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Original Article

Collagen Based Biomaterial And Its Uses As Wound Healing:- A Comprehensive Review

Pratham Jain[1*], Ms. Sonika Rathi[1], Dr. Pragnesh Patani[2]

[1]Assistant Professor, Department of Pharmacology, Khyati College of Pharmacy, Palodia, Ahmedabad.

[2]Principal and Professor, Department of Pharmacology, Khyati Collage of Pharmacy, Palodia, Ahmedabad

***Corresponding Author:** Pratham Jain
*Khyati Collage of Pharmacy, Palodia, Ahmedabad, Email:- pharmasistkcp01@gmail.com

Abstract
Collagen has become more and more popular in the last several decades. This study's primary goal is to present a summary of the most current information on the benefits of collagen and its derived material in animal experiments and clinical trials. Some of these beneficial benefits include antioxidant, anti-aging, anti-tumor, anti-osteoporotic, anti-arthritis, anti-inflammatory, wound-healing, anti-hypertensive, and anti-atherosclerotic activity. About 30% of the dry weight of the human body is composed of collagen, the most prevalent structural protein. For the construction of bones, tendons, cartilage, connective tissues, and skin, it is essential. Progress has been achieved in comprehending the composition and stability of triple helices in collagen. For use in biomedicine and nanotechnology, synthetic collagen fibrils that resemble natural ones are being produced. The vertebrate collagen superfamily, which consists of more than 50 collagens and collagen-like proteins, is described in detail in this chapter along with its variety, synthesis, and assembly. It describes the many supramolecular assembly forms and structures of collagens, the procedures involved in the manufacture of collagen, and the post-translational changes unique to collagen. The processes that govern the construction of collagen fibrils in vitro and in vivo, as well as the interactions that take place, are discussed.

Keywords: Kolla, metalloproteinase, Heterotrimer, Homotrimer, Polymorphonuclear leucocyte, inflammatory phase, proliferative phase, maturation phase

Introduction

The majority of the extracellular matrix is composed of the triple-helical protein collagen. Originating from the Greek word "kolla" (glue), collagen plays a crucial role in preserving the structural integrity of many tissues such as skin, muscle, bones, tendon and ligament. About 30% of dry weight of human body is made up of collagen. Due to its availability, biodegradability, and biocompatibility, it is a useful biomaterial. Three helical chains make up collagen: two are the same (α1) and one is distinct (α2) collagen[(1)]. It experiences a number of post-translational changes, including as glycosylation and hydroxylation. Collagenases and matrix metalloproteinase (MMPs) are among the enzymes involved in the breakdown [(2)]. The way collagen-based biomaterials function is by offering a matrix that encourages cell migration, growth, and differentiation. In order for a wound to heal, they also aid in keeping the surrounding wet[(2)].

Structure of collagen, Biosynthesis and Its types

Structure of collagen

The nomenclature of the protein indicates that a collagen molecule is made up of three α-chains, each with a molecular weight of about 100 kDa and roughly 1,000 amino acids. Due to the high Gly content of amino acids, their molecular weight is often smaller than that of most proteins. Collagen's three α-chains can vary (a heterotrimer) or be identical (a homotrimer) according on the kinds and sources.[3,4]

Biosynthesis of collagen

The most prevalent protein in the human body, collagen is essential to the strength and structure of many tissues, including the skin, bones, tendons, and ligaments. Several essential stages are involved in the production of collagen.[4]

Step 1:- Gene Expression: Specific genes, mainly COL1A1 and COL1A2 for type I collagen, are translated into messenger RNA (mRNA) in the nucleus of cells, where the process starts.[4]

Step 2:- Translation: In the rough endoplasmic reticulum (RER), the mRNA is subsequently translated into pre-procollagen. A signal peptide makes up pre-procollagen, which is separated to become procollagen.

Step 3:- Post-Translational Changes: Procollagen experiences a number of changes, such as the hydroxylation of lysine and proline residues, which is necessary for the collagen triple helix to remain stable. Vitamin C is needed as a cofactor in this process.[5]

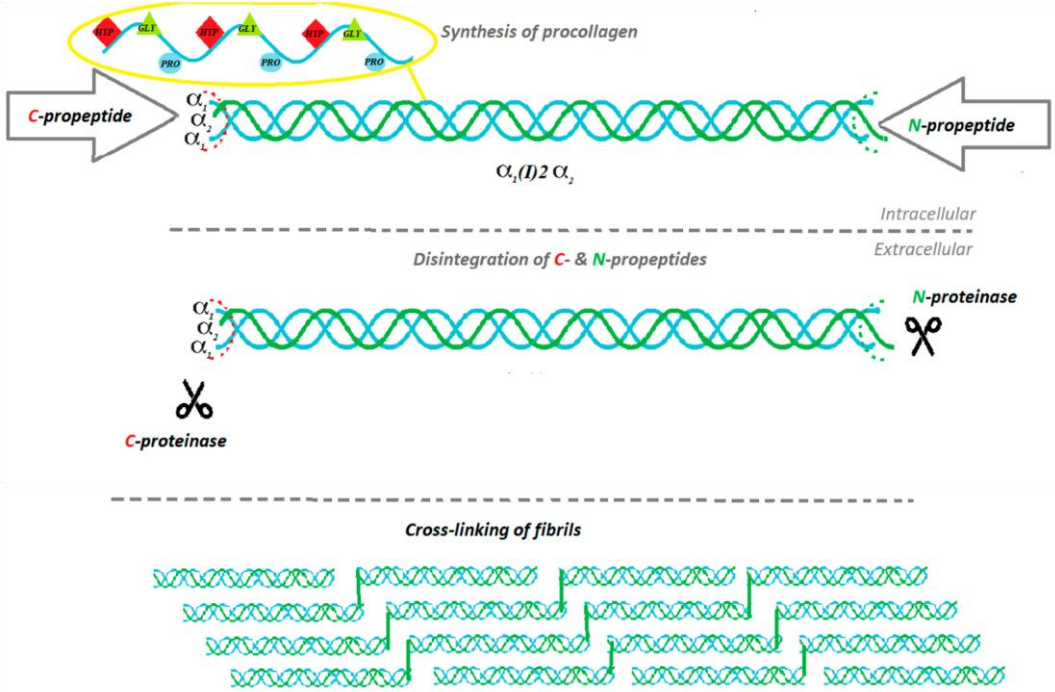
Step 4:- Triple Helix Formation: A triple helix structure is formed when two alpha-1 procollagen chains and one alpha-2 chain for type I collagen come together. This happens in the RER.

Step 5:- Secretion: After being delivered to the Golgi apparatus, the procollagen is encapsulated and released into the extracellular milieu.[5,6]

Step 6:- Conversion to Collagen: After leaving the cell, procollagen is broken down into mature collagen molecules by certain enzymes called procollagen peptidases. This process removes the terminal propeptides from procollagen.[6]

Step 7:- Collagen fibrils are formed when collagen molecules spontaneously organize into fibrils. These fibrils then further aggregate to create collagen fibers, which give tissues their tensile strength.

Step 8:- Cross-Linking: The stability and mechanical characteristics of collagen fibers are improved by the enzymatic cross-linking process.[7,8]



1.1:- Diagram showing biosynthesis of collagen

Types of collagen

Under electron microscopy, the traditional collagen fibrils with a repeated banding pattern are formed by the 28 fibrillar collagens that are known to exist in humans. Important varieties consist of[9]

Type I: Present in the lungs, cornea, bone, tendon, skin, and vascular system.

Type II: Cartilage is the source.

Type III: Found in elastic tissues such as blood vessels, the lung, and the skin of embryos.

Types II and V: are found in relation to each other, respectively.

Collagens without fibers[9,10]

Type IV: collagens found in the basement membrane, type VII anchoring filaments, and types XV and XVIII multiplexins are examples of non-fibrillar collagens. Each performs distinct structural roles in various tissues.[9]

The first collagen to be found, type I collagen, is referred to as a heterotrimer because it has one α2-chain and two identical α1-chains in the chemical form [α1(I)]2α2(I). Moreover, α1(I)α2(I)α3(I), another heterotrimer of type I collagen, has also been found in the muscles and skin of rainbow trout. It has three distinct α-chains, with the α3-chain having a molecular weight that is comparable to the α1-chain. Nonetheless, discovered that the predominant component of skin collagen from the chordate gigantic Red Sea cucumber is a [α1(I)]3 homotrimer.[10]

Pathology of wound healing

There are several stages that overlap in the intricate biological process of wound healing. The inflammatory phase, proliferative phase, and maturation phase are the three primary phases into which these stages may be roughly divided. An comprehensive synopsis of every phase is provided below.[11]

1.Inflammatory Phase:-

-Duration: Starts as soon as an injury occurs and lasts for around three days.

-Hemostasis: Platelets clump together to create a clot, and blood arteries narrow to lessen blood loss. This clot gives arriving cells a matrix and acts as a transient barrier to pathogens.[11]

-Vasodilation: Blood vessels dilate after hemostasis, boosting local blood flow. Warmth and redness are the outcomes of this.[11,12]

-Cellular Response: o Within hours, phagocytizing bacteria and debris, polymorphonuclear leukocytes, or neutrophils, are the initial responders.

Within a day, macrophages arrive. They keep up the phagocytic activity and release growth factors and cytokines that are essential for the subsequent stage of recovery.

-Exudate Formation: A fluid-filled exudate made of cells and proteins fills the affected region. [12]

2.Proliferative Phase.

-Duration: Usually starts on day 3 and lasts until around day 14 after the injury.

-Fibroblast Proliferation: After migrating into the wound site, fibroblasts multiply. They are necessary for the production of collagen and the creation of extracellular matrix.

-Collagen Formation: Extracellular collagen fibrils start to form. These fibrils are thin and amorphous at first, but they eventually gain structure.[12]

-Angiogenesis: As old blood arteries regenerate, new ones grow out of them, bringing nutrition and oxygen to the mending tissue. Growth factors generated by fibroblasts and macrophages drive this process.

-Formation of Granulation Tissue: Granulation tissue, which fills up the wound and has a pink, soft appearance, is created when blood vessels and new connective tissue combine.

-Re-epithelialization: To restore the epithelial barrier, keratinocytes move over the wound bed and cover the surface.[12,13,14]

3.Maturation Phase:-

-Duration: Depending on the size and location of the wound, this phase may persist for weeks or years.[13]

-Collagen Remodeling: Stronger, better-organized collagen fibers replace the initially deposited collagen. The tissue's tensile strength is increased by the cross-linking and rearrangement of the collagen.

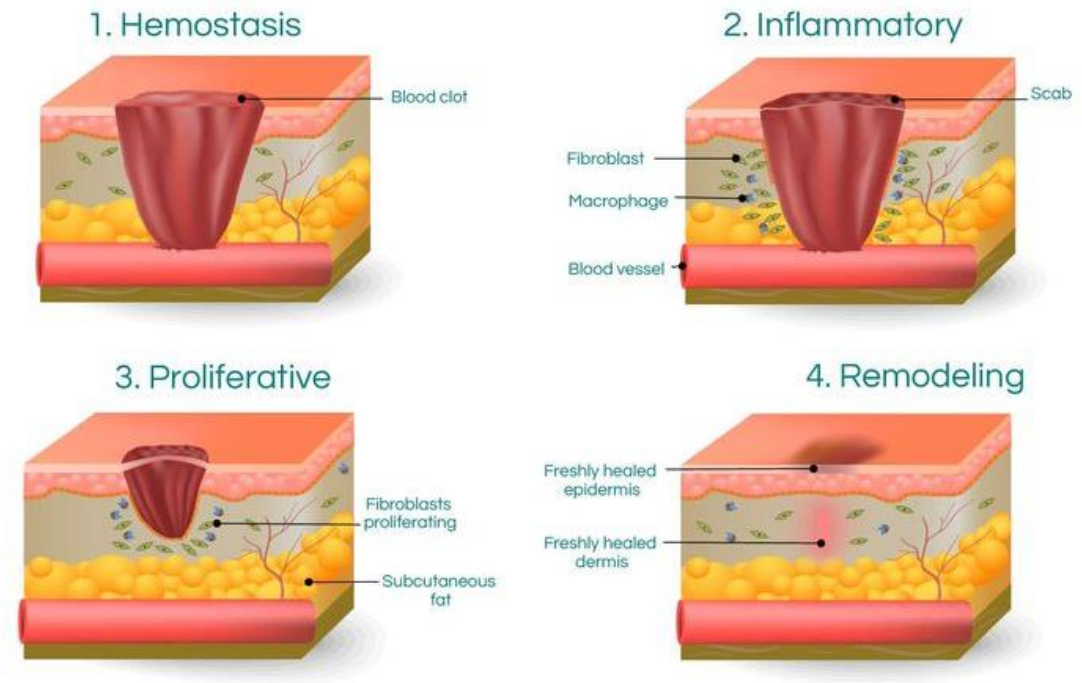
-Decline in Cellularity: As the tissue ages, fewer fibroblasts and other cells are present. The wound thickens and becomes less vascularized.[13,14]

-Scar Formation: Compared to normal skin, the final scar tissue is less vascularized and has a different composition. It usually has less elasticity and might have a paler appearance than the surrounding tissue.

-Functional Restoration: Although scar tissue may eventually restore some of its original properties, it frequently falls short of the original tissue structure and function.[14]

Key cell type involved in these process:-

- **Platelets**: Initiate hemostasis and release growth factors.
- **Neutrophils**: First responders that clear debris and pathogens.
- **Macrophages**: Play a critical role in inflammation and transition to the proliferative phase by releasing cytokines and growth factors.
- **Fibroblasts**: Responsible for collagen synthesis and extracellular matrix formation.
- **Keratinocytes**: Essential for re-epithelialization during the proliferative phase.[14]



1.2 **Diagram showing 4 phases of mechanism of wound healing**

Role of collagen in wound healing

A vital component of healthcare is wound care, which includes a variety of approaches and procedures meant to speed up the healing process. Collagen is a structural protein that is essential to the body's self-healing processes and is one of the main participants in this complex biological dance. This article will examine the role of collagen in wound care, including its kinds, functions, and several

applications that may be used to accelerate the healing process.[15] The most prevalent protein in the human body, collagen gives different tissues including skin, bones, tendons, and ligaments structural support. Collagen primarily aids in the creation of a robust, flexible matrix that promotes tissue regeneration and healing in the setting of wound treatment[16]. In order to promote wound healing, collagens can "directly modulate the wound microenvironment, serve as a scaffold for cellular attachment and function, or deliver biologically active principles or antimicrobials," according to a recently published study titled Collagen in Wound Healing.[17,18]

The types of collagen that aid in various wound healing processes are listed below:-

Type 1 collagen:- Helps in regeneration of skin and provides tensile strength and stability at wound site

Type 2 collagen:- It is involved in formation of extracellular matrix(ECM) in proliferation phase and also incorporation of type 2 collagen helps in repairing cartilage injuries[19,20]

Type 3 collagen:- In the early phases of wound healing, this kind of collagen predominates. It creates a fragile, elastic matrix that promotes the migration of cells and the granulation tissue's early development.[21]

Type 4 collagen:- Support for Basement Membrane .Type IV collagen is present in the basement membrane and serves as a basis for the adhesion and migration of epithelial cells[22]. It promotes angiogenesis during wound healing and is essential for the healthy development of new blood vessels. To promote epithelialization and improve vascularization, wound dressings containing Type IV collagen may be used[23,24].

Application of collagen and its bio enhancements

1:- Enhanced Tissue Regeneration: As a primary structural protein in the extracellular matrix, collagen supports the regeneration of tissues. Future developments may focus on collagen scaffolds that enhance the healing of chronic wounds and injuries.[25]

2:- Biomaterial Advancements: Advancements in collagen-based biomaterials, such as hydrogels and sponge-like structures, can improve the delivery of growth factors and therapeutic agents, facilitating more effective wound healing.[26]

3:- Personalized Medicine: The future may see the use of patient-specific collagen formulations, tailored to individual healing responses and conditions, offering a more personalized approach to wound care.[27]

4:- Nanotechnology Integration: The integration of nanotechnology with collagen could lead to novel wound dressings that improve absorption, provide antibacterial properties, and enable controlled drug release, enhancing overall healing outcomes.[28]

5:- Regenerative Medicine and Stem Cell Therapy: Collagen can be used in combination with stem cells to promote tissue repair. The future may see innovations that harness this synergy to improve healing in complex wounds.[29]

6:- Bioactive Peptides Development: Research into bioactive collagen-derived peptides could lead to new therapeutics that promote cellular activities relevant to wound healing, such as angiogenesis and fibroblast activation.[30]

7:- Anti-Inflammatory Properties: Enhanced understanding of collagen's role in modulating inflammation may lead to therapies that can reduce excessive inflammatory responses in wound healing, improving outcomes for patients with chronic wounds.[31]

8:- Collagen-based Dressings: Future developments may include advanced collagen-based dressings that actively promote healing through moisture retention, improved oxygenation, and support for cell migration.[32]

9:- Incorporation of Other Biomolecules: Future products may include collagen in combination with other biomolecules like hyaluronic acid or chitosan, creating multifunctional agents that address various stages of wound healing more effectively.[33]

10:- Sustainability and Biocompatibility: As concerns about sustainability grow, future collagen products may focus on using environmentally friendly sources, such as plant-based or recombinant collagen, along with ensuring high biocompatibility and minimal side effects.[34]

Products or biomaterials based or derived from collagen

There are several related or derived items on the market that are based on collagen and its derivatives. The following is a list of some of them that are utilized in wound healing and other medicinal applications.[35,36,37]

1.1:-Table showing products and application and its formulation available base on collagen

Formulation	Product	Applications
Sponge	Kollagen , Genta-coll	Hemostasis, Hard tissues
	Septocoll , TissueFleece	Hemostasis
	Biopad	Wound healing ,Hard tissues
	Revamil , Collatamp, Bionectpad, Collexa	Wound healing
	TachoTop , CollGARA , Gentafleece , TachoComb, TachoSil	Hemostasis, Wound healing
Powder	Bio-gen , Bioart	Hard tissues
	Versuspray	Wound healing
Gel	Nithya	Soft tissues, Antiaging
	Salvecoll -E	Wound healing
Membrane	Biocollage	Hard tissues
	MeRG, MaioRegen	Soft tissues
	Bio-conneKt	Wound healing
	Parasorb	Hemostasis, Hard tissues
Sheet	T-Barrier	Hemostasis, Hard tissue
	TissuFoil E, TissuDura	Wound healing
	Xenomatrix	Soft tissues
	Antema	Hemostasis , Wound healing

Conclusion

Collagen-based biomaterials are critical for pharmaceutical applications as well as medical applications. Collagen remains the preferred protein for the creation of biomaterials due to its exceptional biocompatibility and minimal immunogenicity. It may be isolated and combined with other molecules to form a variety of tissue sources. In basic research, it may be used as a decellularized extracellular matrix (ECM), and in medicinal applications, it can be used as tissue replacement material.High tensile strength scaffolds that are innately biocompatible, biodegradable, and nontoxic

when applied externally may be fashioned from natural collagen. These scaffolds are highly organized and three-dimensional. Collagen is the preferred material for tissue engineering and wound healing because of these qualities. This piece examines the composition and molecular interactions of collagen in living organisms, as well as the application of natural collagen in sponges, injectable, films and membranes, dressings, and skin grafts. Additionally, the ongoing research and development of synthetic collagen mimetic peptides as anchors for cytoactive agents in wound beds is covered. Collagen-based formulations, including scaffolds, dressings, films, pellets, and mixtures containing liposomes, have shown useful in promoting directed tissue regeneration, Dural closure, wound healing, and strengthening of damaged tissue. The primary amplifications for medical use are hemostatic agents, reabsorb able surgical sutures, collagen for burn and wound cover dressings, osteogenic and bone filling materials, and immobilization of therapeutic enzymes.

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