., 2021).

Collagen in Beverages

Collagen-containing beverages have recently emerged in the market, with various options available, including cocoa collagen, soy collagen, bird nest drinks with collagen, collagen juice, andcappuccino collagen. Notably, energy drinks containing collagen are important for helping the body synthesize fatty tissues (Ridzwan, n.d.; Musayeva et al., 2022). For example, Avon has developed a drink called Life Marine Fish Peptide Collagen Drink, which combines vitamin C, salmon fish skin, high-quality fish peptide collagen, and fructooligosaccharides (Yuswan et al., 2021; Musayeva et al., 2022).

Nutraceuticals

Collagen plays a crucial role in the healing, development, and maintenance of tissues and organs (L. Wang et al., 2018; Rajabimashhadi et al., 2023). It is available in various forms, including food, capsules, drink additives, and powder (Bhaskar Bhadra et al., 2021). Collagen peptides exhibit antibacterial and antioxidant properties, making them suitable for use as dietary supplements. The use of oral collagen supplements has increased significantly in recent years (J. Wang et al., 2018; Rajabimashhadi et al., 2023). Additionally, the growth of beneficial gut flora has been stimulated by the addition of collagen with vitamin C in probiotic drinks by Malaysia Dairy Industries (MDI) (Bhaskar Bhadra et al., 2021).

Cosmetics

The skin, being the largest organ in the human body, has various functions, including protection from external damage and regulation of temperature and other bodily functions. The intake of collagen peptides can restore the functional organization of the skin and promote the growth of fibroblasts (León-López et al., 2019; Bhaskar Bhadra et al., 2021). (HC) has become a widely used bioactive component in products such as hair masks, lip masks, and facial masks. For instance, a collagen hair mask can support hair follicle regeneration and has several additional benefits, including treating split ends, reducing hair breakage, enhancing shine, strengthening hair, and increasing volume by maintaining moisture (Bhaskar Bhadra et al., 2021). Furthermore, fish collagen has demonstrated the ability to retain water and absorb moisture, which contributes to its anti-aging effects on the skin, making it a potential active ingredient in skincare products (Bolke et al., 2019; Rajabimashhadi et al., 2023). Marine-derived peptides (MPC) extracted from marine sponges have also shown significant antioxidant properties, protecting cells from UV-induced apoptosis (Pozzolini et al., 2018; Lim et al., 2019).

Before talking about collagen application in wound healing, it is important to introduce wound types and the wound healing process.

Wound healing and its types

Acute wound healing

Wounds can be classified according to their healing nature into two main categories: acute and chronic wounds (Qi et al., 2022; Mir Hosseini et al., 2023). Acute wounds typically result from exposure to burns, chemicals, or mechanical trauma, and healing generally occurs within 8 to 12 weeks, often without scarring (Kumar et al., 2022; Mir Hosseini et al., 2023). The skin consists of two layers: the epidermis, which is the outermost layer acting as a barrier (Lai-Cheong and McGrath, 2017; Mir Hosseini et al., 2023), and the dermis, which contains the extracellular matrix, fibroblasts, glycosaminoglycans, and elastin (Losquadro, 2017; Mir Hosseini et al., 2023).

Collagen is a primary constituent of the dermis and plays a crucial role in the wound healing process (Subhan et al., 2021b; Rezvani Ghomi et al., 2021). Normal wound healing occurs through four sequenced stages, as illustrated in **Figure 3**: hemostasis, inflammation, proliferation, and maturation/remodeling (Rodrigues et al., 2019; Mathew-Steiner et al., 2021). Hemostasis occurs immediately following injury, during which lymphatic vessels, antigens, and microorganisms are removed as blood flows (Trinh et al., 2022). In response to injury, collagen induces platelet aggregation and the deposition of a fibrin clot, preventing further bleeding; this process takes seconds to hours (Xue and Jackson, 2015; Mathew-Steiner et al., 2021).

The inflammation stage serves to prepare for the regeneration of new tissues at the wound site (Trinh et al., 2022). Macrophages engulf debris and secrete growth factors during this phase (Trinh et al., 2022). The activation of immune cells leads to the secretion of pro-inflammatory cytokines, which influence the migration of epithelial, fibroblast, and endothelial cells (Xue and Jackson, 2015; Mathew-Steiner et al., 2021).

The proliferation stage is the central phase of wound healing (Darby et al., 2014; Trinh et al., 2022), during which fibroblasts are actively involved in collagen deposition. This results in wound contraction and the formation of new tissue (Darby et al., 2014; Mathew-Steiner et al., 2021; Trinh et al., 2022). Myofibroblasts help bring the wound edges together using tension to facilitate closure. A key achievement of this phase is the replacement of the temporary fibrin matrix with a new matrix composed of proteoglycans, collagen fibers, and fibronectin, which restores tissue function and structure while also promoting the formation of new capillaries

(Johnson and Wilgus, 2014; D et al., 2021; Trinh et al., 2022).

In the final remodeling stage, collagen degradation produces fragments that enhance fibroblast proliferation and the secretion of growth factors, leading to re-epithelialization and angiogenesis. This stage can take weeks, months, or even years to complete (Xue and Jackson, 2015; Mathew-Steiner et al., 2021).

Chronic wound healing

Chronic wound healing is more complicated than normal healing, since it has more serious symptoms (Tottoli et al., 2020; Mir Hosseini et al., 2023). This type of wound shows no healing and cannot heal properly within three months (Mir Hosseini et al., 2023). Many reasons cause chronic wounds including hyperglycemia, persistent inflammatory responses, or tissue damage (Kharaziha et al., 2021; Mir Hosseini et al., 2023). There are a few hazards with chronic wounds, not only they are not healing quickly but they also have high costs in their treatment (Mir Hosseini et al., 2023; Xiong et al., 2023). Their infection may lead to death and these wounds can cause nutritional deficiencies, weakening the body's resistance and giving rise to various complications (Chen et al., 2022; Mir Hosseini et al., 2023).

Application in wound healing

The treatment of wounds is crucial, as it not only reduces but also stops bleeding, which can lead to severe complications or even death. One common method for wound management is the use of wound dressings. While traditional wound dressings come in various types and forms, they often have disadvantages, such as being non-degradable or absorbent, which can lead to significant environmental issues. Consequently, collagen-based wound dressings have been developed, offering potential advantages over traditional options.

Collagen is frequently chosen as a biomaterial for wound dressings due to its biodegradability, non-toxicity, and safety. In addition to these benefits, collagen possesses antimicrobial properties and facilitates the hemostasis process. Various types of collagens wound dressings include hydrogels, sponges, and more (Nezhad-Mokhtari et al., 2021; Ladhani et al., 2021; Elibol et al., 2021; Rajabimashhadi et al., 2023). These dressings can be manufactured in different forms, such as powders, amorphous gels or pastes, gel-impregnated dressings, sheets, and pads, all of which aid in the healing and recovery of wounds.

Collagen scaffolds provide mechanical support, reduce fluid loss from the wound area, and promote the migration of fibroblasts to the site of injury. Additionally, they absorb reactive oxygen and nitrogen species and serve as substrates for collagenase, thereby decreasing enzymatic degradation of the tissue (Ghosal et al., 2017; Bhaskar Bhadra et al., 2021).

Collagen-scaffolds

Here, we focus on marine scaffolds, specifically marine collagen wound dressings, to enhance the wound healing rate. Various types of scaffolds exist, categorized by their application methods, manufacturing techniques, material properties, shape, and other characteristics, (**Figure 5**).

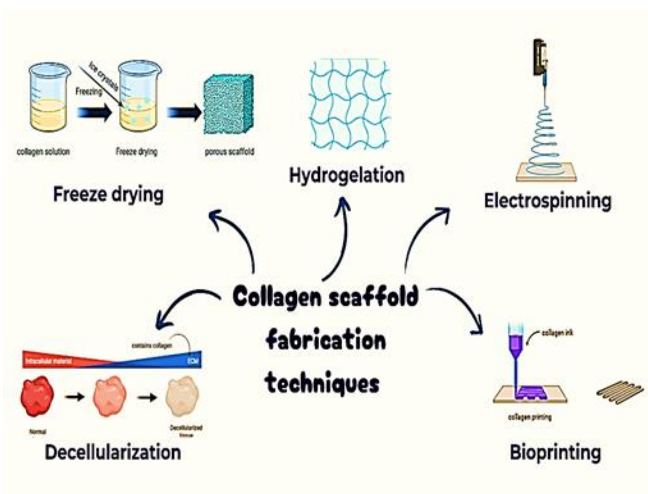

Fig 5. Illustration of collagen scaffold fabrication techniques, including freeze drying, hydrogelation, electrospinning, decellularization, and bioprinting, showcasing innovations in tissue engineering and regenerative medicine.

Table 3. Different types of collagens wound dressings

Dressing name	Properties and uses
Collagen Films	• Made from biodegradable materials • Films made by combining collagen–poly (vinyl alcohol) and glutaraldehyde vapors have been tried for transferring recombinant human growth hormone • Recombinant type I collagen from *Pichia pastoris* yeast is used in manufacturing films that are used in tissue engineering and tissue regeneration after dental surgery (Chattopadhyay and Raines, 2014)
Collagen membranes	• Important in tissue regeneration reinforcement of compromised tissues • Dural closures • Used as scaffolds for fibroblasts (Chattopadhyay & Raines, 2014)
Collagen sponges	• Their pores size is different according to collagen content and freezing rate. • Gives a moist environment to the wound • Protecting against mechanical trauma • Protecting against bacterial infection (Chattopadhyay & Raines, 2014) • Used for pressure sores, dangerous burns, leg ulcers, donor sites, and in vitro experiments (Chattopadhyay & Raines, 2014). • Also, used for transferring steroids, antibodies, and growth factors that help in wound healing • When added to the wound can absorb a large quantity of tissue secretions (Chak et al., 2013; Bhaskar Bhadra et al., 2021) • Intense infiltration of neutrophils in the sponge helps fast recovery of the wound • Helps in tissue regeneration. • When cells are associated with an ECM, like an implanted collagen sponge, increases collagen yield (Chattopadhyay & Raines, 2014; Naffa et al., 2019) • After a few days, they are absorbed and do not cause harm (Chattopadhyay & Raines, 2014).
Collagen hydrogels	• It is done by combining both natural and synthetic polymers with the Strongest match properties (Chattopadhyay & Raines, 2014) • Can absorb large quantities of water and body fluids • Provides a moisture environment (Patil et al., 2019; Bhaskar Bhadra et al., 2021) • Relieve pain by cooling so, it is very efficient in the wound healing *process* (Siaghi et al., 2024) • Used as a drug delivery system (Chattopadhyay & Raines, 2014). • Hydration abilities (Vashist, 2014; Siaghi et al., 2024). • Some drawbacks mechanical instability or fast loss of water which makes wound healing difficult as it inhibits cell migration • There are many methods done to improve the mechanical properties of collagen hydrogel like chemical and physical crosslinking (Sarrigiannidis et al., 2021; Siaghi et al., 2024), but both methods have some disadvantages chemical cross-linkers are toxic, and physical cross-linking are physically weak. • For manufacturing dense collagen hydrogel scaffolds that are like tissue structures plastic compression (PC) method is used (Karimizade et al., 2018; Siaghi et al., 2024).

Collagen-scaffold fabrication methods

Scaffold fabrication offers a significant advantage in its ability to form scaffold-like tissues. As illustrated in **Table 4**, there are numerous methods for fabricating marine collagen scaffolds (Liu et al., 2022).

Some applications of marine collagen scaffolds in wound healing and skin regeneration

Traditional methods for treating skin wounds are often inadequate for achieving rapid wound healing (Lim et al., 2019). This limitation highlights the need for innovative temporal barriers to protect wounded skin from infection using tissue engineering methods. Notably, various collagen scaffolds have been applied to surgical procedures and validated by the FDA (Shahrokhi et al., 2014; Do Amaral et al., 2019).

One such scaffold is the porous collagen-glycosaminoglycan (collagen-GAG) scaffold, one of the earliest developments in tissue engineering (Do Amaral et al., 2019). These scaffolds are widely utilized in treating burns, diabetic foot ulcers, and scar contractures, yielding positive outcomes (Driver et al., 2015; Do Amaral et al., 2019). Additionally, tilapia skin collagen (marine collagen) exhibits effects comparable to those of bovine collagen regarding wound healing, collagen synthesis, fibroblast proliferation, dermal reconstitution, and re-epithelialization. This is accompanied by upregulated expressions of epidermal growth factor, vascular endothelial marker, and fibroblast growth factor (FGF) (Chen et al., 2019; Lim et al., 2019). Wound healing can be further enhanced using poly(3-hydroxybutyrate-co-4-hydroxybutyrate) (P(3HB-co-4HB)) scaffolds derived from tilapia skin, which serve as a source of marine collagen peptide (MCP) integrated with an aminolyzed surface. This scaffold holds significant promise for the future of wound healing (Vigneswari et al., 2016; Lim et al., 2019). The tilapia fish scale, featuring a collagen/chitosan/glycerin porous scaffold manufactured by freeze-drying, promotes rapid wound healing when combined with human fibroblasts and keratinocytes in a 3D co-culture system (Ullah et al., 2018; Lim et al., 2019). Electrospinning was employed to manufacture a multifunctional and biomimetic tilapia skin collagen/bioactive glass nanofiber wound dressing (Zhou et al., 2017; Lim et al., 2019). This type of nanofiber exhibits antibacterial properties against Staphylococcus aureus, promotes proliferation, enhances the attachment and transference of human keratinocytes (HaCaT), accelerates wound healing, encourages the growth of human vascular endothelial cells, and stimulates human dermal fibroblasts to secrete type I collagen and VEGF. Collectively, these functions make it an effective wound dressing (Zhou et al., 2017; Lim et al., 2019). Additionally, other sources of (MCP), such as chum salmon skin, have also been shown to enhance the wound healing process (Wang et al., 2015; Lim et al., 2019).

Bio-based topical treatments, including polymeric films or powders, have been developed using the horny skeleton of marine sponges (Porifera, Dictyoceratida). To further accelerate wound healing, drugs may be incorporated into the scaffold to enhance cell migration. An example of this is a luteolin-incorporated fish collagen hydrogel scaffold (Siaghi et al., 2024). Luteolin, a flavonoid abundant in fruits and vegetables, has been recognized for its significant role in wound healing, particularly in diabetic wounds, by promoting antioxidative capacity and preventing inflammation (Zhou et al., 2022; He et al., 2023; Siaghi et al., 2024). After luteolin is broken down in an alkaline solution, it is added to collagen hydrogel extracted from the skin of crucian carp (Carassius carassius) in situ. This scaffold can effectively regulate drug release. Experiments have shown that the addition of luteolin to the hydrogel results in the highest rate of wound healing, achieved through mechanisms such as re-epithelialization, collagen deposition, and granulation tissue formation (Siaghi et al., 2024).

Conclusion

Collagen from marine sources is a promising raw material for the manufacturing of collagen wound dressings due to its safety, various advantages, and its role in accelerating the wound-healing process. However, despite these numerous benefits, several disadvantages hinder the widespread adoption of collagen wound dressings. These drawbacks include high costs, an unpleasant odor for patients, and the complexity of the application, which often necessitates a secondary dressing. To address these challenges and promote broader public use, continued research and development are essential. One promising prospect involves modifying collagen wound dressings to create absorbable versions that eliminate the need for disposal. Additionally, incorporating AI technology into these dressings could provide more accurate and informative data for patients, further enhancing their effectiveness and user experience.

Conflict of interest

The authors declare that they have no conflict of interest.

Table 4. Collagen-scaffold fabrication methods and techniques

Name	Fabrication technique	References
Freeze drying	• This method is known as collagen sponges • drying of collagen solution after its preparation then adding it to a mold and freeze-drying. • Ice crystals help in collagen entrapment at freezing, which is eliminated at drying by sublimation. • Many factors regulate the shape of collagen scaffolds, including temperature, the sublimation of ice crystals, collagen concentration, and freezing rate. These elements interact in complex ways to influence the final structure and properties of the scaffold, thereby impacting its suitability for various applications in tissue engineering and regenerative medicine.	(Pot et al., 2015; Liu et al., 2022). (Haugh et al., 2010; Shi et al., 2020; Ramanathan et al., 2020; Liu et al., 2022).
Hydrogenation	• Have a 3D water-swollen network that mimics ECM (extracellular matrix) which makes it highly used in tissue engineering • Collagen molecules are collected to form a fibrillar hydrogel under physiological conditions	(Riley et al., 2019; Liu et al., 2022) (Iwashita et al., 2019; Liu et al., 2022)
Electrospinning	• This method relies on the high potential difference between the collector and the needle to deposit polymer fibers onto the collector. • As a result, scaffolds with a large surface area and multi-pore structures, featuring fibers on the micrometer to the nanometer scale, can be easily produced. These scaffolds closely mimic the porous structure of the extracellular matrix (ECM)	(Ghorani and Tucker, 2015; Liu et al., 2022) (Rahmati et al., 2021; Liu et al., 2022).
Bioprinting	• The most used technique is extrusion-based bioprinting. • This method is favored due to its use of bio-compliant natural polymers, including collagen, which are compatible with other materials. In this approach, collagen hydrogel serves as the ink for manufacturing tissue scaffolds, as pure collagen is not suitable for printing. • Furthermore, marine collagen offers distinct advantages over other collagen types for use in extrusion bioprinting	(Osidak et al., 2020; Lee et al., 2021; Liu et al., 2022). (Lee et al., 2021; Liu et al., 2022).
Decellularization	• In this process, cells are removed from connective tissue, leaving behind the extracellular matrix (ECM) that contains collagen and other structural proteins. • The presence of an intact acellular matrix promotes tissue regeneration by serving as a scaffold. • Decellularized tissues offer numerous advantages, including the conservation of structure and components, which provide a similar environment for host cells to adhere and grow	(Keane et al., 2016; Lau et al., 2019; Liu et al., 2022). (Taylor et al., 2018; Lau et al., 2019; Liu et al., 2022).

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