Since 1987
REVIEW OF CLINICAL PHARMACOLOGY AND PHARMACOKINETICS, INTERNATIONAL EDITION |38 (1): 73-86 (2024) Rcpp

Received: 1 February 2024 | **Reviewed**: 8 March 2024 | **Accepted**: 8 March 2024 | **Published**: 09 April 2024

Open Access | **Review**

Biomedical applications of collagen: A Review

Mashiur Rahman[1] , Mainul Huda[1] , Anamul Hasan[1] , Mala Khan[1,*]

[1]Bangladesh Reference Institute for Chemical Measurements (BRICM), Dhaka-1205, Bangladesh

***Corresponding author**
Dr. Mala Khan, Bangladesh Reference Institute for Chemical Measurements, Dr. Qudrat-e-Khuda Road (Laboratory Road), Dhanmondi, Dhaka-1205, Bangladesh
Email: dg.mic@bricm.gov.bd.

Abstract
Collagen is an excellent biomaterial. Biological characteristics of collagen including biodegradability and weak antigenicity made it a primary resource in medical application. In biomedical field collagen is mainly used as sponges for wound/burn, supplement in rheumatoid arthritis, drug delivery system, controlling material for transdermal delivery and basic matrices for cell culture system due to its ability to stimulate formation of tissue and organ. Moreover, collagen is also applied in tissue engineering including bone defect, tissue regeneration, skin replacement and artificial blood vessels and valves. The article reviews biomedical application of collagen in wound healing, rheumatoid arthritis, drug delivery system, tissue engineering and lung function improvement in pulmonary fibrosis due to viral infection.

KEYWORDS
collagen, wound healing, arthritis, tissue regeneration, pulmonary fibrosis

How to cite this article: Rahman M., Huda M., Hasan A., Khan M., Biomedical applications of collagen: A Review. *Rev. Clin. Pharmacol. Pharmacokinet. Int. Ed.* 38 (1): 73-86 (2024).
https://doi.org/10.61873/KJDF4893

Publisher note: PHARMAKON-Press stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Copyright: © 2024 by the authors.
Licensee PHARMAKON-Press, Athens, Greece.
This is an open access article published under the terms and conditions of the Creative Commons Attribution (CC BY) license.

1. INTRODUCTION

Collagen is a naturally occurring polymer accounts for 30% of the total protein in the body. It is the major component of extracellular matrix (ECM) and involved in formation of fibrillar and microfibrillar network which plays a pivotal role in diverse cellular processes including cell proliferation, differentiation, migration, and adhesion [1,2,3,4,5,6]. Collagen contributes to the stability and structural integrity of tissues and organs by forming stable insoluble fibrils with excellent tensile strength. Many synthetic and natural polymers and their analogues are used as biomaterials, but the distinct mode of interaction of collagen and its characteristics as a biomaterial made it more prominent than others [7].

Collagen possesses unique characteristic features in terms of structure, size, and amino acid sequence [8,9]. The basic collagen molecule (with ~300kDa molecular weight) is a rod-shaped trimetric molecule made up of three polypeptide chains,

twined around one another as in a three-stranded rope [10]. Glycine (Gly) is the major amino acid in collagen molecule (accounting approximately 35%) and positions in every third amino acid residue in a single polypeptide chain. Proline (Pro) is considered the second abundant amino acid (around 12%) of all amino acids, while the others include lysine (Lys), alanine (Ala), aspartic (Asp), glutamic (Glu) and arginine (Arg) are rarely occurring nevertheless crucial amino acids. Another characteristic feature in the molecular structure of collagen is that it contains almost equimolar amounts of basic and acidic amino acids. Additionally, the alignment of the polypeptide chain created during post-translational and enzymatic protein processing contains a sizable concentration of hydroxyproline (Hyp) and hydroxylysine (Hyl), which are responsible for the creation of higher-order structures [11,12,13,14].

Based on the α-chain composition, there are different types of collagens. 28 types of collagens have been identified among them 5 categories are mostly common (type I–V)[15,16]. Due to collagen's superior degradability, flexibility, and biocompatibility, it can be used in a wide range of applications [17,18]. Again, collagen has a minimal immunogenicity; hence the likelihood of rejection after ingestion or injection into the body is relatively low. Despite having lower antigenicity, this property can be enhanced by chemical modification to suppress any immune response [19,20]. Additionally, collagen peptides and gelatin (denatured collagen) have been widely utilized in different fields such as food, medicine, cosmetics, leather and film industries, diagnostic imaging, and therapeutic delivery [21].

The purpose of this article is to review biomedical applications in terms of their mechanism of action of collagen including the collagen sponge, collagen supplement and collagen film in wound healing, rheumatoid arthritis, drug delivery system, tissue regeneration, tissue engineering and lung function after viral infection.

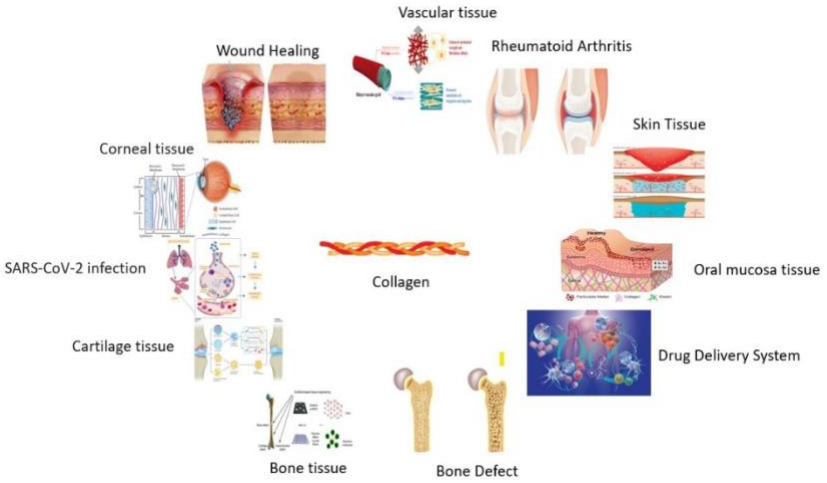

Figure 1. Biomedical applications of collagen

2. BIOMEDICAL USE OF COLLAGEN

Collagen has a wide range of uses as it is involved in formation of tissues and organs and also participate in different functional expression of cells. It has great impact on biomedical science because the fiber form of collagen has extra strength and stability through its self-aggregation and cross-linking properties. Another vital point is that, collagen can be found abundantly in nature.

2.1. Collagen in Wound Healing

Collagen plays a critical function in all stages of the wound healing process, promoting cellular activity and assisting in the formation of new tissue [22]. Wound healing is a multi-phased process that includes hemostasis, inflammation, proliferation & maturation. This process involves in platelet activation and inflammatory cytokine secretion, migration of macrophages, fibroblasts, and keratinocytes and expression of matrix metalloproteinase (MMPs) and growth factors which leads to mature ECM and the formation of functional neo-tissue [23].

Collagen structure consists of large amino acids chain mostly characterized as the repeating sequence of Gly-Pro-X or Gly-X-Hyp where X represents other amino acids.

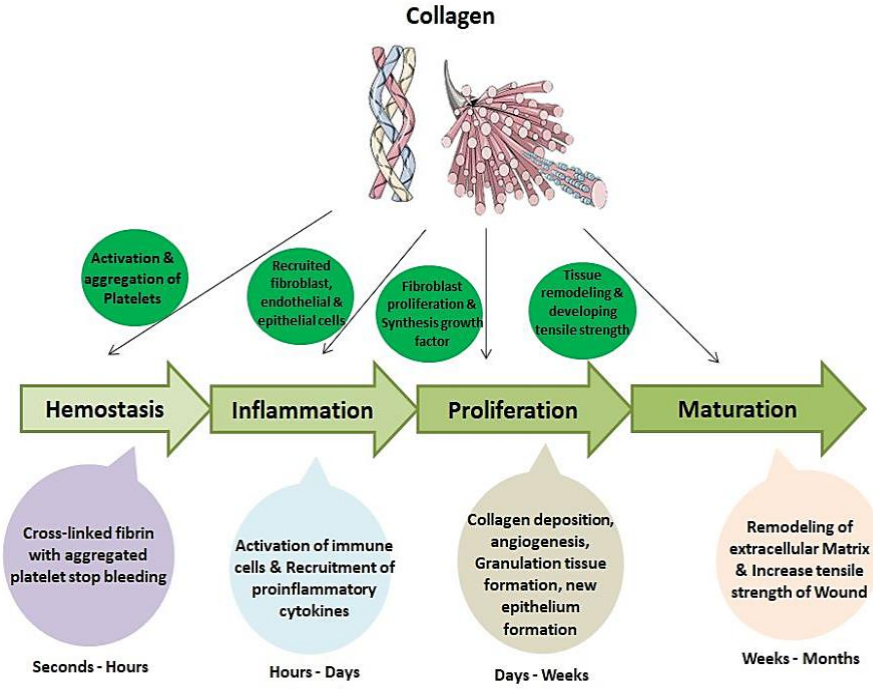

Figure 2: Function of collagen in wound healing process

This large molecule undergoes eight different posttranslational steps including cleavage to single peptides, hydroxylation of proline or lysine to 4-hydroxyproline or 4-hydroxylysine, glycosylation of few hydroxylysine molecules with glucose or galactose, addition of oligosaccharides to previously formed propeptides, association of C-terminal propeptides, formation of disulfide bonds, formation of triple helix structure until secreted as procollagen into the extracellular matrix [24]. In extra cellular environment the propeptide ends are specifically cleaved by procollagen C-proteinases and procollagen N-proteinases which decrease the solubility of the molecule and trigger up the fibrillation process [25].

Collagen increases the mechanical strength and elasticity of tissues and promotes cellular attachment, proliferation and differentiation (Figure 1). Upregulation of MMP-2 via microRNA generate a collagenolytic environment in wounded region. This can reduce the collagen-I/collagen-III ratio and compromising the biomedical properties of the repaired skin and try to make it vulnerable to wound recurrence [26].

Several aquatic collagen-derived peptides with modest molecular weights (5KDa) have been demonstrated to have a chemotactic impact when administered to skin cells (keratinocytes). These peptides have the capacity to induce cellular proliferation and migration to the wound site, speeding up wound healing. Collagen peptides from the skin of nile tilapia (*O. niloticus*) have recently been found to have wound healing capabilities by Hu *et al*. [27]. Both in vitro and in vivo wound healing investigations yielded encouraging results for future wound healing applications. Yang *et al*. also extracted collagen peptides from fish and demonstrated that oral treatment of collagen peptides to wounded rats boosted healing rates compared to control groups [28]. Hydroxyproline was shown to be higher in the collagen-treated group over time than in the control group, indicating that it promotes collagen deposition and consequently healing [29]. Wang *et al*. [30] reported that oral intake of Chum salmon skin collagen peptides may promote angiogenesis, collagen deposition, and wound contraction, like the experiments discussed above.

These findings are comparable to those of Zhang *et al*., who found that marine collagen peptides improved wound closure rates as well as tensile strength and collagen deposition at the site of incision in rats [31]. At 7 and 11 days after injury, histological analysis of the collagen-treated groups revealed increased epithelization, vascularization, and fibroblast infiltration. Collagen deposition was also greater in the treated groups [31,32].

Pozzolini *et al*. extracted and purified marine collagen hydroxylates from a marine sponge (*Chondrosia reniformis*) [33]. Collagen peptide fractions were administered in vitro at a specific concentration level and cells were examined for several hours after administration. At the 24-hour time period, cells were seen moving and populating the scratch gap area, followed by enhanced cell proliferation. These findings point to the marine collagen hydroxylates derived from *C. reniformis* having promising wound-healing properties.

2.2. Drug Delivery Systems

A drug delivery system is a device that is used to deliver a pharmacological agent to a patient in order to create a therapeutic effect. Concerns that large-sized materials in drug delivery encounter include in vivo instability, limited bioavailability, solubility, and absorption into human tissues with target-specific delivery and tonic effectiveness, as well as possible adverse effects. As a result, adopting innovative drug delivery methods to tailor medications to specific body areas could be a viable solution to these pressing problems [34]. Collagen has been established in several studies to be a viable carrier for various drug delivery systems.

Collagen is non-antigenic, non-toxic, biodegradable polymer which is absorbed simply in the body, shows synergism with other bioactive compound and compatible with synthetic polymers. Transdermal delivery of 17b-estradiol-hemihydrate during hormone replacement therapy, renal cartilage sponge collagen nanoparticles were employed as an osmotic accelerator which revealed that hydrogels of estradiol-collagen nanoparticles might delay estradiol release time and increase estradiol absorption substantially. As a result, sponge collagen nanoparticles are a viable transdermal medication delivery vehicle [35]. The high content of glycosaminoglycan in naturally keratinized sponges (Porous fungus, Dictyoceratida) can promote wound healing when used topically as a bio-based dressing and a biologically active bionic carrier [36]. Collagenous peptide-chelated calcium (CPCC) from marine fish scales can use as a transporter of required nanoparticle in target site and as a supplementation of calcium which can significantly boosted bone mineral density [37]. Collagen hybrid gel made from chitosan and chum salmon skin was discovered as a good carrier for tissue filler and a drug delivery technique [38].

Collagen has the potential to be used as a microprotein delivery device. Being a polymer matrix, the microgranular protein delivery method was developed utilizing collagen [39]. They were extracted using an emulsification-gel-solvent method and CMP collagen microparticles were cross-linked with 1-ethyl-3-(3-dimethylaminopropyl) carbon diimine (EDC) which increased the stability of CMP in water, allowing for delayed release of microgranular proteins.

2.3. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune illness marked by chronic inflammatory synovitis and consequent articular tissue loss. Although the exact origin of RA has yet to be determined, evidence suggests that CD4+ T cell–mediated autoimmune responses play a key role in the disease's pathophysiology [40].

By infiltrating fibrovascular tissue, RA induces cartilage and bone degradation [41]. Oral administration of cartilage-derived collagen type II was clinically helpful and safe in individuals with RA [42].

A randomised trial on 274 individuals with active RA were randomized to receive either placebo or various doses of oral cartilage derived collagen type II. The collagen therapy group showed positive results at the lowest dose tested, and the therapeutic agent had no negative effects.

Wei *et al*. [43] used type II collagen (chicken breast) (CCII) in the treatment of RA in a 24-week randomized methotrexate-controlled research and evaluated safety and efficacy. CCII is a protein derived from the cartilage of chicken breasts. By developing oral tolerance, it has the potential to cure autoimmune illnesses. A total of 533 RA patients were split into two groups. CCII was found to be effective in the treatment of RA and to be safe to consume. Furthermore, Xue *et al*. suggested that, the discovery of therapeutic DNA vaccines may open new avenues for the treatment of RA [44].

Song *et al*. [45] created a novel therapeutic DNA vaccine encoding CCII (pcDNACCOL2A1), and it has been shown that a single injection of the pcDNA-CCOL2A1 vaccination can generate substantial immunological tolerance to experimental RA. As a result, this vaccination could be used to treat RA and appears to be as effective as methotrexate, which is now the "gold standard" treat-

ment. In Wistar rats, the immunogenicity and safety of the pcDNA-CCOL2A1 vaccination were examined [46]. The pcDNA-CCOL2A1 vaccination was well tolerated and safe at a maximum dose of 3 mg/kg, according to the findings.

2.4. Oral mucosa tissue regeneration

Different types of natural and synthetic, collagen-based biomaterials have been used to engineer oral mucosa. Terada *et al*.[47] constructed a

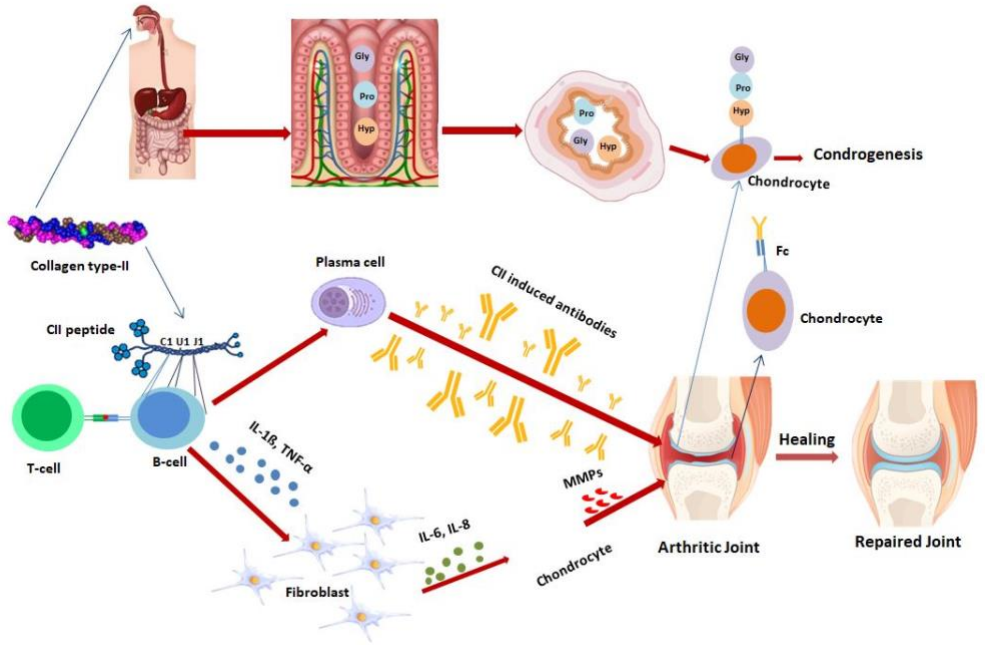

Figure. 3: Function of collagen in Rheumatoid arthritis

chitosan–collagen composite scaffold (C3) by incorporating commercial chitosan and tilapia scale collagen and also assessed its biocompatibility with oral mucosa keratinocytes. Their finding suggested that C3 has a potential application for epithelial tissue engineering and provides a new potential therapeutic device for oral mucosa regenerative medicine. In another study, Suzuki at el. [48] constructed biomimetic tissue engineered oral mucosa from 1% type I collagen scaffold (CS) from tilapia fish scale. This microstructure mimics the dermal–epidermal junction of oral mucosa. Marine collagen peptides (MCP) extracted from tilapia skin was treated against the oral ulcer on the tongue mucosa of C57/BL6 mice by phenol liquids [49]. MCPs accelerate the oral ulcer healing process effectively because of the high Pro-Hyp content. Acceleration of healing process was occurred as decreased of inflammatory cells infiltration, TNF-α and IL-1β expression and increased fibroplasia, angiogenesis and collagenesis trend. Blagushina *et al*. [50] conducted a comparative examination of biodegradable collagen membranes for the rabbit model's oral mucosa post-operative defects. According to their findings, the wound's epithelization and cicatrization times were sped up and the hard mucous palate wound defect was effectively closed with pericardium and collagen film.

2.5. Skin Tissue construction

Collagen is a major component of skin responsible for the maintenance of skin tone. Decreased collagen density decreases the synthesis and replacement of important structural proteins of the skin which can stimulate the process of skin aging. Oral supplement of collagen significantly protects skin moisture and increase skin elasticity [51]. Cosmetics containing collagen induce synthesis of hyaluronic acid which promotes fibroblast growth and migration, responsible for the improvement of skin barrier function [52,53].

Oral collagen supplement improves skin moisture content and prevent fragmentation and reduc-

tion of dermal collagen network. Collagen drink containing collagen, biotin, acelrola extract, zinc and vitamin E significantly improve skin hydration, roughness, elasticity and formation of collagen in skin [54].

Low molecular weight collagen peptide improves skin hydration and skin elasticity without any side-effect [55]. Collagen improves UV-B induced skin damage because of its antioxidant properties [56]. Antioxidant property of collagen is also responsible for skin aging, wrinkle formation, laxity, roughness, and irregular pigmentation.

2.6. Vascular tissue regeneration

Collagen has been widely used as a substitute of synthetic materials in biomedical industries because of its inherent biocompatibility such as low antigenicity, low inflammation, and less cytotoxic responses. Cellularised collagen gels help vascular tissue regeneration. Vascular graft prepared by combining collagen with poly-Ɛ-caprolactone (PCL) grafts have shown more promising outcomes than vascular graft made from synthetic material. To find suitable combination, Bertram *et al*. [57] used PCL with various concentrations of (ranging from 5% to 75%) collagen (type I). Electrospun nanofibers were then applied in endothelial progenitor cell line T17b and facilities cell adherence and growth. PCL graft containing 25% collagen type I proved to be more effective.

Jeong *et al*. [58] synthesized a tissue-engineered vascular graft by combining collagen extracted from jellyfish (*Stomolophus nomurim eleagris*) and PLGA poly(D, L lactide-co-glycolide) in electrospinning technique. It was discovered that co-culturing SMCs and ECs on collagen/PLGA hybrid scaffolds under pulsatile perfusion increased cellular alignment, improved vascular EC development, and preserved differentiated cell phenotype. Their findings also suggested that collagen/PLGA scaffolds did the up-regulation of smooth muscle expressions and endothelial cell activity-related molecules. Fish scale-derived collagen exhibited a favorable incorporation to the surrounding tissues utilizing a mouse lymphatic endothelial cell line, with good infiltration of cells, blood vessels (BVs), and lymphatic vessels (LVs), as well as increased cell attachment and proliferation [59].

2.7. Bone tissue construction

Bone tissues are continuously changing commensurate with the age of a personal. Human body itself has natural bone healing process but, in some, it may not be adequate because of mechanical and biological problems. Therefore, it required assisted bone reconstruction. Biomaterials are playing vital role in bone tissue engineering. Large bone deficiencies caused by congenital disorders, injuries, or trauma have been treated with bone graft alternatives such as autologous bone grafts, allogeneic bone grafts, and synthetic bone grafts [60]. An ideal synthetic bone graft should be biocompatible and biodegradable and support osteoconduction, osteoinduction and osteointegration [61,62]. Minerals, mostly hydroxyapatite (HAp), and proteins like type I collagen make up bone tissue. Collagen scaffolds can spoof the extracellular matrix of bone in some ways [63,64].

Echazu *et al*. [65] synthesized collagen (extracted from rat tail) silica-based (C/Sol-Si) bio composite for potential application in bone tissue engineering and performed the physicochemical characterization and biocompatibility tests in experimental model in male Wistar rats. The injected bio composite in the bone marrow compartment developed agglomerates with the help of tissue silica particle and act as “larger structures” with different surface roughness. It was suspected that the body recognizes the agglomerated particles as micro particles instead of nanoparticles, and this may account for the absence of an inflammatory response [66]. One of the major components of bone is hydroxyapatite (HA), composed of calcium and phosphate which is adjacent to and bound to the collagen fibers. These collagen fibers provide tensile strength, and the HA crystals are responsible for imparting compressional strength [67].

Liu *et al*. [68] have developed a new method named self-assembly/mineralization (SSM) for doping of collagen where amorphous mineral nanoparticles (AMN) are combined with collagen fiber under acidic condition. It was shown that bone marrow-stimulating Sr-doped collagen (Sr-CS) scaffolds increased osteogenesis of rBMSCs by modifying the macrophage response, accelerated in vitro cell proliferation, and osteogenic differentiation of mesenchymal stromal cells (rBMSCs). Tacrolimus was mixed with collagen-based hydrogel for bone tissue regeneration [69]. Tacrolimus has been reported that it increases osteogenic differentiation by activating the Bone morphogenetic protein (BMP) receptors [70]. Nabavi *et al*. demonstrated that the porosity of collagen I hydrogel is 89.2 12.5%, and it behaves appropriately in terms of swelling, drug release, and blood compatibility. Aquamin, a multi mineralized food supplement, found in algae species Lithothamninon has been shown effective result in reducing symptoms of osteoarthritis [71]. Brennan *et al*. [72] produced collagen-Aquamin (CollAqua) scaffolds and cultured osteoblast in CollAqua scaffolds. Culture result re-

vealed that the scaffolds improved osteogenesis as measured by alkaline phosphatase, osteopontin and osteocalcin expression [73].

2.8. Cartilage tissue regeneration

As a stress and load-bearing tissue, cartilage has a limited ability to repair on its own [74] . Cartilage defects caused by aging and degenerative pathologies, sports-related injuries, unforeseen occurrences, fatness, illnesses, and other factors have been seen for over the years [75]. The limited regeneration of cartilage is due to its non-vascular and finite cellular component. Surgical approaches and tissue engineering are the two major healing processes for cartilage defects [76]. Recently, tissue engineering is the most popular process for cartilage tissue regeneration and reconstruction [77].

Horbert *et al*. [78] tested clinically approved hydrogel collagen type 1 implant in a standardized bovine cartilage punch model. Bovine cartilage was extracted from the knee joint of German Holstein Friesian cow (24 months old) [79]. They constructed collagen implants both cell-free and cell-seeded with bovine chondrocytes. The constructs were cultured in an agarose cylinder (48-well plates) for 0, 4, 8, 10, and 12 weeks at 37°C and 5% CO2 in Dulbecco's modified Eagle's culture medium. Media were changed 3 times a week. Their main findings were (1) The "host" cartilage ring showed gradual, albeit minor, proteoglycan degradation, and decreased proteoglycan release into the culture supernatant in cartilage-implant constructions and (2) cell-free or cell-loaded collagen implants both showed substantial cell immigration/colonization and gradually increased aggrecan level.

Hyaluronic acid–transglutaminase (HA-TG) is an enzymatically cross linkable adhesive hydrogel with chondrogenic properties [80], [81]. Levinson *et al*. [82] investigated the viability of treating chondral lesions in an ovine model utilizing HA-TG on a collagen (Optimaix) scaffold. They evaluated the cartilage regeneration in a joint environment (mechanically and biologically). Collagen scaffolds were punched into 6mm-diameter cylinder shaped chondral defects and placed in the defect prior to addition of HA-TG hydrogels in order to improve the stability of the HA-TG gel. HA-TG in combination with a collagen I/III sponge (Optimaix) can adhere to the surrounding tissues which is paramount to long-term success of cartilage repair strategies [83,84]. In one study, Bermuller *et al*. [85] performed nasal cartilage replacement matrix using marine collagen scaffolds. They isolated collagen from the jellyfish *Rhopilema esculentum* and produced scaffolds from it. In comparison to no replacement, the data revealed a substantial decrease in the number of nasal septum perforations.

Diogo *et al*. [86] studied the blue shark (*Prionace glauca*) skin collagen induced chondrogenic differentiation of human adipose stem cells (hASC) in presence and absence of externals simulation. To create highly interconnected porous 3-dimensional (3D) constructions comprised of collagen and collagen:hyaluronic acid (20:1), a cryogelation process was used. New tissue creation requires cell migration and infiltration into the interior of a 3D object. The pore size of the scaffolds has a significant impact on the rate of cell adhesion, motility, and infiltration [87,88].

2.9. Corneal tissue regeneration

The cornea is a tough, clear anterior surface of the eye that is necessary for good vision. Over 1 million new patients are diagnosed with corneal injuries and abnormalities each year, resulting in blindness [89].

Chen *et al*. [90] have developed a bio-orthogonally cross-linked hyaluronate-collagen hydrogel that can heal in situ corneal defects without sutures, initiators, or catalysts. The effects of biorthogonal crosslinking on the hydrogel's light transmittance, which was higher than 97 percent water, were investigated. In the visible light range, the optimized hydrogel had a transmittance of almost 94 percent. Their findings showed that this bio- orthogonally cross-linked hyaluronate-collagen hydrogel has good promise as a biomaterial for cornea repair and regeneration in vitro, in vivo, and ex vivo.

Corneal injury is one of the most common causes of visual problems that lead to limbal stem cell insufficiency [91]. Krishnanet *et al*. developed a biocompatible collagen scaffold (FSC) from *Lates calcarifer* fish scale to culture limbal stem cells, that did the perfect replacement of human amniotic membrane (HAM). Furthermore, potential stem cell markers were identified using an RT-PCR on cultivated corneal cells. When compared to HAM, FSC produced better outcomes. When compared to HAM, the physical and mechanical strengths of FSC were 5 times higher as FSC consists of only collagen type I while HAM consists of both Collagen type I and IV. Epithelial migration was observed under microscopic inspection in limbal explants plated on FSC after 48 hours and on HAM after 72 hours. By the 15th day, 90% to 100% confluent development was visible, resembling the morphological characteristics of limbal epithelium. Another study was done by Essen and colleague [92] where they suggested a fish-scale (*Oreochromis*

mossambicus) derived collagen matrix (FSCM) as an alternative for human corneal tissue. A stray light meter was used to quantify light scattering, and a broadband absorption spectrometer was used to evaluate light transmission. The FSCM was soaked in antibiotics (polyspectran containing gramicidine, neomycine, and polymyxine B) for 5 minutes before to implantation. Total a 3 weeks period, transparency, neovascularization, and epithelial lesions were tracked in rat model. The visible spectrum light transmission was measured in 0.56-nm wavelength increments and compared to the overall light transmission of the human cornea using van den Berg and Tan's formula [93].

According to the SEM data, the micro pattern on top of the FSCM varied depending on the area, with one quarter having a spider-web look with micro ridges and channels, two quarters having circular running ridges and channels but no intersecting lines, and the final quarter having spikes. This pattern's non-homogeneity does not stop corneal stromal cells from filling the scaffold's surface, and it may even encourage cell spread [94]. The amount of light dispersed was comparable to that seen in early cataracts, according to preliminary findings. The proportion of light transmission was comparable to that of the human cornea. Apart from the two cases described, all implanted animals were healthy, maintained their weight, and exhibited no signs of eye infection or discomfort. Their research into the FSCM's physical and biological short-term impacts as a corneal replacement proved its future potential.

2.10. Collagen in pulmonary fibrosis

A lung condition known as pulmonary fibrosis develops when lung tissues are injured and scarred. Lung function is made more difficult by this stiff, thicker tissue. Patient's breathlessness shortens with worsening of pulmonary fibrosis [95]. There is now a lot of evidence in people that shows a strong relation between the development of pulmonary fibrosis and respiratory viral infections [96]. TGF-1 (transforming growth factor-1) and collagen both may be important in the development of airway remodelling [97].

The lungs show symptoms of fibrosis, in (weeks 2–5) of SARS-CoV-2 infection, with fibrin deposition and infiltration of inflammatory cells and fibroblasts near to the epithelial cells in the alveolar gaps. In the last stage of SARS-CoV-2 infection (weeks 6–8), lung tissue fibrosis with collagen deposition is developed[98]. In individuals with worsened lung fibrosis, airway remodelling has been linked to higher plasma levels of AngII (angiotensin II), which has been related to the synthesis of TGF-1 and the deposition of collagen [99,100,101]. During lung fibrosis, the ACE2 expression is extremely downregulated, which increase the content of type I pneumocytes [102]. Thus, the protective system of Lung is deregulated and enhance AngII activity. In COVID induced fibrosis, epithelial cells experience increased oxidative stress, which stimulates the production and release of TGF-β, causing excessive fibroblast migration, proliferation, activation, and myofibroblastic differentiation, resulting in an abnormal accumulation of these cells and reflecting the airway remodelling process. Collagenous and non-collagenous matrix molecules are produced excessively by myofibroblasts [103,104]. TGF- would also oversee inhibiting the production of the MAS receptor for Ang1-7 in fibroblasts, antagonizing the heptapeptide's anti-fibrotic properties [105].

AngII activity increases the risk of acute lung injury by causing pulmonary vasoconstriction, as well as inflammatory and oxidative organ damage. The immune system's uncontrolled overreaction to the virus causes the overproduction of inflammatory cytokines, superoxide, collagen, and other matrix components, which are responsible for the onset of (acute respiratory distress syndrome) ARDS, which can result in fibrosis [106,107,108].

3. CONCLUSION

Collagen is an essential component of cell survival and plays a critical function in cellular and tissue healing. Lots of research works have been done in collagen application. In our review, we have tried to go through papers regarding collagen biomedical and clinical application. Importantly, various biomedical studies have revealed that this biomolecule has significant pharmacological effects, notably on tissue regeneration. In future, collagen can be used as substitute for synthetic materials which will ease the side effect of the surgery. More rigorous research needs to be done, to isolate collagen efficiently and apply it more effectively in food, cosmetics, pharmaceutical and medical sectors.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

REFERENCES

1. M. Azizur Rahman. Collagen of extracellular matrix from marine invertebrates and its medical applications. *Mar Drugs*.17(2): 118 (2019).
DOI: **10.3390/md17020118**
[**PubMed**] [**Scopus**] [**Google Scholar**]

2. F. Rodriguez-Pascual and D. A. Slatter. Collagen cross-linking: Insights on the evolution of metazoan extracellular matrix. *Sci Rep*. 6: 37374 (2016).
DOI:**10.1038/srep37374**
[**PubMed**] [**Scopus**] [**Google Scholar**]

3. C. Frantz, K. M. Stewart, and V. M. Weaver. The extracellular matrix at a glance. *J Cell Sci*. 123(Pt 24): 4195-200 (2010).
DOI: **10.1242/jcs.023820**
[**PubMed**] [**Scopus**] [**Google Scholar**]

4. Y. Zhang *et al.* Tissue-specific extracellular matrix coatings for the promotion of cell proliferation and maintenance of cell phenotype. *Biomaterials*. 30(23-24): 4021-8 (2009).
DOI: **10.1016/j.biomaterials.2009.04.005**
[**PubMed**] [**Scopus**] [**Google Scholar**]

5. C. Gérard and A. Goldbeter, The balance between cell cycle arrest and cell proliferation: Control by the extracellular matrix and by contact inhibition. *Interface Focus*. 4(3): 20130075 (2014).
DOI: **10.1098/rsfs.2013.0075**
[**PubMed**] [**Scopus**] [**Google Scholar**]

6. S. E. Townsend and M. Gannon Extracellular Matrix-Associated Factors Play Critical Roles in Regulating Pancreatic β-Cell Proliferation and Survival. *Endocrinology*. 160(8):1885-1894 (2019).
DOI: **10.1210/en.2019-00206**
[**PubMed**] [**Scopus**] [**Google Scholar**]

7. J. M. McPherson, S. Sawamura, and R. Armstrong. An examination of the biologic response to injectable, glutaraldehyde cross-linked collagen implants. *J Biomed Mater Res*. 20(1): 93-107 (1986).
DOI: **10.1002/jbm.820200109**
[**PubMed**] [**Scopus**] [**Google Scholar**]

8. M. Van Der Rest and R. Garrone. Collagen family of proteins. *The FASEB Journal*. 5(13): 2814–2823 (1991).
DOI: **10.1096/fasebj.5.13.1916105**
[**Google Scholar**]

9. W. Traub and K. A. Piez. The chemistry and structure of collagen. *Adv Protein Chem.* 25(c): 243-352 (1971).
DOI: **10.1016/S0065-3233(08)60281-8**
[**PubMed**] [**Scopus**] [**Google Scholar**]

10. S. Paul. Fish bone chemistry and ultrastructure: implications for taphonomy and stable isotope analysis. *J Archaeol Sci*. 38(12): 3358–3372 (2011).
DOI: **10.1016/j.jas.2011.07.022**
[**Scopus**] [**Google Scholar**]

11. M. Meyer. Processing of collagen based biomaterials and the resulting materials properties. *Biomed Eng Online*. 18(1): 24 (2019).
DOI: **10.1186/s12938-019-0647-0**
[**PubMed**] [**Scopus**] [**Google Scholar**]

12. D. E. Birk and P. Bruckner Collagen suprastructures. *Top Curr Chem*. 247: 185–205 (2005).
DOI: **10.1007/b103823**
[**Scopus**] [**Google Scholar**]

13. T. V. Burjanadze. New analysis of the phylogenetic change of collagen thermostability. *Biopolymers*, 53(6): 523–528 (2000).
DOI: **10.1002/(SICI)1097-0282(200005)53:6<523::AID-BIP8>3.0.CO;2-7**
[**PubMed**] [**Scopus**] [**Google Scholar**]

14. K. A. Czubak and H. M. Żbikowska. Struktura, funkcja i znaczenie biomedyczne kolagenów. *Ann. Acad. Med. Siles.* 68(4): 245–254 (2014).
[**Google Scholar**]

15. M. I. Avila Rodríguez, L. G. Rodríguez Barroso, and M. L. Sánchez. Collagen: A review on its sources and potential cosmetic applications. *J Cosmet Dermatol*, vol. 17(1): 20-26 (2018).
DOI: **10.1111/jocd.12450**
[**PubMed**] [**Scopus**] [**Google Scholar**]

16. K. S. Silvipriya, K. Krishna Kumar, A. R. Bhat, B. Dinesh Kumar, A. John, and P. Lakshmanan. Collagen: Animal sources and biomedical application. *J Appl Pharm Sci*. 5(3): 123–127 (2015).
DOI: **10.7324/JAPS.2015.50322**
[**Scopus**] [**Google Scholar**]

17. M. A. Karsdal, D. J. Leeming, K. Henriksen, and A. C. Bay-Jensen. Biochemistry of Collagens, Laminins and Elastin: Structure, Function and Biomarkers. *Biochemistry of Collagens, Laminins and Elastin: Structure, Function and Biomarkers*, pp. 1–238 (2016).
[**Google Scholar**]

18. H. Wahyudi, A. A. Reynolds, Y. Li, S. C. Owen, and S. M. Yu. Targeting collagen for diagnostic imaging and therapeutic delivery. *Journal of Controlled Release*. 240: 323-331 (2016).
DOI: **10.1016/j.jconrel.2016.01.007**
[**PubMed**] [**Scopus**] [**Google Scholar**]

19. C. Dong and Y. Lv. Application of collagen scaffold in tissue engineering: Recent advances and new perspectives. *Polymers (Basel)*. 8(2): 422016).
DOI: **10.3390/polym8020042**
[**PubMed**] [**Scopus**] [**Google Scholar**]

20. J. B. Park and Y. C. Fung. Biomaterials, an Introduction. *J Biomech Eng*. 102(2): 161 -161(1980).
DOI: **10.1115/1.3138215**

21. P. Bama, M. Vijayalakshimi, R. Jayasimman, P. T. Kalaichelvan, M. Deccaraman, and S. Sankaranarayanan. Extraction of collagen from cat fish (tachysurus maculatus) by pepsin digestion and preparation and characterization of collagen chitosan sheet. *Int J Pharm Pharm Sci*. 2(4): 133–137 (2010).
[**Google Scholar**]

22. Z.T. *et al.* Electrospun tilapia collagen nanofibers accelerating wound healing via inducing keratinocytes proliferation and differentiation. *Colloids Surf B Biointerfaces*. 143: 415-422 (2016).
DOI: **10.1016/j.colsurfb.2016.03.052**
[**PubMed**] [**Scopus**] [**Google Scholar**]

23. J. Ho, C. Walsh, D. Yue, A. Dardik, and U. Cheema, “Current Advancements and Strategies in Tissue Engineering for Wound Healing: A Comprehensive Review,” *Adv Wound Care (New Rochelle)*. 6(6): 191-209 (2017).
DOI: **10.1089/wound.2016.0723**
[**PubMed**] [**Scopus**] [**Google Scholar**]

24. K. Gelse, E. Pöschl, and T. Aigner. Collagens - Structure, function, and biosynthesis. *Adv Drug Deliv Rev*. 55(12):1531-46 (2003).
DOI: **10.1016/j.addr.2003.08.002**
[**PubMed**] [**Scopus**] [**Google Scholar**]

25. Broughton G., Janis J.E., Attinger C.E. The basic science of wound healing. *Plast Reconstr Surg*. 117(7 Suppl): 12S-34S (2006).
DOI: **10.1097/01.prs.0000225430.42531.c2**
[**PubMed**] [**Scopus**] [**Google Scholar**]

26. Mathew-Steiner S. S., Roy S., Sen C.K. Collagen in wound healing. *Bioengineering*, 8(5): 63. MDPI AG. (2021)
DOI: **10.3390/bioengineering8050063**
[**PubMed**] [**Scopus**] [**Google Scholar**]

27. Hu Z, Yang P., Zhou C., Li S. Hong P. Marine Collagen Peptides from the Skin of Nile Tilapia (Oreochromis niloticus): Characterization and Wound Healing Evaluation. *Mar Drugs*. 15(4):102 (2017).
DOI: **10.3390/md15040102**
[**PubMed**] [**Scopus**] [**Google Scholar**]

28. Yang T., Zhang K., Li B., Hou H. Effects of oral administration of peptides with low molecular weight from Alaska Pollock (Theragra chalcogramma) on cutaneous wound healing. *J Funct Foods*. 48: 682–691 (2018).
DOI: **10.1016/j.jff.2018.08.006**
[**Google Scholar**]

29. Geahchan S., Baharlouei P., Rahman M.A., Marine Collagen: A Promising Biomaterial for Wound Healing, Skin Anti-Aging, and Bone Regeneration. Marine Drugs, vol. 20, no. 1. MDPI, Jan. 01 (2022).
DOI: **10.3390/md20010061**
[**PubMed**] [**Scopus**] [**Google Scholar**]

30. Wang J., Xu M., Liang R., Zhao M., Zhang Z., Li Y. Oral administration of marine collagen peptides prepared from chum salmon (Oncorhynchus keta) improves wound healing following cesarean section in rats,” *Food Nutr Res* 59: 26411 (2015).
DOI: **10.3402/fnr.v59.26411**
[**PubMed**] [**Scopus**] [**Google Scholar**]

31. Zhang Z., Wang J., Ding Y., Dai X., Li Y. Oral administration of marine collagen peptides from Chum Salmon skin enhances cutaneous wound healing and angiogenesis in rats. *J Sci Food Agric*, 91(12): 2173-9 (2011).
DOI: **10.1002/jsfa.4435**
[**PubMed**] [**Scopus**] [**Google Scholar**]

32. Peng X., Xu J., Tian Y., Liu W., Peng B. Marine fish peptides (Collagen peptides) compound intake promotes wound healing in rats after cesarean section. Food Nutr Res. 64 (1–12) (2020).
DOI: **10.29219/fnr.v64.4247**
[**PubMed**] [**Scopus**] [**Google Scholar**]

33. Pozzolini M. *et al.*, Elicited ROS scavenging activity, photoprotective, and wound-healing properties of collagen-derived peptides from the marine sponge Chondrosia reniformis. *Mar Drugs*. 16(12): 465 (2018).
DOI: **10.3390/md16120465**
[**PubMed**] [**Scopus**] [**Google Scholar**]

34. Fraceto L.F. *et al.* Nano based drug delivery systems: recent developments and future prospects. *J Nanobiotechnology*. 16(1): 71 (2018).
DOI: **10.1186/s12951-018-0392-8**
[**PubMed**] [**Scopus**] [**Google Scholar**]

35. Langasco R. *et al.* Natural collagenic skeleton of marine sponges in pharmaceutics: Innovative biomaterial for topical drug delivery. *Materials Science and Engineering C*. 70(Pt 1): 710-720 (2017).
DOI:**10.1016/j.msec.2016.09.041**
[**PubMed**] [**Scopus**] [**Google Scholar**]

36.Veeruraj A., Arumugam M., Ajithkumar T., Balasubramanian T. Isolation and characterization of drug delivering potential of type-I collagen from eel fish Evenchelys macrura. *J Mater Sci Mater Med*, 23(7): 1729-38 (2012).
DOI: **10.1007/s10856-012-4650-2**
[**PubMed**] [**Scopus**] [**Google Scholar**]

37. Calejo M.T., Almeida A. J., Fernandes A. I. Exploring a new jellyfish collagen in the production of microparticles for protein delivery. *J Microencapsul*, 29(6): 520-31 (2012).
DOI: **10.3109/02652048.2012.665089**
[**PubMed**] [**Scopus**] [**Google Scholar**]

38. Nicklas M., Schatton W., Heinemann S., Hanke T., Kreuter J. Enteric coating derived from marine sponge collagen. *Drug Dev Ind Pharm*. 35(11):1384-8 (2009).
DOI: **10.3109/03639040902939239**
[**PubMed**] [**Scopus**] [**Google Scholar**]

39. Nicklas M., Schatton W., Heinemann S., Hanke T., Kreuter J. Preparation and characterization of marine sponge collagen nanoparticles and employment for the transdermal delivery of 17beta-estradiol-hemihydrate. *Drug Dev Ind Pharm*. 35(9): 1035-42 (2009)
DOI: **10.1080/03639040902755213**
[**PubMed**] [**Scopus**] [**Google Scholar**]

40. Wang W. *et al.* Development of an injectable chitosan/marine collagen composite gel. *Biomedical Materials*. 5(6): 065009 (2010).
DOI: **10.1088/1748-6041/5/6/065009**
[**PubMed**] [**Scopus**] [**Google Scholar**]

41. Caplazi P. *et al.* Mouse Models of Rheumatoid Arthritis. *Vet Pathol*. 52(5): 819-26 (2015)
DOI: **10.1177/0300985815588612**
[**PubMed**] [**Scopus**] [**Google Scholar**]

42. Barnett M.L. *et al.* Treatment of rheumatoid arthritis with oral type II collagen: Results of a multicenter, double-blind, placebo-controlled trial. *Arthritis Rheum*. vol. 41, no. 2, pp. 290–297 (1998)
DOI:**10.1002/1529-0131(199802)41:2<290::AID-ART13>3.0.CO;2-R**
[**PubMed**] [**Scopus**] [**Google Scholar**]

43. Wei W.*et al.* A multicenter, double-blind, randomized, controlled phase III clinical trial of chicken type II collagen in rheumatoid arthritis. *Arthritis Res Ther*. 11(6): R180 (2009).
DOI:**10.1186/ar2870**
[**PubMed**] [**Scopus**] [**Google Scholar**]

44. Xue H. *et al.* Potent antirheumatic activity of a New DNA vaccine targeted to B7-2/CD28 costimulatory signaling pathway in autoimmune arthritis. *Hum Gene Ther*. 22(1): 65-76 (2011).
DOI: **10.1089/hum.2010.110**
[**PubMed**] [**Scopus**] [**Google Scholar**]

45. Xinqiang S. *et al.* Construction and characterization of a novel DNA vaccine that is potent antigen-specific tolerizing therapy for experimental arthritis by increasing CD4+CD25+Treg cells and inducing Th1 to Th2 shift in both cells and cytokines. *Vaccine*. 27(5):690-700 (2009).
DOI: **10.1016/j.vaccine.2008.11.090**
[**PubMed**] [**Scopus**] [**Google Scholar**]

46. Juan L. *et al.* Safety and immunogenicity of a novel therapeutic DNA vaccine encoding chicken type II collagen for rheumatoid arthritis in normal rats. *Hum Vaccin Immunother*. 11(12): 2777-83 (2015).
DOI: **10.1080/21645515.2015.1073425**
[**PubMed**] [**Scopus**] [**Google Scholar**]

47. Terada M. *et al.* Construction and characterization of a tissue-engineered oral mucosa equivalent based on a chitosan-fish scale collagen composite. *J Biomed Mater Res B Appl Biomater*. 100(7): 1792-802 (2012).
DOI: **10.1002/jbm.b.32746**
[**PubMed**] [**Scopus**] [**Google Scholar**]

48. Suzuki A. *et al.* Development of microstructured fish scale collagen scaffolds to manufacture a tissue-engineered oral mucosa equivalent. *J Biomater Sci Polym Ed*. 31(5): 578-600 (2020).
DOI: **10.1080/09205063.2019.1706147**
[**PubMed**] [**Scopus**] [**Google Scholar**]

49. Shang Y. *et al.* Evaluations of Marine Collagen Peptides from tilapia skin on experimental oral ulcer model of mice. *Mater Today Commun*. 26 :101893 (2021).
DOI: **10.1016/j.mtcomm.2020.101893**
[**Scopus**] [**Google Scholar**]

50. Blagushina N., Diachkova E., Volkova M., Pankush S., Tarasenko S. Comparative analysis of the use of domestic bioresorbable collagen membranes at the closure of postoperative defects of the oral mucosa in an experiment in vivo. *Biointerface Res Appl Chem*, 11(2): 9804–9812 (2021).
DOI: **10.33263/BRIAC112.98049812**
[**Scopus**] [**Google Scholar**]

51. Jhawar N., Wang J. V., Saedi N. Oral collagen supplementation for skin aging: A fad or the future? *J Cosmet Dermatol*. 19(4): 910-912 (2020).
DOI: **10.1111/jocd.13096**
[**PubMed**] [**Scopus**] [**Google Scholar**]

52. Asserin J., Lati E., Shioya T., Prawitt J. The effect of oral collagen peptide supplementation on skin moisture and the dermal collagen network: Eevidence from an ex vivo model and randomized, placebo-controlled clinical trials. *J Cosmet Dermatol*. 14(4): 291-301 (2015).
DOI: **10.1111/jocd.12174**
[**PubMed**] [**Scopus**] [**Google Scholar**]

53. Kang M.C., Yumnam S., Kim S.Y. Oral intake of collagen peptide attenuates ultraviolet B irradiation-induced skin dehydration in vivo by regulating hyaluronic acid synthesis. *Int J Mol Sci*. 19(11): 3551 (2018).
DOI: **10.3390/ijms19113551**
[**PubMed**] [**Scopus**] [**Google Scholar**]

54. Bolke L., Schlippe G., Gerß J., Voss W. A collagen supplement improves skin hydration, elasticity, roughness, and density: Results of a randomized, placebo-controlled, blind study. *Nutrients*, 11(10): 7–11 (2019).
DOI: **10.3390/nu11102494**
[**PubMed**] [**Scopus**] [**Google Scholar**]

55. Kim D.U., Chung H.C., Choi J., Sakai Y., Lee B.Y. Oral intake of low-molecular-weight collagen peptide improves hydration, elasticity, and wrinkling in human skin: A randomized, double-blind, placebo-controlled study. *Nutrients*. 10(7): 826 (2018).
DOI: **10.3390/nu10070826**
[**PubMed**] [**Scopus**] [**Google Scholar**]

56. Tanaka M., Koyama Y. I., Nomura Y. Effects of collagen peptide ingestion on UV-B-induced skin damage," *Biosci Biotechnol Biochem*, 73(4): 930-2 (2009).
DOI: **10.1271/bbb.80649**
[**PubMed**] [**Scopus**] [**Google Scholar**]

57. Bertram U. *et al.* Vascular Tissue Engineering: Effects of Integrating Collagen into a PCL Based Nanofiber Material. *Biomed Res Int*. 2017: 9616939 (2017). DOI: **10.1155/2017/9616939**
[**PubMed**] [**Scopus**] [**Google Scholar**]

58. Jeong S. In *et al.* Tissue-engineered vascular grafts composed of marine collagen and PLGA fibers using pulsatile perfusion bioreactors. *Biomaterials*, 28(6): 1115-22 (2007).
DOI: **10.1016/j.biomaterials.2006.10.025**
[**PubMed**] [**Scopus**] [**Google Scholar**]

59. Wang J.K. *et al.* Fish scale-derived collagen patch promotes growth of blood and lymphatic vessels in vivo. *Acta Biomater* 63:246-260 (2017).
DOI: **10.1016/j.actbio.2017.09.001**
[**PubMed**] [**Scopus**] [**Google Scholar**]

60. Sheikh Z., Hamdan N., Abdallah M.N., Glogauer M., Grynpas M. Natural and synthetic bone replacement graft materials for dental and maxillofacial applications.

Advanced Dental Biomaterials. 347–376 (2019).
DOI: **10.1016/B978-0-08-102476-8.00015-3**
[**Scopus**] [**Google Scholar**]

61.Wang W, Yeung K.W.K. Bone grafts and biomaterials substitutes for bone defect repair: A review. *Bioact Mater*, 2(4): 224-247 (2017).
DOI: **10.1016/j.bioactmat.2017.05.007**
[**PubMed**] [**Scopus**] [**Google Scholar**]

62. Bow A., Anderson D.E., Dhar M. Commercially available bone graft substitutes: the impact of origin and processing on graft functionality. *Drug Metab Rev.* 51(4): 533-544 (2019).
DOI: **10.1080/03602532.2019.1671860**
[**PubMed**] [**Scopus**] [**Google Scholar**]

63. Cacciotti I. Multisubstituted hydroxyapatite powders and coatings: The influence of the codoping on the hydroxyapatite performances. *Int J Appl Ceram Technol*. 16(5): 1864–1884 (2019).
DOI: **10.1111/ijac.13229**
[**Scopus**] [**Google Scholar**]

64. Harley B.A., Leung J.H, Silva E.C.C.M., Gibson L.J. Mechanical characterization of collagen-glycosaminoglycan scaffolds. *Acta Biomater.* 3(4): 463-74 (2007).
DOI: **10.1016/j.actbio.2006.12.009**
[**PubMed**] [**Scopus**] [**Google Scholar**]

65. Alvarez Echazú M., Renou S., Alvarez G., Desimone M., Olmedo D. A collagen-silica-based biocomposite for potential application in bone tissue engineering. *J Biomed Mater Res A*. 110(2): 331-340 (2022).
DOI: **10.1002/jbm.a.37291**
[**PubMed**] [**Scopus**] [**Google Scholar**]

66. Guglielmotti M.B., Domingo M.G., Steimetz T., Ramos E., Paparella M.L., Olmedo D.G. Migration of titanium dioxide microparticles and nanoparticles through the body and deposition in the gingiva: An experimental study in rats. *Eur J Oral Sci*. 123(4): 242-8 (2015).
DOI: **10.1111/eos.12190**
[**PubMed**] [**Scopus**] [**Google Scholar**]

67. Sheikh. Z., Hamdan N., Abdallah M.N., Glogauer M., Grynpas M. Natural and synthetic bone replacement graft materials for dental and maxillofacial applications. *Advanced Dental Biomaterials*. 347–376 (2019).
DOI: **10.1016/B978-0-08-102476-8.00015-3**
[**Scopus**] [**Google Scholar**]

68. Liu H. *et al.* Doping bioactive elements into a collagen scaffold based on synchronous self-assembly/ mineralization for bone tissue engineering. *Bioact Mater*. 5(4): 844-858 (2020).
DOI: **10.1016/j.bioactmat.2020.06.005**
[**PubMed**] [**Scopus**] [**Google Scholar**]

69. Nabavi M.H. *et al.* A collagen-based hydrogel containing tacrolimus for bone tissue engineering. *Drug Deliv Transl Res*.10(1): 108-121 (2020).
DOI: **10.1007/s13346-019-00666-7**
[**PubMed**] [**Scopus**] [**Google Scholar**]

70. Kugimiya F. *et al.* Mechanism of osteogenic induction by FK506 via BMP/Smad pathways. *Biochem Biophys Res Commun*. 338(2): 872-9 (2005).
DOI: **1016/j.bbrc.2005.10.024**
[**PubMed**] [**Scopus**] [**Google Scholar**]

71. Frestedt J.L., Kuskowski M.A., Zenk J.L. A natural seaweed derived mineral supplement (Aquamin F) for knee osteoarthritis: a randomised, placebo controlled pilot study. *Nutr J*. 8(1):7 (2009).
DOI: **10.1186/1475-2891-8-7**
[**PubMed**] [**Scopus**] [**Google Scholar**]

72. Brennan O., Stenson B., Widaa A., O'Gorman D.M., O'Brien F.J. Incorporation of the natural marine multimineral dietary supplement Aquamin enhances osteogenesis and improves the mechanical properties of a collagen-based bone graft substitute. *J Mech Behav Biomed Mater*. 47: 114-123 (2015).
DOI: **10.1016/j.jmbbm.2015.03.015**
[**PubMed**] [**Scopus**] [**Google Scholar**]

73. Eyckmans J., Roberts S.J., Bolander J., Schrooten J., Chen C.S., Luyten F.P. Mapping calcium phosphate activated gene networks as a strategy for targeted osteoinduction of human progenitors. *Biomaterials*, 34(19): 4612-21 (2013).
DOI: **10.1016/j.biomaterials.2013.03.011**
[**PubMed**] [**Scopus**] [**Google Scholar**]

74. Hafezi M., Khorasani S.N, Zare M., Neisiany R.E., Davoodi P. Advanced hydrogels for cartilage tissue engineering: Recent progress and future directions. *Polymers*.13 (23): 4199 (2021).
DOI: **10.3390/polym13234199**
[**PubMed**] [**Scopus**] [**Google Scholar**]

75. Krishnan Y., Grodzinsky A.J. Cartilage diseases. *Matrix Biology*. 71-72:51-69 (2018).
DOI: **10.1016/j.matbio.2018.05.005**
[**PubMed**] [**Scopus**] [**Google Scholar**]

76. Jeznach O., Kołbuk D., Sajkiewicz P. Injectable hydrogels and nanocomposite hydrogels for cartilage regeneration. *J Biomed Mater Res A*. 106 (10): 2762-2776 (2018).
DOI: **10.1002/jbm.a.36449**
[**PubMed**] [**Scopus**] [**Google Scholar**]

77. Vega S.L., Kwon M.Y., Burdick J.A. Recent advances in hydrogels for cartilage tissue engineering. *Eur Cell Mater* 33: 59-75 (2017).
DOI: **10.22203/eCM.v033a05**
[**PubMed**] [**Scopus**] [**Google Scholar**]

78. Horbert V. *et al.* In Vitro Analysis of Cartilage Regeneration Using a Collagen Type I Hydrogel (CaReS) in the Bovine Cartilage Punch Model *Cartilage*. 10(3): 346-363363 (2019).
DOI: **10.1177/1947603518756985**
[**PubMed**] [**Scopus**] [**Google Scholar**]

79. Pretzel D. *et al.* A novel in vitro bovine cartilage punch model for assessing the regeneration of focal car-

tilage defects with biocompatible bacterial nanocellulose. *Arthritis Res Ther*. 15(3): R59 (2013).
DOI: **10.1186/ar4231**
[**PubMed**] [**Scopus**] [**Google Scholar**]

80. Broguiere N., Isenmann L., Zenobi-Wong M. Novel enzymatically cross-linked hyaluronan hydrogels support the formation of 3D neuronal networks. *Biomaterials*. 99: 47-55 (2016).
DOI: **10.1016/j.biomaterials.2016.04.036**
[**PubMed**] [**Scopus**] [**Google Scholar**]

81. Broguiere N., Cavalli E., Salzmann G.M., Applegate L.A., Zenobi-Wong M. Factor XIII Cross-Linked Hyaluronan Hydrogels for Cartilage Tissue Engineering. *ACS Biomater Sci Eng*. 2(12): 2176-2184 (2016).
DOI: **10.1021/acsbiomaterials.6b00378**
PubMed Scopus Google Scholar

82. Levinson C., Cavalli E., von Rechenberg B., Zenobi-Wong M., Darwiche S.E. Combination of a Collagen Scaffold and an Adhesive Hyaluronan-Based Hydrogel for Cartilage Regeneration: A Proof of Concept in an Ovine Model. *Cartilage*. 13(2_suppl): 636S-649S (2021).
DOI: **10.1177/1947603521989417**
[**PubMed**] [**Scopus**] [**Google Scholar**]

83. Hunziker E.B. Articular cartilage repair: Basic science and clinical progress. A review of the current status and prospects. *Osteoarthritis Cartilage*. 10(6): 432-63 (2002).
DOI: **10.1053/joca.2002.0801**
[**PubMed**] [**Scopus**] [**Google Scholar**]

84. Khan I.M., Gilbert S.J., Singhrao S.K., Duance V.C., Archer C.W. Cartilage integration: Evaluation of the reasons for failure of integration during cartilage repair. A review. *Eur Cell Mater*. 16:(0): 26-39 (2008).
DOI: **10.22203/ecm.v016a04**
[**PubMed**] [**Google Scholar**]

85. Bermueller C. *et al.* Marine collagen scaffolds for nasal cartilage repair: Prevention of nasal septal perforations in a new orthotopic rat model using tissue engineering techniques. *Tissue Eng Part A*, 19(19-20): 2201-14 (2013).
DOI: **10.1089/ten.tea.2012.0650**
[**PubMed**] [**Scopus**] [**Google Scholar**]

86. Diogo G.S *et al.* Prionace glauca skin collagen bioengineered constructs as a promising approach to trigger cartilage regeneration. *Materials Science and Engineering C*. 120: 111587 (2021).
DOI: **10.1016/j.msec.2020.111587**
[**PubMed**] [**Scopus**] [**Google Scholar**]

87. Murphy C.M., Duffy G.P. Schindeler A, O'Brien F.J. Effect of collagen-glycosaminoglycan scaffold pore size on matrix mineralization and cellular behavior in different cell types. *J Biomed Mater Res A*. 104(1): 291-304 (2016).
DOI: **10.1002/jbm.a.35567**
[**PubMed**] [**Scopus**] [**Google Scholar**]

88. Irawan V., Sung T.C., Higuchi A., Ikoma T. Collagen Scaffolds in Cartilage Tissue Engineering and Relevant Approaches for Future Development. *Tissue Eng Regen Med*, 15(6): 673-697 (2018).
DOI: **10.1007/s13770-018-0135-9**
[**PubMed**] [**Scopus**] [**Google Scholar**]

89. Jameson J.F., Pacheco M.O., Nguyen H.H., Phelps E.A., Stoppel W.L. Recent advances in natural materials for corneal tissue engineering. *Bioengineering*. 8(11): 161 (2021).
DOI: **10.3390/bioengineering8110161**
[**PubMed**] [**Scopus**] [**Google Scholar**]

90. Chen F., Le P., Fernandes-Cunha G.M., Heilshorn S.C. Myung D. Bio-orthogonally crosslinked hyaluronate-collagen hydrogel for suture-free corneal defect repair. *Biomaterials*. 255: 120176 (2020).
DOI: **10.1016/j.biomaterials.2020.120176**
[**PubMed**] [**Scopus**] [**Google Scholar**]

91. El Blidi O. *et al.* Extraction methods, characterization and biomedical applications of collagen: A review. *Biointerface Res Appl Chem*.11(5): 13587–13613 (2021).
DOI: **10.33263/BRIAC115.1358713613**
[**Scopus**] [**Google Scholar**]

92. Huibertus van Essen T. *et al.* A fish scale-derived collagen matrix as artificial cornea in rats: Properties and potential. *Invest Ophthalmol Vis Sci*, 54(5): 3224-33 (2013).
DOI: **10.1167/iovs.13-11799**
[**PubMed**] [**Scopus**] [**Google Scholar**]

93. Van Den Berg T.J.T.P, Tan K.E.W.P. Light transmittance of the human cornea from 320 to 700 nm for different ages. *Vision Res*. 34(11): 1453-6 (1994).
DOI: **10.1016/0042-6989(94)90146-5**
[**PubMed**] [**Scopus**] [**Google Scholar**]

94. Lin C.C. *et al.* A new fish scale-derived scaffold for corneal regeneration. *Eur Cell Mater*.19: 50–57 (2010).
DOI: **10.22203/eCM.v019a06**
[**Scopus**] [**Google Scholar**]

95. Donoghue F.E., Woolner L.B. Pulmonary fibrosis. *Med Clin North Am*, vol. New York N. 1009–1018 (1954).

96. Sheng G. *et al.* Viral Infection Increases the Risk of Idiopathic Pulmonary Fibrosis: A Meta-Analysis. *American College of Chest Physicians.* 157(5): 1175-1187 (2020).
DOI: **10.1016/j.chest.2019.10.032**
[**PubMed**] [**Scopus**] [**Google Scholar**]

97. Delpino M.V, Quarleri J. SARS-CoV-2 Pathogenesis: Imbalance in the Renin-Angiotensin System Favors Lung Fibrosis. *Front Cell Infect Microbiol*. 10: 1–5 (2020).
DOI: **10.3389/fcimb.2020.00340**
[**PubMed**] [**Scopus**] [**Google Scholar**]

98. Ye J. *et al.* Molecular pathology in the lungs of severe acute respiratory syndrome patients. *American Journal of Pathology*. 170(2): 538-45 (2007).
DOI: **10.2353/ajpath.2007.060469**
[**PubMed**] [**Scopus**] [**Google Scholar**]

99. Uhal B., Kyong Kim J., Li X. Molina-Molina M. Angiotensin-TGF-beta 1 Crosstalk in Human Idiopathic Pulmonary

Fibrosis: Autocrine Mechanisms in Myofibroblasts and Macrophages. *Curr Pharm Des*. 13(12): 1247-56 (2007).
DOI: **10.2174/138161207780618885**
[**PubMed**] [**Scopus**] [**Google Scholar**]

100. Gao X., He X., Luo B., Peng L., Lin J., Zuo Z. Angiotensin II increases collagen I expression via transforming growth factor-beta1 and extracellular signal-regulated kinase in cardiac fibroblasts. *Eur J Pharmacol*. 606(1-3): 115-20 (2009).
DOI: **10.1016/j.ejphar.2008.12.049**
[**PubMed**] [**Scopus**] [**Google Scholar**]

101. Yang F., Chung A.C.K., Huang X.Ru, Lan H.Y. Angiotensin II induces connective tissue growth factor and collagen i expression via transforming growth factor-β-dependent and -independent Smad pathways: The role of Smad3. *Hypertension*. 54(4):877-84 (2009).
DOI: **10.1161/HYPERTENSIONAHA.109.136531**
[**PubMed**] [**Scopus**] [**Google Scholar**]

102. Uhal B.D. *et al.* Cell cycle dependence of ACE-2 explains downregulation in idiopathic pulmonary fibrosis. *European Respiratory Journal*. 42(1): 198-210 (2013).
DOI: **10.1183/09031936.00015612**
[**PubMed**] [**Scopus**] [**Google Scholar**]

103. Yang Y.C, Zhang N., Van Crombruggen K., Hu G.H., Hong S.L., Bachert C. Transforming growth factor-beta1 in inflammatory airway disease: A key for understanding inflammation and remodeling. *Allergy: European Journal of Allergy and Clinical Immunology*, 67(10): 1193-202 (2012).
DOI: **10.1111/j.1398-9995.2012.02880.x**
[**PubMed**] [**Scopus**] [**Google Scholar**]

104. Sakai N., Tager A.M. Fibrosis of two: Epithelial cell-fibroblast interactions in pulmonary fibrosis. *Biochim Biophys Acta Mol Basis Dis*, 1832(7):911-2 (2013).
DOI: **10.1016/j.bbadis.2013.03.001**
[**PubMed**] [**Scopus**] [**Google Scholar**]

105. Cofre C. *et al.* Transforming growth factor type-β inhibits Mas receptor expression in fibroblasts but not in myoblasts or differentiated myotubes; Relevance to fibrosis associated to muscular dystrophies. *BioFactors*. 41(2):111-20 (2015).
DOI: **10.1002/biof.1208**
[**PubMed**] [**Scopus**] [**Google Scholar**]

106. Wu D., Yang X.O. TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Fedratinib. *Journal of Microbiology, Immunology and Infection*. 53(3): 368-370 (2020).
DOI: **10.1016/j.jmii.2020.03.005**
[**PubMed**] [**Scopus**] [**Google Scholar**]

107. Zhou F. *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet*. 395(10229): 1054-1062 (2020).
DOI: **10.1016/S0140-6736(20)30566-3**
[**PubMed**] [**Scopus**] [**Google Scholar**]

108. Luo P., Liu Y., Qiu L., Liu X., Liu D., Li J. Tocilizumab treatment in COVID-19: A single center experience. *J Med Virol*. 92(7): 814-818 (2020).
DOI: **10.1002/jmv.25801**
[**PubMed**] [**Scopus**] [**Google Scholar**]