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Progress and opportunities in gellan gum and collagen as wound healing materials: A review

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ABSTRACT

Gellan gum and collagen are two biomaterials that have been extensively studied for their potential use in wound healing and tissue engineering applications. Gellan gum is a biologically inert natural polymer that is increasingly favored as a biomaterial to form hydrogels. Collagen, on the other hand, is a major component of the extracellular matrix and is widely used in tissue engineering applications due to its biocompatibility and ability to promote cell adhesion and proliferation. In this review, the recent research will be discussed related to gellan gum and collagen, their properties, and their potential applications in wound healing and tissue engineering.

Keywords: gellan gum; collagen; biomaterials; wound; healing

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1. INTRODUCTION

Wound dressing plays an important role in the wound healing process since it can prevent wounds from microorganisms and the feeling of pain. Wounds covered with dressing heal better than uncovered wounds because the dressing helps protect the wound from proteinases, chemotactic factors, complement proteins, and growth factors (Dhivya et al., 2015). It can accelerate re-epithelialization, collagen synthesis, and angiogenesis by inducing hypoxia in the wound bed, and reducing the chances of wound infection. Selective wound dressings must be made carefully to prevent secondary trauma and harm when wound dressing is required (Bosworth and Downes, 2011). For example, the manufacture of occlusive dressing began in the late 1900s. They had a waxy surface and were non-adherent, designed to protect the wound from air and water or the outside environment (Eaglstein, 2001). In addition, the function of wound dressings in burn and chronic wound cases is to absorb the exudates on the wound, as well as provide a moist environment, because a moist wound cures faster than a dry wound (Azam et al., 2023). As oxygen is essential in the stage of wound healing, the wound dressing should be oxygen-breathable (Ambekar and Kandasubramanian, 2019). At present, more than 3,000 products have been developed to treat different types of wounds for various kinds of healing processes (Hishamuddin et al., 2022). However, to attain speedy healing, the choice of material for a specific wound is vital. An ideal wound dressing should maintain a moist environment, boost epidermal migration, aid angiogenesis and connective tissue synthesis, and permit the exchange of gas between the wound tissue and surrounding environment. It should also maintain an ideal temperature to improve blood flow, exhibit the growth of bacteria, be non-adherent to the wound and easy to remove after healing, facilitate debridement to enhance leucocyte migration and support

enzyme activity. Additionally, it must be sterile, non-toxic and non-allergenic (Barbu et al., 2021).

Wound dressing has been classified into traditional and advanced wound dressings. Traditional wound care products, such as gauze, plaster, bandage, and cotton wool, are dry and used as primary or secondary dressings to shield from contamination. Gauze dressing that consists of woven and non-woven fiber gives several protections against bacterial infection, while sterile gauze pads aid in absorbing exudates at the wound bed (Souza et al., 2019). To protect the maceration of healthy tissue, frequent changing of dressings is essential. Dressings become damp due to uncontrolled wound drainage, causing them to adhere to the wound, which drives to painful removal. For that reason, advanced wound dressings have replaced traditional dressings (Boateng et al., 2008). The development of advanced wound dressings not only protects the wound but also supports its healing process. The responsibility of these dressings is to keep a moist environment and stimulate wound healing. They are classified as passive, interactive, and bioactive products and are typically made of synthetic polymers. Inactive products are non-occlusive such as gauze and tulle dressings. In contrast, interactive dressings, such as hydrogel, film, and foam, are semi-occlusive or occlusive and play a role in shielding against the penetration of bacteria into the wound (Muktar et al., 2018; Nabilah et al., 2016; Tavakoli and Klar, 2020). Commonly used biopolymers as wound dressing materials are listed in Table 1.

Table 1. Common biopolymers used as wound dressing materials

No.	Biopolymer	Type	Filler	References
1.	Gellan gum	Hydrogel, film	Clay, titanium dioxide, collagen, virgin coconut oil (VCO), honey, ball clay	(Azam et al., 2023; Bonifacio et al., 2020; Ismail et al., 2014, 2019; Mohd Azam and Amin, 2017; Muktar et al., 2018; Razali et al., 2020; Syazwani Mohd et al., 2016)
2.	Chitosan	Hydrogel, film	ZnO, urethane, collagen, alginate, poly(vinyl alcohol), titanium dioxide, montmorillonite, zeolite, silver sulfadiazine, graphene	(Ambrogi et al., 2017; Behera et al., 2017; Hissae Yassue-Cordeiro et al., 2019; Lu et al., 2017; Rahmani et al., 2020; Shao et al., 2017; Sun et al., 2024; Xie et al., 2018; L. Zhang et al., 2019)
3.	Alginate	Electrospun fibers, hydrogel, film	Polycaprolactone, borosilicate bioglass, gelatin, silk fibroin, carboxymethyl chitosan, graphene oxide, copper (II) sulfate, wool fiber, pectin	(Ahmad et al., 2021; Gao et al., 2019; Li et al., 2017; Ma et al., 2019; Oh et al., 2020; Türe, 2019; Wichai et al., 2019)
4.	Cellulose	Film	Gelatin, turmeric, chitosan, copper (II) sulfate	(D. Kim et al., 2019; Wei et al., 2022; Wichai et al., 2019; Ye et al., 2019)
5.	Carrageenan	Hydrogel, films	Chitosan, montmorillonite, Na-alginate, graphene, poly(vinyl alcohol), essential oils	(Biranje et al., 2020; Chandika et al., 2021; Fahmy et al., 2021; Li et al., 2020; Polat et al., 2020; Sathuvan et al., 2023; Zia et al., 2020)

However, in this review, the focus is on the use of the gellan gum (GG) biopolymer in biomedical applications including as a wound dressing material.

2. GELLAN GUM BIOPOLYMER

GG is a linear, negatively charged exopolysaccharide produced by microbial fermentation from the bacterium *Sphingomonas elodea* or *Pseudomonas elodea*. It is also excreted by *Sphingomonas paucimobilis* with a lesser yield (Warren and Panhuis, 2015). GG can be obtained in two forms which are high acyl GG and low acyl GG (Mahdi et al., 2015). High acyl GG has two acyl substituents: acetate and glycerate, while low acyl GG is a deacylated form of the native GG (Zhang et al., 2015). High acyl GG forms a soft and flexible hydrogel upon cooling at 65°C, meanwhile, low acyl GG forms a rigid and brittle hydrogel upon cooling at 40°C (Danalache et al., 2015). The chemical structure of GG is demonstrated in Figure 1.

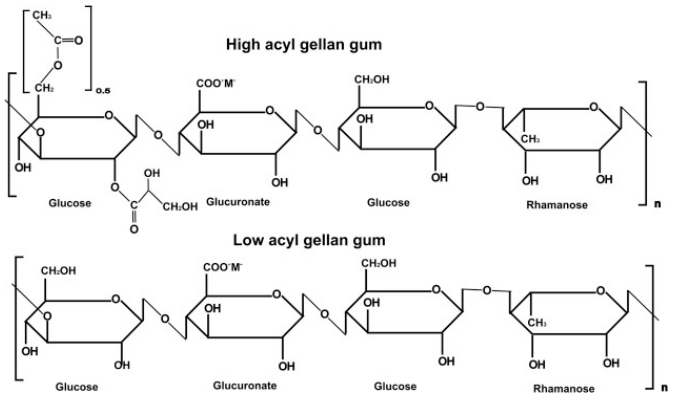

Figure 1. Structure of gellan gum (Milivojevic et al., 2019)

During production, GG can endure heat and acid stress (Morris et al., 2012). It is heat-sensitive, biocompatible, biodegradable, malleable, hypoallergenic, and has mucoadhesive properties (Picone and da Cunha, 2010; Salunke and Patil, 2016; Wang et al., 2016). GG is a negatively charged polysaccharide that can also produce polyelectrolytes when combined with a positively charged polymer (Amin and Panhuis, 2011; Vilela et al., 2015). It is resistant to enzymatic degradation and remains stable under acidic conditions (Nag et al., 2011). The beads of GG are stable at low pH but swell at higher pH levels (Nayak et al., 2014). Key properties of GG that are essential in chromatographic matrices include its porosity, hydrophilicity, high binding capacity, and ability to form ionic interactions with oppositely charged biomolecules (Mat Amin et al., 2012; Zia et al., 2018).

Various studies have been carried out to reduce the limitations of the GG biopolymer. One limitation of GG in pharmaceutical applications is its high cost compared to other commonly used polymers. This cost factor can make it less economical for large-scale pharmaceutical production, especially when considering cost-effectiveness and budget constraints in drug formulation. Furthermore, the viscosity of GG solutions can be challenging to control (Gering et al., 2021), which may pose difficulties in achieving desired drug release profiles or in the manufacturing of pharmaceutical dosage forms. Despite these limitations, GG's unique properties and benefits in pharmaceutical applications, such as its gelling ability and biocompatibility, continue to make it a valuable ingredient in certain formulations where its advantages outweigh the cost and availability considerations.

2.1 Application of GG biopolymer

GG has been used in many applications as a thickening and gelling ingredient (Madni et al., 2021). It can be administered without fear of hazardous side effects because it is well tolerated. In several food applications, GG serves as a thickening, binder, and stabilizer. It mainly stabilizes water-based gels like those found in desserts and beverage jellies. Even in gluten-free products, gellan replaces gelatin in several dairy foods like yogurt and sour cream. It is also utilized in low-calorie jams where pectin is ineffective, as well as in fruit preparations, yogurt, sauces, nonfat salad dressings, and films. Using gellan is the quickest way to shorten the setting time of starch-based confections. It also keeps candy from sticking together in warm environments (Mariod and Adam, 2013).

Recently, GG has been extensively studied due to its promising properties in biomedical applications. It has been studied in drug release studies, due to its complex interaction between swelling, diffusion, and erosion (Jana et al., 2022), cartilage tissue engineering (Kim et al., 2021), and oral drug delivery applications (Prezotti et al., 2020). Moreover, GG has been used in oral insitu gelling systems as low acyl gellan can encounter sol-gel transition in acidic conditions (Permana et al., 2023). With its easy-to-swallow formulation, people with pediatric or geriatric problems are well suited to GG. The oral administration of liquid gellan results in the formation of sustained release formulation in the stomach. At the same time, gellan gels are applied in obesity treatment as fillers in the stomach to lessen appetite due to their self-structuring property (Norton et al., 2011). Natural polymer-based beads and capsules have recently attracted a lot of interest. Beads are created when a gellan solution is added dropwise through a needle into an aqueous solution of ions while continuously stirring (Salunke and Patil, 2016). The GG has also been used in bone grafting (Cho et al., 2020), bioimaging (Cho et al., 2020), printing inks in tissue engineering (Cernencu and Ioniță, 2023), injectable hydrogels for cartilage (Lee et al., 2021), skeletal muscle (Kim et al., 2021) and wound dressing materials (Ismail et al., 2019; Muktar et al., 2018, 2021; Sebri and Amin, 2016). Table 2 summarizes the use of GG in various biomedical applications.

Table 2. The use of gellan gum with others biopolymers in biobiomedical applications

No.	Biopolymers	Type	Filler	References
1.	Silk fibroin/chondroitin sulfate ternary, silk fibers, clay, manuka honey,	Hydrogel	Cartilage tissue	(Bonifacio et al., 2020; Kim et al., 2021; Lee et al., 2021; Oliveira et al., 2010; Vilela et al., 2018)
2.	Pectin, chitosan, starch, hydroxyethylcellulose	Hydrogel, film, microbead	Drug release/ delivery	(Destruel et al., 2020; Dewan et al., 2017; Jana et al., 2022; Norazemi et al., 2017; Oliveira Cardoso et al., 2017; Prezotti et al., 2020; Zhang et al., 2020)
3.	Ibuprofen, collagen, titanium dioxide, clay, virgin coconut oil, chitosan, manuka honey	Hydrogel, film	Wound dressing	(Abu Bakar and Mat Amin, 2021; Azam et al., 2023; Ismail et al., 2014, 2019; Mohd Azam and Amin, 2017; Ng et al., 2021; Sebri and Amin, 2016; Zhang et al., 2020)
4.	Collagen, demineralized bone particles, hydroxyapatite, tuna skin,	Scaffold	Bone grafting	(Jung et al., 2020; D. Kim et al., 2019, 2020; Manda et al., 2018)
5.	Fluorescein isothiocyanate	Scaffold	Bioimaging	(Cho et al., 2020)
6.	Collagen, nano fibrillated cellulose, graphene oxide, poly (ethylene glycol) diacrylate, starch, gelatin,	Hydrogel,	3D-printing	(Lameirinhas et al., 2023; Ng et al., 2023; Wu et al., 2018; Zhang et al., 2021; Zhu et al., 2021)
7.	Laminin	Hydrogel	Skeletal muscle	(Alheib et al., 2022; Berti et al., 2017)

GG is used as a wound dressing material due to its biocompatibility, biodegradability, and ability to form a gel that maintains a moist wound environment. It helps promote wound healing by providing a protective barrier, absorbing excess exudate, and facilitating cell migration and proliferation (Mahmood et al., 2021; Mohd et al., 2016). Additionally, GG can be easily molded into various shapes to fit different wound sizes and shapes, making it a

versatile option for wound care. Various reinforcement agents/ chemicals have been added to GG composite to enhance the biocompatibility and antibacterial activity of the composites tailored as wound dressing materials such as virgin coconut oil (VCO) (Muktar et al., 2021), collagen (Azam et al., 2023), titanium dioxide nanotubes (Razali et al., 2020), clay (Mohd et al., 2016), poly(vinyl alcohol) (PVA) (Mishra et al., 2021), acetaminophen (Kasmi et al., 2020), ibuprofen (Sebri and Amin, 2016), ampicillin (Özkahraman et al., 2022), magnesium ions (Li et al., 2021), honey (Azam and Amin, 2017; Bonifacio et al., 2020; Muktar et al., 2018) and fucoidan (Shanmugapriya et al., 2020). All these fillers have shown promising results in enhancing the proliferation of the cells and wound closure, as well as combating the bacteria.

For example, hybrid hydrogels of fucoidan-loaded GG were tested with fibroblasts (L929 and NIH3T3 cells) (Shanmugapriya et al., 2020). In vitro cytotoxicity experiments were conducted using MTT assay, which demonstrated cell viability of over 70%. This result indicates that these hydrogel scaffolds are nontoxic and biocompatible. In comparison to plain hybrid hydrogels, fucoidan-loaded GG hybrid hydrogels exhibited a higher antioxidant scavenging activity. This finding highlights their capability to address the prolonged inflammatory phase of the wound healing process, as demonstrated by in vitro antioxidant experiments employing the DPPH scavenging assay. Moreover, in the in vivo wound healing studies, the group treated with fucoidan-loaded GG hybrid scaffolds showed a faster wound closure rate than the other groups (Shanmugapriya et al., 2020). By adding magnesium ions, Li et al. (2021) reported that the GG/polyacrylamide hybrid hydrogels combined with magnesium ions showed enhanced tensile strength from 86 to 392 kPa and elongation at break from 84 to 231% compared to normal GG hydrogels, demonstrating the improvemed mechanical performance of the materials (Li et al., 2021). The hydrogel also accelerated wound closure, based on in vivo investigations utilizing the rat full-thickness burn model.

The incorporation of VCO in GG (GVCO) hydrogels has shown that the healing process was the highest at 95±2% compared to GG and Opsite dressing at 91±4% and 93±4%, respectively on day 14 (Figure 2a) (Muktar et al., 2021). The ultrasound images of the thickness growing on the wound skin treated with GVCO exhibited the optimum recovery compared to other samples on days 2, 4, 7, 11, and 14 (Figure 2b). The intensity of white, yellowish, and green colors indicates good formation of the epidermis, dermis, and subcutis of GVCO hydrogel followed by Opsite. Epidermal regeneration was observed in all experimental groups after the 14th day of treatment (Muktar et al., 2021). VCO has long been recognized as a potent remedy for wound treatment, owing to its antibacterial, anti-inflammatory, antioxidant, and angiogenic properties (Nitbani et al., 2022; Patinggi et al., 2023; Wong et al., 2019; Zeng et al., 2022). A few other studies have reported promising results of using VCO for healing activities (Chew, 2019; Silalahi et al., 2019; Wong et al., 2019). It is suggested that the VCO is involved in the regulation of the vascular endothelial growth factor receptor 2 (VEGFR2) signaling pathway (Ibrahim et al., 2017). These previous studies collectively demonstrate the substantial impact of VCO on wound healing, exhibiting promising potential for biomedical applications.

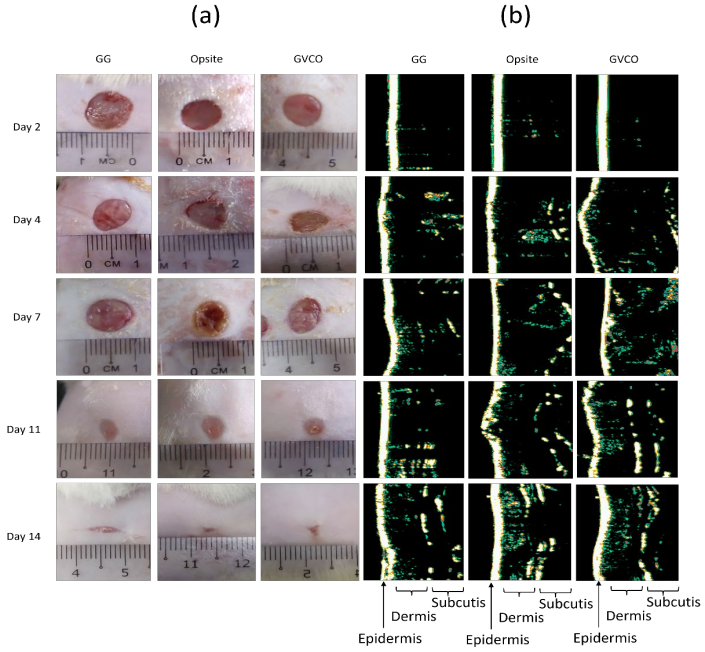

Figure 2. (a) Wound healing studies and (b) typical ultrasound images of wound skin on gellan gum (GG), Opsite, and GVCO80 hydrogels on days 2, 4, 7, 11, and 14 (Muktar et al., 2021)

Bilayer hydrogels based on GG-gelatin loaded with the antibiotic ampicillin were fabricated. The bilayer hydrogels were depicted in scanning electron microscopy (SEM) micrographs, which revealed porous structures with a mean pore size ranging from 268.6±305 to 337.3±179 μm. The ampicillin-loaded hydrogels show

ideal wound dressing criteria for treating infected wounds since the in vitro antimicrobial test using the agar disc diffusion test revealed that no inhibition zone was found in the ampicillin-free bilayer hydrogels whereas ampicillin-loaded hydrogels formed notable inhibition zones against *Staphylococcus aureus* and *Escherichia coli* (Özkahraman et al., 2022). Using the electrospinning technology, Mishra et al. (2021) created GG/PVA hybrid nanofibers containing cinnamaldehyde to eradicate Candida biofilm. These nanofibers can mimic the extracellular matrix (ECM) and support cell growth, as shown in the field emission scanning electron microscopy (FESEM) micrographs, which depict the fibrous morphology of GG-based hybrid nanofibers containing cinnamaldehyde and blank GG. The average diameters of the nanofibers were 278.5±57.8 nm and 204.03±39.14 nm, respectively. A drug release study showed cinnamaldehyde release from nanofibers quickly, which may quickly stop microbial development. Besides, GG containing cinnamaldehyde nanofibers efficiently eliminated 50.45% and 89.29% of *Candida albicans* and *Candida glabrata*, respectively. When compared to the pure GG nanofibers, the cinnamaldehyde-loaded one shows potent antibacterial activity against S. aureus and *Pseudomonas aeruginosa*, indicating their potential use as antimicrobial wound dressing materials (Mishra et al., 2021).

3. COLLAGEN

Collagen is the most prevalent structural protein in the human body and supports a variety of tissues, including tendons, skin, and teeth. The triple-helix structure of collagen is depicted in Figure 3. The family of proteins known as collagen includes all proteins with a three-helix polypeptidic chain structure, of which there are currently 26 different varieties (Sillat et al., 2012). The three polypeptidic fibrils can range in size from 10 to 500 nm in diameter, 285 kDa in molecular weight, and 1400 amino acids in length, with glycine, often found every three residues, thus giving them their unique fibrillar helicoidal shape (Martinez et al., 2019). Collagen fibers are frequently white, opaque, and easily identifiable in tissue. It is regarded as a viscoelastic substance with great tensile strength and minimal extensibility. Its isoelectric point is around pH 5.8. The shrinkage temperature (Ts) of most mammalian fibrils is between 62°C and 65°C, while the Ts of fish fibrils range from 38°C to 54°C. The denaturation temperature, however, is 25–30°C lower than the Ts (Avila Rodríguez et al., 2018).

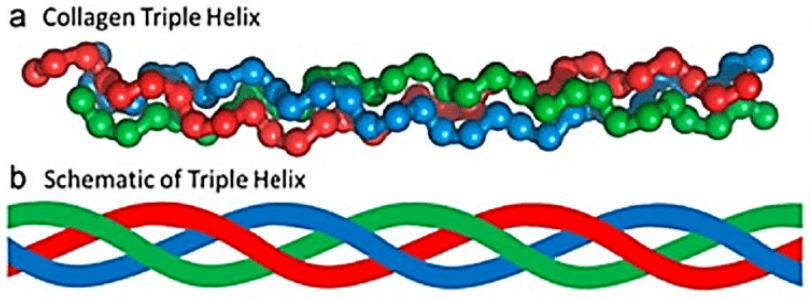

Figure 3. Collagen triple-helix structure (Patel et al., 2022)

3.1 Types of collagen

Collagen has been categorized into 26 different types divided into eight families according to the molecule's structure, chain bonding, and location in the human body. However, the most common collagen that has been used in biomedical applications is type I (Rezvani Ghomi et al., 2021). Having said that, the other types of collagen can also be used to mix with GG or other biopolymers for other biomedical applications. Each type of collagen brings unique properties and functions to the composite material, making them suitable for different applications in tissue engineering, wound healing, and drug delivery systems (Radhakrishnan et al., 2018).

By combining collagen (types I to XVIII) with biopolymers such as chitosan, alginate, hyaluronic acid, or synthetic polymers, it is possible to create composite materials with a wide range of properties that can be tailored for specific biomedical applications. These composite materials can mimic the natural extracellular matrix environment in the body and promote cell adhesion, proliferation, and tissue regeneration. The versatility of collagen when mixed with biopolymers allows for the development of innovative biomaterials that can be used in regenerative medicine, tissue repair, and other biomedical applications (Shekhter et al., 2019). Researchers continue to explore the potential of these collagen-based composite materials for improving healthcare outcomes and advancing biomedical technology.

Even though collagen has been reported to have promising properties, there are a few precautions that should be considered and improved. One limitation of collagen in biomedical applications is its potential for immunogenicity (Wang, 2021). Collagen is a naturally occurring protein in the body, and when used in pharmaceutical products, it can trigger an immune response in some individuals. This immune response can lead to allergic reactions or the formation of anti-collagen antibodies, which can reduce the effectiveness of the biomedical product or cause adverse effects in patients. Another limitation is the variability in collagen sourcing and quality (De Melo Oliveira et al., 2021). Collagen can be derived from different animal sources, such as bovine, porcine, or marine animals, and the quality and purity of the collagen can vary depending on the source and extraction methods. This variability can impact the consistency and safety of pharmaceutical products containing collagen. Additionally, collagen-based

biomedical products may have limited stability and shelf life. Collagen is a protein that can degrade over time, especially when exposed to certain environmental conditions such as temperature, pH, or enzymatic activity (Cao et al., 2022). This can pose challenges in the formulation and storage of collagen-based pharmaceuticals, potentially affecting their efficacy and safety. Overall, while collagen has many beneficial properties for pharmaceutical applications, its immunogenicity, variability in sourcing and quality, and limited stability can be significant limitations that need to be carefully considered in the development and use of collagen-based pharmaceutical products.

Figure 4 depicts the structure of the most commonly found groups, whilst Table 3 summarizes the family, types, and position of collagen in the human body.

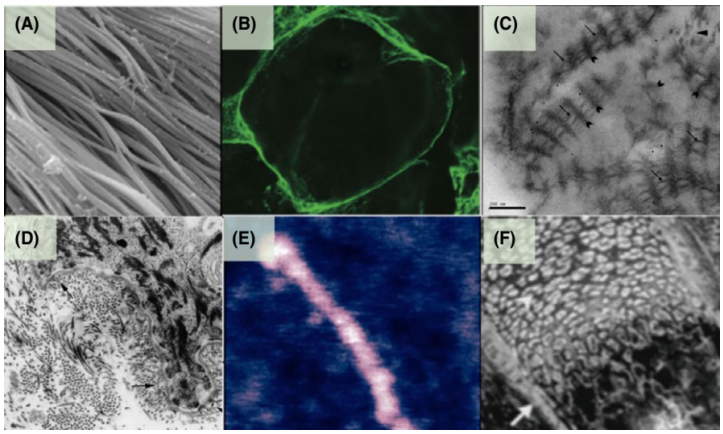

Figure 4. Microscopy of the most frequent collagen, (A) fibril forming, (B) basement membrane, (C) microfibrillar, (D) anchoring fibrils, (E) FACIT, and (F) transmembrane (Grässel and Bauer, 2012)

Table 3. Family, types, and position of collagen in the human body (Ricard-Blum, 2011)

Family	Type	Distribution in tissue
Fibril-forming	I	Tendon, ligaments, bone, and cornea
	II	Lung, cornea, reticular fibers, cartilage, vessel
	III	wall, nucleus pulposus, bone, vitreous body,
	IV	and skin
	XI	Vitreous body and cartilage
Basement membrane	IV	Basement membranes
Microfibrillar	VI	Dermis, placenta, lungs, cartilage, intervertebral disk, and placenta
Anchoring	VII	Oral mucous, cervix, dermal, and epidermal junctions, and skin
Fibril-associated collagens with interrupted triple helix (FACIT)	IX	Cornea, cartilage, and vitreous humor
	XII	Tendon, perichondrium, and ligaments
	XIV	Vessel wall, placenta, liver, dermis, and lungs
	XIX	Human rhabdomyosarcoma
	XX	Embryonic skin, tendon, corneal epithelium, and sternal cartilage
	XXI	Blood vessel wall
Transmembrane	XIII	The hair follicle, intestine, liver, dermal and epidermal junctions, epidermis, and lungs
	XVII	Dermal and epidermal junctions
Multiplexins	XV	Kidney, smooth muscle cells, fibroblasts, and pancreas
	XVI	Keratinocytes and fibroblasts
	XVIII	Liver and lungs

3.2 Noise exposure level and stress symptoms

Collagen, a fibrous protein found in the extracellular matrix of various tissues, has numerous applications in various fields. It has been used in biomedical and tissue engineering, the cosmetic and skincare industry, the food and beverage industry, biopharmaceuticals and drug delivery, biomaterials, and regenerative medicine (Sionkowska et al., 2017). In biomedical and tissue engineering, it is used as a healing material, and for bone regeneration and cartilage repair. Collagen-based scaffolds have shown remarkable efficacy in promoting wound healing. These scaffolds provide a three-dimensional framework that supports cell attachment, migration, and proliferation (Yu et al., 2022). Moreover, collagen stimulates the secretion of various growth factors, cytokines, and chemokines that orchestrate the wound-healing cascade (Y. Zhang et al., 2019). The presence of collagen in the scaffold mimics the natural extracellular matrix, facilitating cell adhesion and promoting the formation of new blood vessels (angiogenesis) (Strang et

al., 2020). Additionally, collagen scaffolds can modulate the release of growth factors, providing a controlled microenvironment for tissue regeneration. Collagen-based scaffolds have also emerged as a key component in skin tissue engineering due to their structural similarity to the dermal matrix. These scaffolds provide mechanical support, promote cell adhesion, and facilitate the migration and proliferation of skin cells (Pal et al., 2019). Collagen scaffolds can also be modified to incorporate bioactive molecules, growth factors, and cytokines to further enhance cell behavior and tissue regeneration (Y. Zhang et al., 2019). Through the interaction between cells and collagen scaffolds, skin tissue engineering approaches seek to restore the functionality and aesthetics of damaged skin (Irawan et al., 2018).

In bone regeneration, collagen scaffolds provide an ideal environment for osteoblasts, the bone-forming cells, to attach, proliferate, and deposit new bone tissue (Wang et al., 2019). Collagen's ability to mimic the native extracellular matrix supports the differentiation of mesenchymal stem cells into osteoblasts, stimulating osteogenesis. By incorporating bioactive molecules, such as growth factors and osteogenic factors, into collagen scaffolds, researchers can further enhance bone regeneration by promoting cell proliferation, differentiation, and extracellular matrix deposition (Ho-Shui-Ling et al., 2018). Collagen also plays a crucial role in cartilage repair, addressing challenges associated with cartilage defects and osteoarthritis. Collagen-based scaffolds provide a suitable microenvironment for chondrocytes, the cells responsible for cartilage formation, to attach and proliferate (Wang et al., 2020). The porous structure of collagen scaffolds supports cell viability by facilitating nutrient and waste exchange. Additionally, collagen scaffolds can be functionalized with signaling molecules like transforming growth factor-beta (TGF-β), promoting chondrogenesis and stimulating the synthesis of cartilage-specific extracellular matrix components (Li et al., 2015).

Hydrogels based on collagen have emerged as promising biomaterials for regenerative medicine applications. Collagen hydrogels possess excellent biocompatibility, water-holding capacity, and structural resemblance to the extracellular matrix (Tang et al., 2022). These hydrogels can be easily synthesized and modified to incorporate bioactive molecules, growth factors, and cells, enhancing their regenerative potential. Collagen hydrogels provide a favorable microenvironment for cell encapsulation, proliferation, and differentiation, promoting tissue regeneration and wound healing. Moreover, the physical properties of collagen hydrogels, such as gel stiffness and porosity, can be adjusted to mimic specific tissue characteristics and optimize cellular responses (Gao et al., 2020). Not limited to that, it has been produced in film form. These films can be applied as dressings, providing a protective barrier for wounds while creating an optimal environment for tissue repair (Jana et al., 2016). Collagen is used as a wound dressing material because it is a natural component of the extracellular matrix, promoting cell adhesion, migration, and proliferation in the wound bed. It provides structural support, helps in tissue regeneration, and accelerates the healing process (Azam et al., 2023). Collagen also has hemostatic properties, reducing bleeding and preventing infection (Sun et al., 2024). Being biocompatible and biodegradable, collagen dressings are well-tolerated by the body and can be easily absorbed as the wound heals. Overall, collagen dressings facilitate wound healing by creating an optimal environment for tissue repair. The films also possess moisture-retaining properties, preventing excessive dehydration of wounds and promoting a moist wound-healing environment (Jana et al., 2016). Collagen-based films can be functionalized with antimicrobial agents, growth factors, and other bioactive molecules to enhance their therapeutic effects and tailor them for specific wound types (Chattopadhyay and Raines, 2014).

Wang et al. (2017) researched the production of collagen incorporating hydroxyapatite (HA) fiber-based composite films for food packaging. Mechanical tests on these composite films show enhancement from 38.98 to 48.20 MPa after adding HA compared to blank collagen film. The DSC analysis on these films showed that collagen incorporating HA exhibited increased thermal stability, with the degradation temperature rising from 86.9°C to 96.2°C, indicating a higher energy requirement for collagen degradation. Furthermore, the water vapor and oxygen barriers of collagen films decreased in value, indicating that the addition of HA may aid in blocking water moisture permeability. Overall, collagen/HA composite films were ideal candidates to be utilized as food packaging and preservation materials (Wang et al., 2017).

In addition, Marangoni et al. (2021) prepared sodium alginate (SA) incorporating hydrolyzed collagen (HC) films to be used as sustainable packaging films. These SA films showed significant enhancement in thermal stability after the insertion of HC, ranging from 215°C to 220°C, ascribed to the hydrogen bonding between SA and HC. The water vapor transmission rate of SA significantly decreased from 1216 to 592 g/m/day as the HC content increased. These results might benefit packaging film applications as moisture transfer through the film will be delayed (Marangoni et al., 2021).

Andonegi et al. (2020) fabricated chitosan incorporating collagen films for biomedical applications. DSC analysis was performed on these samples, and the thermal stability increased after adding chitosan, demonstrating the interaction between collagen and chitosan. The water contact angle of the show declined in value from 103° to 90° after the inclusion of chitosan into the collagen films, which would encourage fibroblast and endothelial cell attachment during healing. Collagen/chitosan also showed an improvement in strength owing to the triple helix structure of collagen. All the samples displayed more than 70% cell viability after 48 hours in an in vitro cytotoxicity assay and may be considered harmless materials (Andonegi et al., 2020).

Grabska-Zielińska et al. (2020) fabricated collagen/silk fibroin/chitosan scaffolds cross-linked by dialdehyde starch (DAS). The porosity of the materials was determined using the liquid displacement method. All the cross-linked scaffolds had a porosity ranging from 86 to 90%. It is common knowledge that a material's porosity should be around 90% for bone tissue engineering applications, as this allows for adequate nutrition and gas exchange, as well as enough room for cell attachment and proliferation. The swelling test on the silk fibroin scaffold showed improvement from 1,792% to 2,091% after the addition of collagen, demonstrating collagen's capability in tying water molecules. Additionally, the biological tests using osteoblast-like MG-63 cells showed the analyzed

samples were cytocompatible with MG-63 cells, as most of the cells were alive after 7 days (Grabska-Zielińska et al., 2020).

4. STUDIES OF GG WITH COLLAGEN

A few studies have been reporting on GG with collagen for different applications. Some studies reported the use of GG/collagen for the coating layer (Almeida and Sato, 2019), tissue engineering (Chen et al., 2018; Kozlowska et al., 2020; Ng et al., 2022; Vuornos et al., 2019, 2020), bone graft materials (Kim et al., 2022), 3D printing (Ng et al., 2023; Xie et al., 2023) and wound dressing (Abu Bakar and Mat Amin, 2021; Ng et al., 2021). From these citations, it shows that the combination of GG with collagen has focussed as biomaterials due to the biocompatibility and safeness of the materials to the living cells.

In tissue engineering, Vuornos et al. (2019) have investigated the effectiveness of GG and collagen hydrogels in promoting osteogenic differentiation of human adipose stem cells (hASCs) for bone construct development. The hydrogels were supplemented with bioactive glass ions and compared to control groups. The results showed that the hydrogels with bioactive glass ions induced efficient osteogenic differentiation of hASCs. Specifically, the GG hydrogels crosslinked with spermidine or bioactive glass extract, as well as the collagen hydrogels, demonstrated strong osteocalcin production, indicating successful osteogenesis. Another study investigated the effectiveness of a functionalized GG/collagen hydrogel in promoting vascularization using bone marrow-derived mesenchymal stem cells (BMSCs). The study demonstrated by wound scratch assay that the hydrogel provided an excellent microenvironment for cell survival and proliferation, as well as having effective vascularization potential (Chen et al., 2018).

For bone grafting, Y. Kim et al. (2019) investigated the effectiveness of a fish collagen/GG and bone graft material (FC/GG-BGM) composite as a guided bone regeneration (GBR) membrane for promoting bone regeneration. The in vivo results of the study showed that the FC/GG-BGM membrane significantly enhanced bone regeneration compared to the control group. At 2 weeks, the defected site of rats treated with FC/GG-BGM membrane showed higher regeneration (0.377±0.012 mm^3) than that of rats treated with the bovine collagen membrane (0.290±0.015 mm^3) and control rats without a membrane (0.160±0.008 mm^3) (Kim et al., 2022).

3D printing is also a focus of research in biomaterials. The use of GG and collagen for 3D printing has been reported by Xie et al. (2023) by investigating the in vivo results of 3D printed collagen scaffolds using a citrate-modulated GG microgel bath. The study aimed to enhance the resolution of 3D-printed collagen scaffolds and evaluate their performance in an in vivo setting. 3D collagen organ structures such as the hand, ear, and heart were successfully constructed with high shape fidelity in the developed bath (Xie et al., 2023). Another study investigated the in vivo results of 3D-printed collagen scaffolds using a citrate-modulated GG microgel bath (Ng et al., 2023). The results show that the bio-ink improved printability for extrusion-based 3D bio fabrication and preserved scaffold quality for stem cell proliferation (Figure 5). Cell proliferation assay and confocal laser scanning microscopy also suggested that adipose-derived stem cells retained their normal cellular functions of adhesion, proliferation, and migration within the 3D bioprinted hydrogel scaffold (Ng et al., 2023).

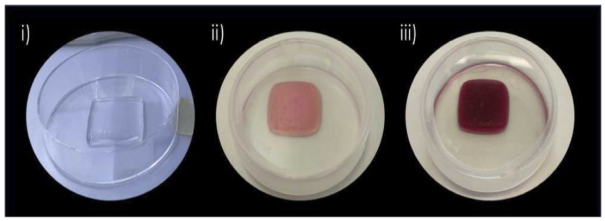

Figure 5. Top view of 3D printed gellan gum-collagen IPN hydrogel films; (i) immediately after 3D printing, (ii) 72 h after incubation, and (iii) 21 days after incubation in cell culture media.
Note: Dimension = standard 35mm cell culture dish (Ng et al., 2023)

Ng et al. (2021) reported the use of GG with a collagen hydrogel with biological wound-dressing properties, which possess the ability to promote human dermal fibroblast migration and secrete an anti-inflammatory paracrine factor, TSG-6 protein. The study found that the hydrogels exhibited superior mechanical properties, with a tensile strength ranging between 43.2±11.1 MPa and 52.4±2.3 MPa, making them compatible with human skin and easy to handle during wound dressing application. The hydrogel also enhanced early wound closure, reduced inflammation, and promoted complete skin regeneration (Ng et al., 2021).

The same observation was reported by Azam et al. (2023) by utilizing the GG and collagen with the addition of gatifloxacin. The study found that the GG/C hydrogel films loaded with collagen and gatifloxacin exhibited improved antibacterial and wound-healing properties. The hydrogel films showed a significant reduction in bacterial growth, with a 99.9% reduction in bacterial count after 24 hours of incubation. The hydrogel films also showed improved wound healing properties, with a 95% reduction in wound size as the incision area steadily healed throughout the 14-day study period. On day 14, GG, GG/C-GAT01, and GG/C-GAT05 wounds had completely closed without visible hypertrophic scars (Figure 6) (Azam et al., 2023).

5. CONCLUSION

In conclusion, recent research on GG and collagen has demonstrated their potential for various applications in wound healing and tissue engineering. GG, with its biodegradable, non-toxic, and biocompatible properties, can be formulated into different forms of wound dressings such as sponges, bandages, foams, wafers, and transdermal patches. Collagen, as a major component of the extracellular matrix, promotes cell growth and tissue regeneration. Combining GG and collagen in interpenetrating network hydrogels has shown promising results for wound healing, reducing inflammation, and promoting tissue regeneration. These hydrogels exhibit excellent biocompatibility, non-toxicity, and mechanical enhancement, making them suitable for burn wound therapy. Overall, recent studies highlight the potential of GG and collagen in addressing the challenges of wound healing and tissue engineering, paving the way for further advancements in this field.

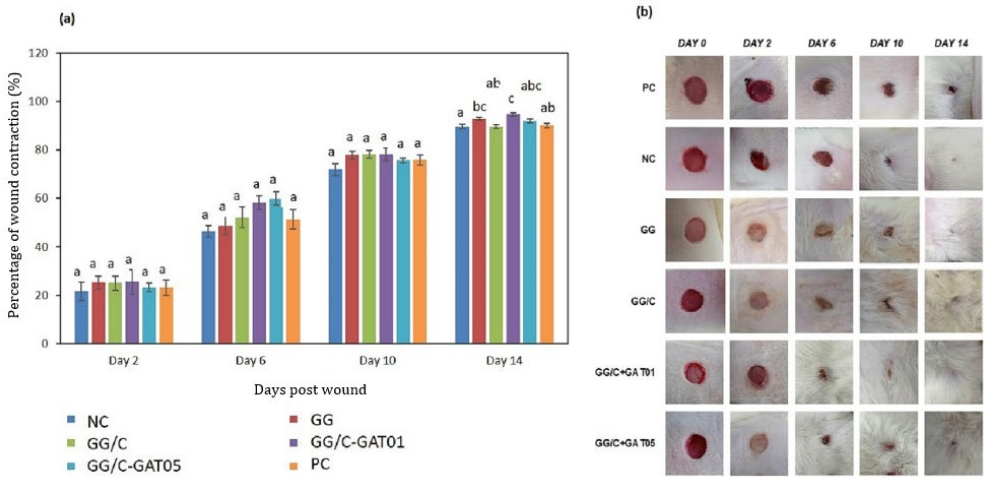

Figure 6. (a) Percentage of wound contraction for each treatment group on days 2, 6, 10, and 14 and (b) a macroscopic image of the wound on the rat from day 0 to day 14.
Note: The bars are expressed as mean±standard error; letters on bars (a, b, c) indicate significant differences at a 5 % level; and PC and NC indicate positive control and negative control, respectively (Azam et al., 2023).

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