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Application of Gellan Gum Biopolymer in Biomedical Applications: A Review

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Abstract

Gellan gum (GG) has gained considerable attention in the food, chemical, and pharmaceutical industries due to its functional characteristics. It has versatile properties, such as water solubility, easy bio-fabrication, good film/hydrogel-formation, biodegradability, and biocompatibility. These properties render GG a promising material in biomedical applications, specifically in the development of wound dressing materials. In this review, the use of GG biopolymer as a wound dressing material was discussed. Various fillers, such as titanium dioxides, clay, drug, and honey, have been incorporated in GG to produce film, hydrogel, or scaffold materials. The effects of filler on the mechanical performance, physical properties, antibacterial activities, and healing activities of GG biocomposites were explained. Overall, this review summarizes the effect of fillers on GG biocomposites for various biomedical uses.

Keywords: biomaterials, films, gellan gum, hydrogels, wound dressing

Introduction

Wound dressing. Wound dressing helps accelerate healing and avoid any infections or complications. Different wound dressings have been developed and used based on the type and severity of the wound. The selection of materials, such as film, hydrogel, and scaffold, is crucial in accelerating wound healing. With advanced technology, many types of wound dressing products with different biopolymers are available in the market. Traditional wound dressings, namely gauze, plasters, and bandages, are utilized to protect the wound from contaminations. However, traditional dressings do not provide a moist environment and accelerate healing relative to wound care products. In addition, they adhere to the wound and cause trauma to the patient when removed. Active wound care dressings not only cover the wound but also facilitate wound healing by utilizing biopolymers. An ideal wound dressing should be biocompatible with tissue surfaces, secure the wound from bacterial infection, and offer a moist and healing environment [1, 2]. Therefore, several studies focused on formulating active wound dressing materials, including biopolymers chitosan [3, 4], sodium alginate [5], xanthan gum [6], carrageenan [7], and gellan gum (GG) [8, 9], to promote wound healing. Biopolymers, particularly GG, are incorporated with various fillers to enhance the properties of composites and promote healing activities.

Gellan gum. GG is a water-soluble polymer produced in the laboratory in 1982 and has gained great importance in the biomedical, food, and chemical industries due to its functional properties. GG is a polysaccharide resulted from the fermentation of the pure culture of *Pseudomonas elodea* [2, 10–12]. It has been approved for use in food products by the Food and Drug Administration, USA. The unique properties of GG have attracted great attention for the application of the material in many fields. The food industry uses GG in emulsifiers, stabilizers, binders, gelling agents, coagulants, lubricants, film formers, and thickening agents. GG has also been used as agar in the preparation of microbiological media to improve clarity and reduce toxicity [13].

Structure of gellan gum. GG has a linear structure of negatively charged exopolysaccharide repeating units consisting of two β-d-glucose (d-Glc), one l-rhamnose (l-Rha), and one d-glucuronic acid (d-GlcA) (Figure 1) [14–16]. Structurally, gellan is a double helix that is promoted by the (1→3) linkage in the gellan repeating unit [17].

Type of gellan gum. GG exists in two forms: high acyl GG (HA) and low acyl GG (LA) [18, 19]. These GG forms differ in structure, resulting in a different range of textural properties. HA GG has acetate and glycerate as its substituents [20]. Acyl substituents in the GG influence the properties of gel produced. Removal of both substituents by treating the fermentation broth with hot alkali produces deacylated polymer, which is also known as LA GG [21, 22]. Figures 2(a) and 2(b) show the chemical structure of HA and LA GG, respectively.

HA GG can achieve complete hydration with heating to above 80 °C, whereas LA GG depends on the type and concentrations of ions in solution. HA GG is in a disordered single-coiled structure at high temperatures (80 °C). LA GG is transformed to a double helix and bonded by internal hydrogen bonding between D-glucoronate and D-glucose C residues upon cooling at 50 °C because of the presence of glycerate, thereby producing smooth and elastic GG gels. Compared with HA GG, the absence of acyl groups on LA GG created a different gelation behavior. LA GG undergoes order transition at low temperature, and gel-promoting cations are necessary to form strong and brittle 3D network gels. The difference in the properties of HA and LA GG is shown in Table 1.

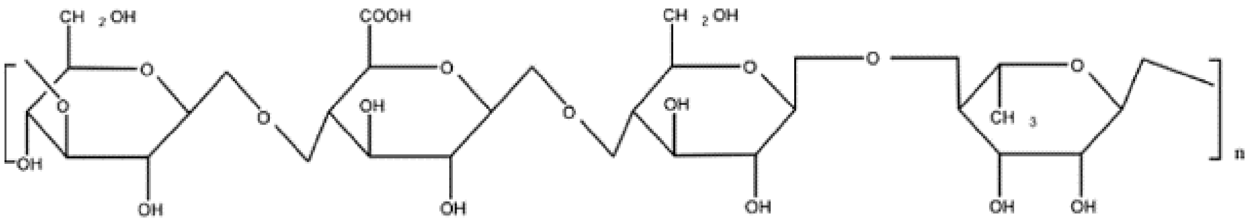

Figure 1. Chemical Structure of Gellan Gum [14]

(a)

(b)

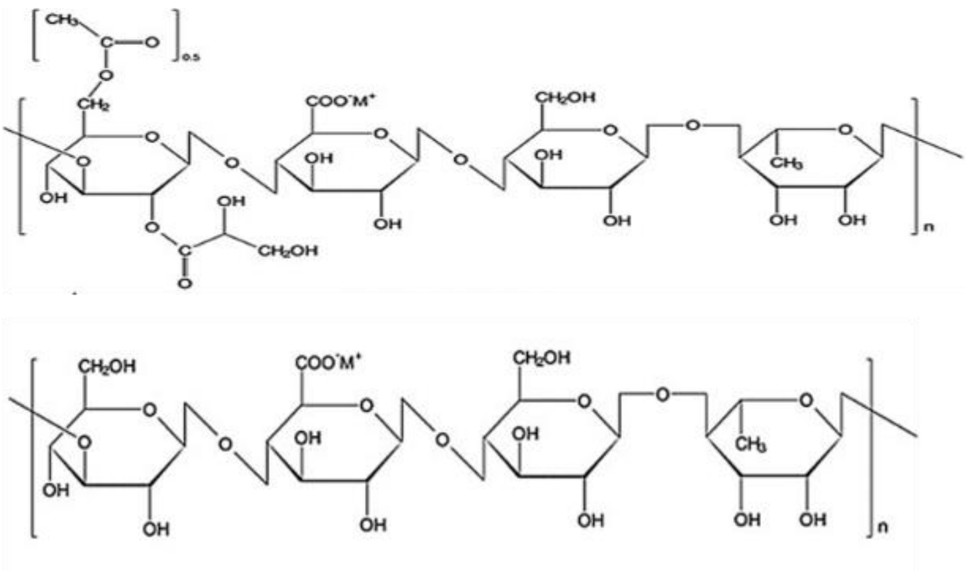

Figure 2. Chemical Structure of (a) High Acyl Gellan Gum and (b) Low Acyl Gellan Gum [23]

Table 1. Comparison of the Properties of High Acyl (HA) and Low Acyl (LA) Gellan Gum

	HA Gellan Gum	LA Gellan Gum
Hydration	>80 °C	>80 °C
Sequestrants	No	Yes
Hot viscosity	Low	Low
Gelling ions	Not required	Yes (mono or divalent or acid)
Setting temperature	50 °C–80 °C	25 °C–60 °C
Melting	Yes	No (except low ionic strength and in milk)
Texture	Soft, elastic	Firm, brittle

Addition of Fillers

Fillers are added to the polymer composites to create properties improvement to a greater extent. Various fillers have been deployed in composite materials, such as carbon-based fillers [24, 25], titanium dioxide [26], clays [25], metal [27], silver [28], zinc oxide [29], copper oxide [30], halloysite [31], zeolite [32], cellulose [33], and fibers [34]. Nowadays, most studies used nano-sized fillers to extend the composite properties. These fillers are incorporated into different polymers (natural or synthetic) to achieve varied applications, such as in organic photovoltaics [35], biopharmaceuticals [36], catalysts [37], water purification [38], conductive materials [39], and medical purposes [40–42]. A few studies have used GG to mix with those fillers and for the applications discussed above [25, 28, 43]. The present review focuses on the biomedical application of GG as a wound dressing material.

Gellan Gum for Biomedical Applications

Drug delivery. In drug delivery, various formulations of GG are designed to transport the drug to the targeted area, such as to the oral cavity, stomach, intestine, colon, ocular, nasal, and transdermal deliveries. The various targeted areas of GG formulation show that GG is a robust material that could be tailored to a specific targeted area in our body due to its physicochemical, mechanical, and functional characteristics [44]. GG can be formulated in different forms, such as gels, films, microcapsules, nanoparticles, and others, for a different route of administration. Dewan *et al*. [45] have reported the gelation behavior of formulation poloxamer 407 and GG to release pilocarpine hydrochloride drug. The addition of GG in poloxamer 407 decreases the gel pore size and gel dissolution rate of poloxamer. In vitro drug release of pilocarpine hydrochloride from poloxamer-GG formulation depicts better delivery than fully poloxamer-based gel.

Vashisth *et al*. [46] encapsulated ofloxacin in GG/PVA nanofibers and characterized the drug delivery efficiency of the developed polymeric nanofibers. The ofloxacin loaded with nanofibers shows a substantial mucoadhesion and gastric retention when tested in the gastric mucosal membrane of rats. Compared with pure drugs, the developed nanofibers demonstrate an immediate release followed by a sustained release of ofloxacin for up to 24 h. The data depict that the usage of GG/PVA can enhance drug release activity. Curcumin is also often used to treat digestive disorders, such as gastric ulcers. Kerdsakundee *et al*. [47] developed a floating GG-based in situ gel incorporated with curcumin-PVP K-30 to overcome low aqueous solubility and to prolong the gastric residence period. The developed in situ gel improves drug solubility by approximately 4000 times compared with pure curcumin.

Tissue engineering. Tissue engineering is an emerging area in exploiting GG biopolymers to improve or replace the biological tissue of humans. GG in general is a highly adaptable material for tissue engineering because it can have a wide range of forms and functions. Most research on GG focused on its use as a material for cartilage reconstruction in tissue engineering. The self-repair for cartilage is limited and takes a long period to heal from degeneration or damage. Therefore, the usage of biomaterials to replace damaged cells is a great alternative.

Ismail *et al*. [40] produced a novel GG incorporated with TiO_2 nanotube films for applications in skin tissue engineering. The nanotube film produced is biocompatible and shows no sign of toxicity when tested using 3T3 mouse fibroblast cells. GG incorporated with TiO_2 induces a higher number of cells proliferated after 3 days compared with control GG film. Figure 3 displays the cell viability and number of cells proliferated for the sample. The films produced accelerate cell growth for wound healing and show a compatible characteristic for skin tissue regeneration.

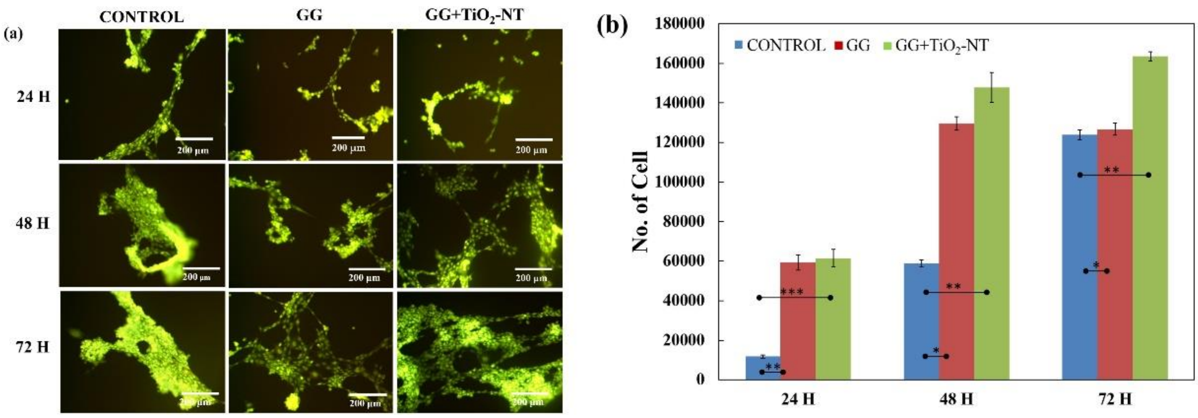

Figure 3. (a) Fluorescence Image Cell Growth and (b) MTT Analysis of Cell Proliferation Count for Control, Gellan Gum, and Gellan Gum/TiO_2 Nanotube Film [40]

Vieira *et al*. [48] studied the use of methacrylate GG (GG-MA) in bone tissue engineering. The crosslinking of GG-MA solution and $CaCl_2$ produces calcium-enriched beads that promote self-mineralization for bone tissue development. Energy-Dispersive X-Ray Spectroscopy (EDS) and X-Ray Diffractometer (XRD) results demonstrated the development of hydroxyapatite on the surface of beads after immersion into simulated body fluid solution. Figure 4 depicts the results of Scanning Electron Microscopy (SEM), XRD, and EDS analyses. XRD and EDS analyses confirmed the development of hydroxyapatite from the SEM image and showed similar characteristics to the theoretical value of hydroxyapatite. The developed beads do not trigger inflammation cytokines and are ideal for bone tissue mineralization.

Wound dressing materials. GG has been applied as a wound dressing material in various forms, such as films, hydrogel, scaffolds, and injectable dressing [25, 49, 50]. Various fillers have been incorporated in GG composites to examine the physical, mechanical, and antibacterial activities and healing behavior of the latter as wound dressing materials. Transparent films and robust scaffold materials form when GG composites are incorporated with titanium dioxide nanoparticles, as depicted in Figure 5 [8]. The transparent material is an advantage to the dressing product because it offers easy visibility to the wound area underneath the product.

Most GG materials are produced in film form [9, 26, 51, 52]. Mahmood *et al*. have developed GG films with the addition of lavender/tea tree oils and ofloxacin to determine the healing activity of the materials [9]. Optimized formulation consists of ofloxacin and 25% w/w lavender/tea tree oil (OL3 and OT3) shows 98% wound contraction in rats after 10 days of treatment (Figure 6).

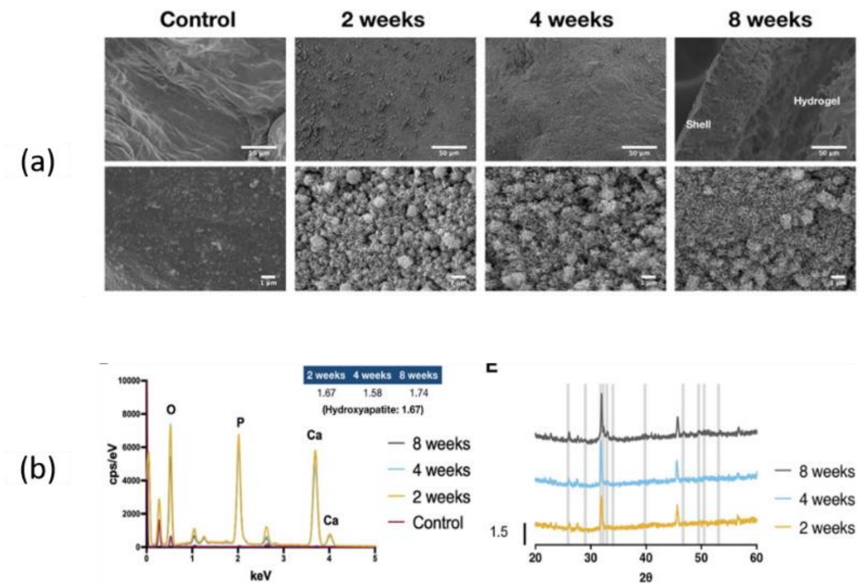

Figure 4. **(a) SEM Images of Ca-enriched GG-MA Beads. Cauliflower-like Morphology Shows the Deposition of Hydroxyapatite on the Surface of Beads, and (b) EDS and XRD Analyses of Ca-enriched GG-MA Beads [48]**

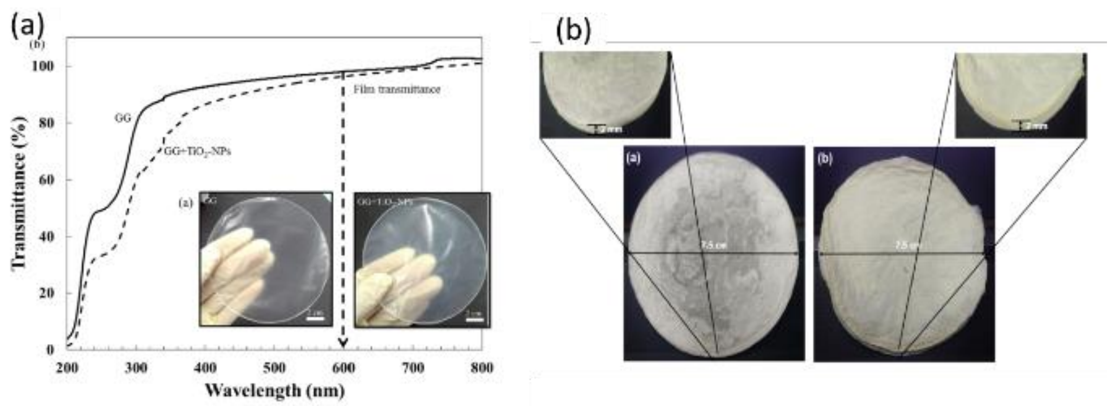

Figure 5. **Gellan Gum Film with Titanium Dioxide Nanoparti-cles as Dressing Materials (a) Film [8] and (b) Scaf-FOLD Materials [41]**

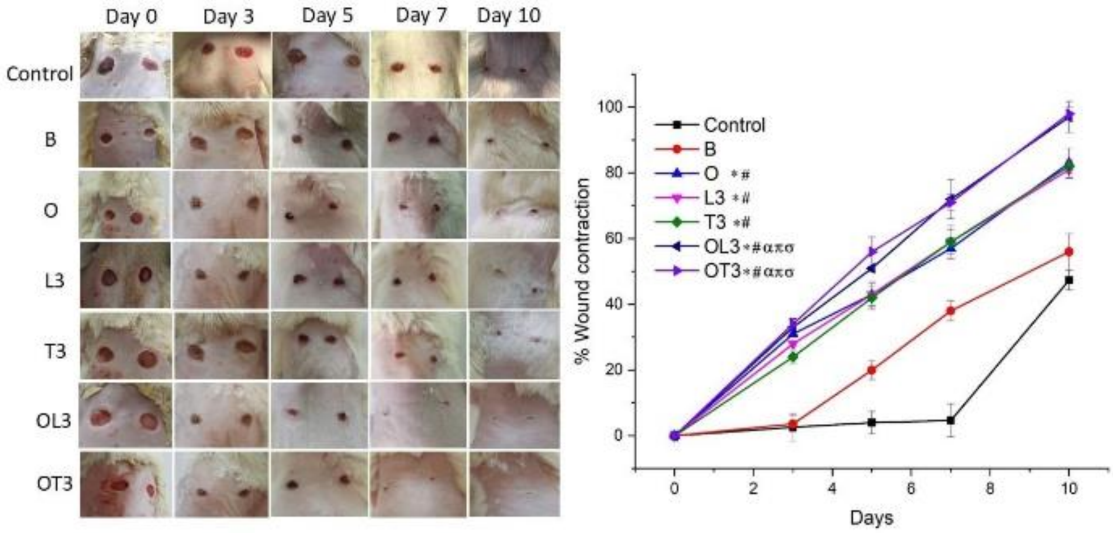

Figure 6. (a) Macroscopic View of Excision Wound Treated with Different Formulations. (b) Graphical Representation of Wound Contraction for Different Formulations (n = 6, p-value < 0.05, *Compared with Control, #Compared with B, αcompared with O, πcompared with L3, Σcompared with T3) [9]

Histological images display a completely healed epidermis. Lavender oil induces tissue remodeling by rapid replacement of type III collagen with type I collagen, and its antioxidant, anti-inflammatory, and antibacterial properties [53] playing a role in wound healing. Tea tree oil also boosts wound healing through its antimicrobial, antioxidant, anti-inflammatory, and immunomodulatory activities [54].

Few studies have incorporated titanium dioxides in different shapes, such as nanoparticles, nanotubes, and nanorods in GG composite film as dressing materials [26, 40–42]. The addition of TiO_2 nanotubes (20% w/w) has increased the tensile strength and Young's modulus of GG films as well as antibacterial activities against *Staphylococcus aureus*, *Streptococcus*, *Escherichia coli*, and *Pseudomonas aeruginosa* [42]. The study also reported an increase in mechanical strength by incorporating TiO_2 nanoparticles in GG films than without the filler [8]. Not limited to that, efficient antibacterial activities were also observed against *S. aureus* and *E. coli* bacteria. Many studies have reported the antibacterial mechanism of TiO_2. TiO_2 nanoparticles/ nanotubes/nanorods can dissolve the outer membranes of bacteria and by the existence of hydroxyl groups causing the death of organisms [55]. The antibacterial impact of TiO_2 nanotubes is usually accredited to the reactive oxygen species (ROS) formation, mainly hydroxyl radicals (OH), decomposes the bacterial outer membranes and ultimately kill the cell [56]. TiO_2 is also photocatalytically active and generates electron–hole pairs [57]. The photogenerated charge carriers act as strong reducing and oxidizing agents. Water molecules react with holes producing hydroxyl radicals (OH), and oxygen molecules react with electrons generating superoxides (O^{2-}). These reactive species assist oxidation of the bacterial cells. The high surface area of mesoporous TiO_2 nanotubes supports generation a great number of electron–hole pairs and, accordingly, shows an improved antibacterial activity. Moreover, TiO_2 nanotubes can infiltrate into the cell membranes of the bacteria, leads to the inactivation of the bacteria. Other studies have reported the strong antibacterial activity of TiO_2 in different biopolymers against Gram-negative and Gram-positive bacteria [58–60], in which the latter has undoubtfully strong activity in combating the bacteria and is beneficial in wound dressing materials.

TiO_2 is biocompatible with cell lines, such as L929 [61], HepG2 [62], 3T3 mouse fibroblast cells [42], human Caucasian foetal foreskin fibroblast (HFFF2) [63], and osteoblast-like HOS (MG-63) [64], and shows good healing activities on rats [65–67]. TiO_2 nanoparticles enhance the action of fibroblasts and collagen in regenerating wound tissues [68]. The increase in collagen production causing the re-epithelialization occurs in open wounds that lead to quick wound healing. Figure 7 shows the wound healing of GG film with TiO_2 nanoparticles within 14 days [8]. It clearly shows that the addition of TiO_2 enhances wound closure than on GG films. Furthermore, TiO_2 is biologically inert and nontoxic either to humans or animals at low concentrations [69].

Honey is another compound used to improve the healing activities of GG composite films. Muktar *et al*. [50] reported the effect of GG-virgin coconut oil containing Manuka honey on wound healing. The composition of the hydrogel enhances the compressive stress by threefold and is applied to a different part of the body because of its flexibility. The water vapor transmission rates (WVTRs) of the hydrogels produced are within the range of commercial wound dressings (112–132 g m^{-2} day^{-1}) and have the potential to treat acute wounds. GG film with 20% honey (w/w%) clearly shows an enhanced healing process than GG films with other concentrations of honey. The action of honey to the wound is due to stimulating the angiogenesis and growth of fibroblast under the skin. To address the excessive ROS during wound healing activity, the antioxidant capacity of honey is crucial, which specifically acts as a secondary messenger to induce proliferation and differentiation of the wound [70].

Collagen is another material that helps improve the properties of GG films. Collagen helps expedite healing by promoting cellular adhesion and proliferation [71, 72] and increasing several growth factors [73]. Ng *et al*. [74] formulated pristine GG–collagen hydrogel to produce wound healing paracrine factors that are involved in wound healing. The team has reported that the cell viability of GG–collagen hydrogel is slightly higher than that of adipose-derived stem cells encased in gold-standard pure type-1 collagen hydrogels. As tested on full-thickness burn wounds of mice, the wound dressing can enhance early wound closure, reduce inflammation, and promote complete skin regeneration.

The incorporation of drugs in wound dressing helps improve drug delivery to the wound. In general, it prolongs drug release and prevents the release of high doses at one time, which can cause undesired side effects [75, 76]. The incorporation of ibuprofen in GG hydrogel leads to a low swelling percentage of 22% ± 1%, which results in a slow drug release with the total drug released within 15 h [77]. The formulation of GG hydrogel with 5.0% ibuprofen exhibits a slight antibacterial activity against *S. aureus* with inhibition zone measured at 9.7 ± 1.15 mm, whereas in vitro cell study shows biocompatibility with the human cell line (CRL2522). The incorporation of acetaminophen, an analgesic drug in Kelcogel hydrogel film, increases its physical characteristics, compressive strength, and thermal behavior, making it suitable to be applied as a dressing material [78]. The addition of acetaminophen in GG films increases the water vapor transmission rate to a value in the range of commercial wound dressing products. The increasing acetaminophen concentration improves crosslinking behavior among the film network and causes the strong hydrogen bond between GG and acetaminophen, thereby increasing the compressive strength and Young's modulus.

Mat Amin *et al*. [61] focused on electrolyte complex material dual-layer films: a chitosan upper layer and a GG lower layer. The addition of levofloxacin in the chitosan layer does not exert a substantial impact on the mechanical properties and displays an effective antibacterial activity. The incorporation of TiO_2, ZnO, and Ag nanoparticles with underlayer GG films improves ductility where the tensile strength and Young's modulus decrease. Compared with the two other nanoparticles, the underlayer GG/TiO_2 composite shows high-viability cells and promotes the development of viable L929 cells (Figure 7).

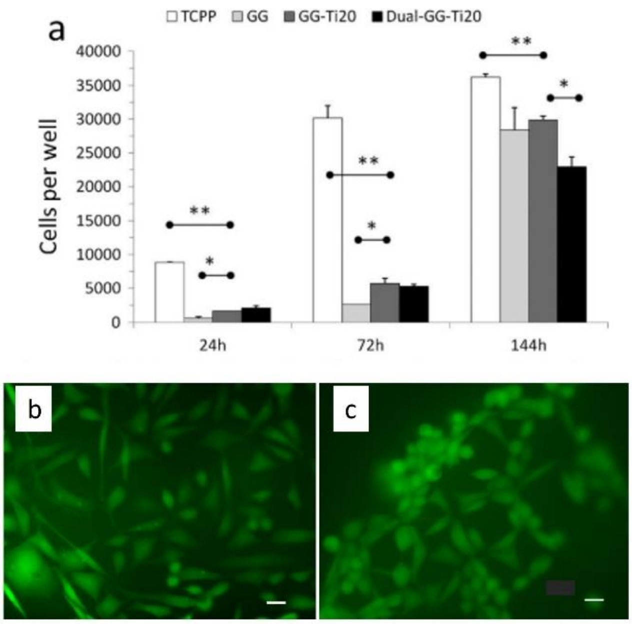

Figure 7. (a) Cell Proliferation for TCPP, GG, GG-Ti20, and Dual-layer (GG-Ti20 Surface) Films. (b) and (c) Fluorescence Microscope Images of L929 Cells on the CH-Lev01 and GG-Ti20 Surfaces of a Dual-layer Film after Incubating for 72 h. Scale Bar Represents 20 µm. [66]

Few studies focused on the crosslinking of clay with biopolymer hydrogel [25, 79]. Mohd *et al*. [25] reported that the addition of sodium montmorillonite (Na-MMT) in GG hydrogel increases the swelling ratio of the hydrogel and produces WVTR values in the range of 1106–1890 g m^{-2} day^{-1}, that is similar to the commercial wound dressing WVTR value. Cell studies revealed that the addition of Na-MMT in GG hydrogel is non-cytotoxic to human cell lines (CRL2522) after being cultured for 72 h. Pacelli *et al*. [80] found that the incorporation of GG-methacrylate with laponite® XLG produces stronger hydrogels compared with single matrices of GG-MA, which undergoes degradation after sterilization. The inclusion of laponite produces stable hydrogels with almost unaltered or intact mechanical properties after thermal treatment. With the same formulation, ofloxacin is added to study the release profile of the nanocomposite hydrogel [80]. The amount of drug is slow release as well as biocompatibility and non-cytotoxicity on human fibroblasts. Both nanocomposite hydrogel formulations may be applied as a wound dressing material for the chronically infected burn wounds treatment.

Injectable wound dressing has been a recent interest for wound healing since it can fit the shape of the wound perfectly. Zheng *et al*. [81] developed an injectable gelatin–gellan hydrogel to be used as a wound dressing. The composition of gelatin–GG hydrogel depicts good gelation properties that are ideal for the injectable form of a hydrogel. The blending of tannic acid into gelatin–GG hydrogel shows a significantly higher epidermal thickness and collagen concentration compared with another group of dressings (Figure 8). The hydrogel exerts no cytotoxic effect, and faster proliferation of L929 cells indicates the biocompatibility of the hydrogel to be applied as wound dressing material. Table 2 summarizes the different fillers incorporated with GG as wound dressing materials.

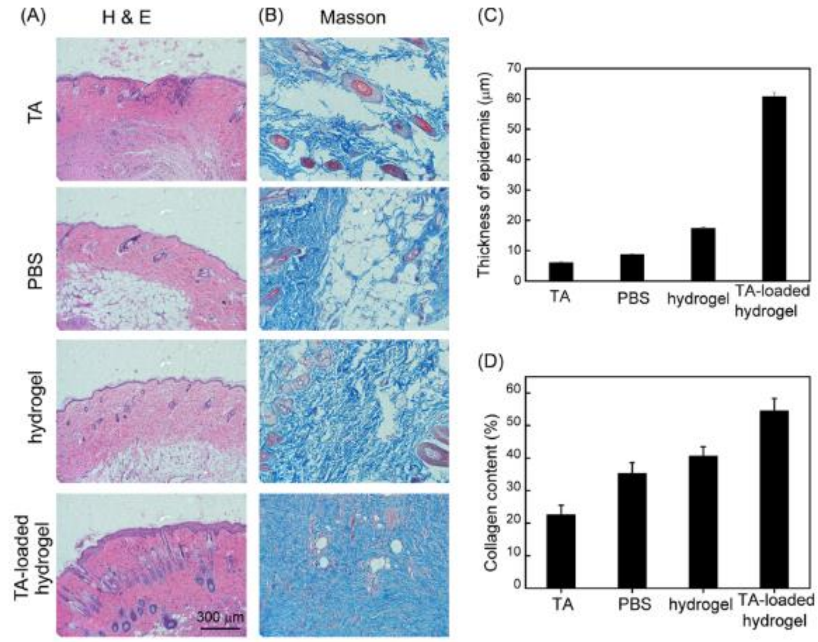

Figure 8. (A) and (B) Histological Image of Mice Epidermis, (C) Thickness of the Epidermis, and (D) Collagen Content of Tannic Acid-loaded Hydrogel at 12-day Wound Healing [81]

Table 2. Summary of GG Composites with Different Fillers as Wound Dressing Materials

No.	Type	Filler	Summary of finding	References
1.	Film	Therapeutic oils and ofloxacin	Optimized formulation containing ofloxacin and 25% w/w lavender/tea tree oil shows 98% wound contraction in rats after 10 days of treatment. Histological images display completely healed epidermis.	[9]
2.	Scaffold	Ball clay	Ball clay improves the mechanical performance, swelling, and thermal behavior of the GG scaffold and could be used as an active wound care product.	[82]

Table 2. Summary of GG Composites with Different Fillers as Wound Dressing Materials (*Continue*)

No.	Type	Filler	Summary of finding	References
3.	Film	Titanium dioxide nanotubes	Bio-nanocomposite films have good biocompatibility against 3T3 mouse fibroblast cells and accelerate healing of open excision-type wounds on Sprague–Dawley rats.	[42]
4.	Hydrogel	Silver nanoparticles	Composite gel exhibits higher antibacterial activity than the parent gel.	[83]
5.	Hydrogel	Collagen	Enhances early wound closure, reduces inflammation, and promotes complete skin regeneration.	[74]
6.	Hydrogels	Manuka honey with silica, bentonite, or halloysite	Mesoporous silica provides the best performance in regards to the in vitro cytocompatibility and antibacterial preventive activity in protecting cells in a co-culture model.	[84]
7.	Hydrogel	Polydopamine (pDA)	Human adipose-derived stem cells (hASCs) seeded on the pDa coated GG hydrogels display larger cell area, increased proliferation rate, and enhanced gene expression of focal adhesion and cytoskeletal proteins.	[85]
8.	Scaffold	Demineralized bone powder extracted from *Gallus var domesticus* (GD)	The prepared pore scaffold was biocompatible and promoted OC regeneration and integration of newly formed tissues with the host tissues in a rabbit.	[86]
9.	Scaffold	Carboxymethyl chitosan	The ratio of 2:1 OG/CMCS has the best efficiency. The mechanical properties of the scaffold improve.	[4]
10.	Film	Norfloxacin	The antibacterial activity is directly proportional to the release rate, which is at a higher concentration of norfloxacin, resulting in stronger antibacterial properties.	[49]
11.	Film	Titanium dioxide nanoparticles	GG + TiO_2 nanoparticle biofilm demonstrates better cell-to-cell interaction properties by promoting cell proliferation and cell migration to accelerate open excision wound healing on Sprague–Dawley rats.	[8, 41]
12.	Film	Glucosamine /clioquinol	The formulation decreases epidermal growth factor receptor (EFGR) expression and suppresses tumor progression.	[87]
13.	Hydrogel film	Acetaminophen	The addition of acetaminophen improves the physical properties, compressive strength, and thermal behavior of the Kelcogel hydrogel film and could be applied as a dressing material.	[78]
14.	Film	Virgin Coconut Oil Film Embedded Norfloxacin	The inhibition zones of GG-NOR and GG-VCONOR film are 5.3 ± 0.06 and 5.7 ± 0.06 mm against Gram-positive (*Staphylococcus aureus*) and 5.0 ± 0.01 mm and 6.3 ± 0.06 mm against Gram-negative bacteria (*Escherichia coli*).	[88]
15.	Hydrogel	Manuka Honey	In vivo healing on dermal wounds exhibits that the inclusion of honey accelerates wound closure and shows complete neo-epidermal of wounds.	[50]
16.	Hydrogel	Manuka Honey	Water vapor transmission is in the range of commercial products and has a higher tensile strain with a low concentration of Manuka honey.	[52]

Table 2. Summary of GG Composites with Different Fillers as Wound Dressing Materials (*Continue*)

No.	Type	Filler	Summary of finding	References

17.	Hydrogel	Clay (sodium montmorillonite (Na-MMT)	GG incorporated with Na-MMT is non-cytotoxic to human skin fibroblast cells (CRL2522) after being cultured for 72 h.	[25]
18.	Hydrogel	Ibuprofen	The hydrogel exhibits a slight antibacterial property toward *Staphylococcus aureus* with inhibition zone measured at 9.7 ± 1.15 mm, whereas in vitro cell study on normal human dermal fibroblast cells (CRL2522) indicated that the hydrogel formulation is biocompatible with the human cell line.	[77]
19.	Hydrogel	Apigenin (APN)	APN GG/chitosan found a higher wound healing effect in diabetic and normal wound tissues with significant antioxidant activity.	[89]
20.	Hydrogels	laponite® XLG	This novel NC hydrogel could be used as a wound dressing material for the treatment of burn wounds, which are subjected to chronic infections.	[80]
21.	Scaffold	MA/ Laponite/ Ofloxacin	The amount of drug release is slowed down and non-specific mechanical damage on human fibroblasts.	[80]
22.	Hydrogel membrane	Xanthan gum/ hyaluronan	Formulations of the XG/GG/HA hydrogel membranes reduce tendon adhesion with equal efficacy but without reducing the tendon strength compared with Seprafilm.	[90]
23.	Film	Virgin coconut oil	VCO is non-cytotoxic to human skin fibroblast cells (CRL2522) with limited cell growth observed on GG-VCO3 films at 1650 cells/well after incubation for 72 h, which could be due to the hydrophobic influence of the material surface.	[91]
24.	Dual-layer films	Levofloxacin and titanium dioxide	The upper layer of chitosan with incorporated levofloxacin displays antibacterial activity, whereas the lower layer of a GG /TiO_2 composite supports the growth of fibroblastic cells.	[61]
25.	Non-woven dressing	Silver	The new hydrophilic non-woven dressings show enhanced water uptake capability, slow dehydration rates, and promising antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa.*	92]
26.	Films	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC)	In in vitro biocompatibility tests, GG40 film exhibits nontoxic effects on L929 cells and inhibits absorption and activation of platelets. When implanted into rat subcutaneous tissue, the GG40 film causes minor inflammation in the early postoperative period. The effects of GG40 film on wound healing, wound size reduction (%), and collagen content are higher than those of commercial products (Duoderm).	[51]

Conclusion

GG has a high degree of versatility and shows superiority to a wide range of utilizations in the food, medicine, microbial growth, and pharmaceutical industries. It has been applied in various biomedical uses, namely drug delivery, tissue engineering, and wound dressing materials. Various fillers have been incorporated to improve the physical characteristics of GG materials, for instance titanium dioxide, drugs, honey, and silver nanoparticles. Moreover, the addition of fillers improves the antibacterial activities and enhances the healing activities of wound dressing materials. This review shows that adding fillers in GG materials offers a synergistic effect in improving the physical properties of the latter, the antibacterial activities, and wound healing.

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