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REVIEW

Two natural glucomannan polymers, from Konjac and *Bletilla*, as bioactive materials for pharmaceutical applications

Yu Wang · Jingjing Liu · Qiu Li · Yitao Wang · Chunming Wang

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Abstract Next-generation biomaterials are expected to possess both desirable mechanical features and unique biological functions. Recently, two plant-derived glucomannans (GMs)—Konjac glucomannan (KGM) and the polysaccharide of *Bletilla striata* (BSP)—have emerged as new sources for development of biomaterials. They have been fabricated into drug delivery vehicles and wound healing dressings in varying shapes and sizes, and demonstrated strong gelling properties, high biocompatibility and remarkable convenience for processing and modification. Notably, they demonstrate bioactivities such as response to enzymes produced in special biological niches and/or affinity for carbohydrate receptors on specific cells. All these mechanical and biological advantages suggest these two GMs have great potential for future development and broader application in various biomedical and pharmaceutical fields.

Y. Wang · J. Liu · Q. Li · Y. Wang · C. Wang (✉)
State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Avenida da Universidade, Macau, Taipa, SAR, China
e-mail: cmwang@umac.mo

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Introduction

Natural polysaccharides, such as alginate, dextran, chitosan and gellan, are widely used as biomaterials for drug delivery and tissue repair. Traditional use focuses on their desirable physical properties (Censi et al. 2012; Manjanna et al. 2010; Wang et al. 2008), while recent research has started to exploit their inherent biological functions, in particular their affinity for growth factors (Murali et al. 2013; Wang et al. 2014a) and specific cell receptors (Dong et al. 2009; Jansen et al. 2004). As we gradually uncover the diverse interactions between carbohydrates and signalling molecules, such as enzymes, growth factors and cell receptors, we are more interested in discovering and engineering carbohydrate polymers with both desirable physical features and unique bioactivities.

Here, we introduce two plant-derived natural glucomannans (GMs)—Konjac glucomannan (KGM) and the polysaccharide of *Bletilla striata* (BSP), which have emerged as new biomaterials tools with favourable physical characteristics and biological activities. Interestingly, although they are both GMs and share similar compositional units, they have been used with different focuses. In this concise review, we will introduce their chemical and material properties,

summarise their applications as biomaterials and discuss their potentials in broader applications.

Chemical and material features of the two GMs

Konjac glucomannan (KGM)

KGM was originally extracted from *Amorphophallus konjac C. Koch,* also known as Konjac, devil's tongue, voodoo lily, snake palm or elephant yam. It is a non-ionic, linear polysaccharide formed by units of 1,4-linked-β-D-mannopyranose and β-D-glucopyranose (Fig. 1a), with acetyl substitutes. The backbone chain of KGM is branched about every 68 monosaccharide units. The branch chains, length of 3-4 monosaccharides, are linked to either the C-3 hydroxyl group of glucose or the C-6 hydroxyl group of glucose/mannose on the main chain (Chen et al. 2013). The ratio of mannose to glucose is 1.6:1 (Katsuraya et al. 2003) and the monosaccharide residues may be randomly distributed (Cescutti et al. 2002). The molecular weight of KGM varies from 200 to 2,000 kDa, depending on cultivars, origin, producing methods and storage time.

Two main physical features of KGM are its high viscosity and gelling properties. It is soluble in water, despite its strong inter-chain association that normally renders a polymer water-insoluble (Dea and Morrison 1975; Ratcliffe et al. 2005). Its water solution is extremely viscous and is considered the most viscous among other natural colloidal solutions (Chua et al. 2010; Du et al. 2012; Wang et al. 2011). Although KGM has both hydrophilic (i.e. hydroxyl groups) and hydrophobic groups (i.e. acetyl groups), it is insoluble in organic solvents such as methanol, ethanol, acetone or ether.

KGM completes sol–gel transition under heating and alkaline pH condition, forming into elastic, strong and heat-irreversible gels (Du et al. 2012; Wang et al. 2011). The exact mechanism of gelation requires further investigation, but at least two major factors are known to play a part. One is the hydrogen bonds—the KGM chains lose their acetyl groups in alkaline solution, aggregate through a linkage of hydrogen bonds, and form a gel network (Case et al. 1992; Maekaji and Kawamura 1984); the other is the hydrophobic interactions between the KGM molecules, as indicated by rheological measurements (Du et al. 2012).

Its rheological properties and safety make KGM a popular emulsifier and stabiliser in the food industry (Chen et al. 2006; Chua et al. 2010). In the biomedical fields, KGM is widely used for drug delivery and, in particular, for the design of colon-specific drug delivery system (CSDDS). This application is based on the biological responses of KGM to the enzymes that are abundantly produced in the colon and that can

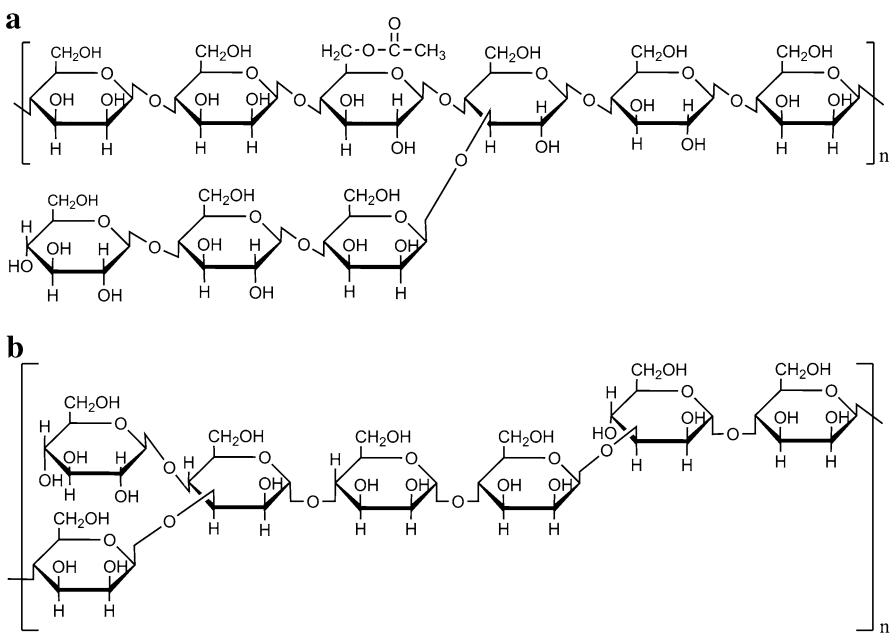

Fig. 1 The proposed chemical structures of **a** Konjac glucomannan (KGM) and **b** the polysaccharide of *Bletilla striata* (BSP)

specifically cleave the KGM chain, which we are to discuss in details later.

Bletilla striata polysaccharide (BSP)

BSP is isolated from *B. striata*, also known as the urn orchid. It has long been used for haemostasis and wound healing in traditional medicine in Asia. Also a glucomannan, BSP is principally investigated for its bioactivity in targeting (Dong et al. 2009) and modulating macrophages (Diao et al. 2008; Wang et al. 2014c) to facilitate drug delivery (Dong et al. 2009) and wound healing (Luo et al. 2010; Venkatrajah et al. 2012).

BSP consists of α-mannose, β-mannose and β-glucose (Fig. 1b). The relative mole ratio of mannose to glucose is about 2.4:1 (Wang et al. 2006). With a molecular size of 135 kDa, BSP is soluble in water.

Biomaterials applications

The two glucomannans are developed into biomaterials with different application focuses. KGM has been extensively studied as colon-specific drug delivery carriers that are responsive to the enzymes or increased pH in the colon. BSP was employed as bioactive macromolecular components for wound dressing and macrophage-targeting gene carriers.

Drug delivery

Colonic diseases, including colorectal cancer, ulcerative colitis, Crohn's disease and diverticulitis, are among the most prevalent diseases causing severe health problems worldwide. Colorectal cancer has both high incidence (∼9.7 %) and high mortality (∼8.5 %), ranking as the third most common cancer worldwide (Ferlay et al. 2013). Drug delivery to colon by oral administration is particularly challenging due to the distal location of colon in the digestive system. Drugs easily diffuse or are destructed in the stomach and intestine (Patel et al. 2012). In numerous studies, KGM has been designed into colon-specific drug delivery systems that are: (1) triggered by the colon bacterial enzymes; (2) pH-dependent, and (3) time-dependent, and demonstrated both desirable physical structure and sensitive response to specific enzymes.

The first strategy is aimed at bio-responsive drug release. Over 400 distinct species of bacteria exist in the human colon, at 10^{11}–10^{12} cfu/ml, in comparison with that in stomach (10–10^3 cfu/ml) and jejunum/ileum (10^4–10^7 cfu/ml) (O'Hara and Shanahan 2006). These bacteria are mainly anaerobes, such as *Bifidobacterium, Clostridium, Bacteriodes* and *Eubacterium* (Patel et al. 2012), and produce abundant glycosidases that specifically cleave the glycosidic links of KGM. Several studies have shown this strategy is promising. Investigations of tablets with KGM as a main excipient and cimetidine as a model drug suggest that the drug was stably kept in the network of KGM and xanthan, but was triggered for rapid release by β-mannase, which is predominantly present in the colon (Fan et al. 2008). Similarly, another study developed an enzyme-sensitive gel based on KGM and showed specific colon degradation (Alvarez-Mancenido et al. 2008). When placed in mimetic colon medium at pH 7.5 without β-mannase, 30–40 % drug was released within 24 h; however, in the presence of β-mannase (0.27 U/ml), above 60 % of the drug was released. These findings indicated the degradation of KGM is induced by bacteria producing β-mannase in the human colon. A possible delivery strategy is illustrated in Fig. 2a.

The second interesting aspect for consideration is the distinct pH difference between colon (∼7) and stomach (0.9–1.5) (Evans et al. 1988). Accordingly, KGM has been modified to develop a pH-sensitive system, and a typical approach is to prepare an interpenetrating polymer network (IPN) hydrogel based on KGM and polyelectrolyte complexes such as poly(acrylic acid) (PAA) and poly(aspartic acid). For example, after deacetylation in NaOH solution, KGM could be cross-linked with PAA by *N,N'*-methylene-bis-(acrylamide) (Wen et al. 2009) (Fig. 2b). In an acidic environment, the carboxyl groups are un-ionised and intramolecular hydrogen bonds are formed. When the pH increases to 7.4, these groups are ionised and the gel network swells because of the electrostatic repulsion—the swelling ratio of these IPN hydrogels was ∼3 at pH 1 but drastically reached 20 at pH 7.4. Another semi-IPN gel made of KGM and poly(aspartic acid) cross-linked by trisodium trimetaphosphate also demonstrated pH-responsive drug release capacity (Liu et al. 2010, Wang et al. 2014b).

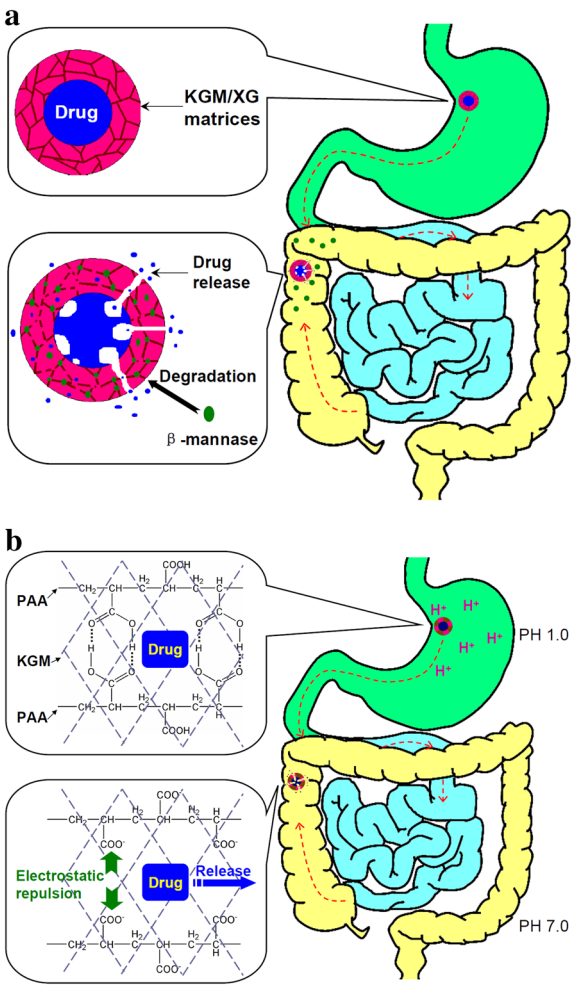

Fig. 2 Mechanisms of **a** microbially triggered colon-specific drug delivery system (CSDDS) based on KGM; and **b** pH dependent CSDDS based on KGM

Another matrix formed by cross-linking chitosan with oxidised KGM also showed pH-dependent properties. In stimulated stomach fluid that was acidic, the cross-link between amino groups in the chitosan and aldehyde groups in oxidised KGM made the matrix swell much slowly than in native chitosan film in which there was repulsion between ionized amino groups. The model drug, sodium diclofenac, was released much slowly from this hybrid film than that from the pure chitosan matrix. Only 1 % drug was released from the crosslinked film in the stimulated stomach fluid (Korkiatithaweechai et al. 2011).

In addition, KGM may also be oxidised or modified with carboxymethyl groups for more desirable properties. Its sugar chain has abundant diol groups that can be oxidised by sodium periodate to generate aldehydes or, more rigorously, to carboxyl groups. These functional groups are readily linked to amine-containing polymers such as glycosamonoglycans, chitosan and proteins. One example is to generate carboxymethyl-KGM (CKGM) and links to cholesterol using *N-tert*-butoxycarbonylglycine. This forms self-aggregated nanoparticles in aqueous medium under sonication (Ha et al. 2011). The diameter of these nanoparticles changes with pH values by which they have the potential to be used as pH-sensitive vehicles (Chen et al. 2014, Huang et al. 2013).

The third strategy is to develop a time-dependent delivery system based on KGM. Usually, an orally-administrated drug takes approx. 5 h to reach the colon. As such, to postpone the time for drug release could be one approach to for colon-specific drug release (Mladenovska 2012). One representative study reported a colon-specific, time-controlled vehicle comprising KGM and impermeable capsule, for the release of 5-aminosalicylic acid (5-ASA) (Liu et al. 2012). The impermeable capsule was sealed with plug tablet whose main ingredient was KGM; in practice, the drug was released from the capsule only after the KGM plug was hydrolysed and dissolved, and the outcomes of in vivo drug release performance were promising. Another hydrogel which was synthesized from oxidized KGM and gelatin also exhibited an obvious retard releasing comparing with native gelatin (Yu and Xiao 2008).

The use of BSP for drug delivery is also emerging. The first study was using it for macrophage-targeting gene delivery (Dong et al. 2009). In this study, BSP was cationised to conjugate antisense oligonucleotide (ODN) and transfect the ODN into in vitro cultured macrophages in an effort to supress the expression of TNF-alpha. The abundant mannose and β-glucose units of BSP have specific receptors highly expressed on macrophages (such as the mannose receptor, CD206). This feature led to preferential accumulation of BSP vehicles in macrophages, in comparison with fibroblasts and cancer cells that were set in parallel as controls. This strategy, to harness the interaction between the saccharide units of GM and macrophage receptors, has opened a new avenue for targeted drug delivery using such carbohydrate vehicles.

Wound healing

Both GMs have potential functions in wound healing. A physiologically-active wound dressing, fabricated

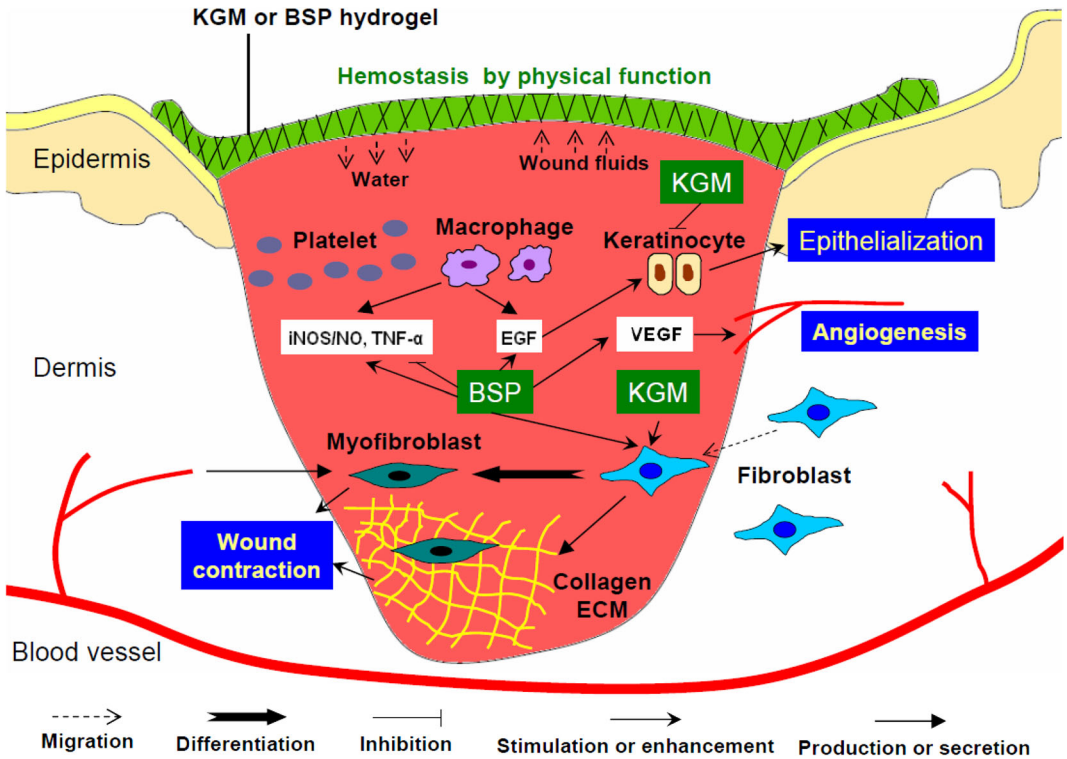

Fig. 3 Possible biological functions of KGM or BSP in wound healing

by cross-linking oxidised BSP and poly-lysine, was tested in a cutaneous trauma mouse model. The wound treated with BSP gel showed milder inflammatory response, non-swelling normal skin and consistent rate of re-epithelialization (Luo et al. 2010). In another study, the cotton gauze coated with aqueous extract of *B. striata* containing BSP showed higher healing efficiency than cotton gauze in rats (Venkatrajah et al. 2012). BSP fibres prepared by wet spinning showed flat shape and excellent mechanical properties (Xiang et al. 2014). The composite dressing made of polyvinyl alcohol (PVA) and *B. striata* also exhibited satisfactory mechanical properties (Lin et al. 2012).

BSP plays both physical and biological roles in facilitating wound healing. Because of its swelling property, the BSP hydrogel could keep a proper balance of fluids on the wound bed by absorbing wound fluids while replenishing liquid to the dry wound (Luo et al. 2010). In addition, this polysaccharide can regulate a series of cell activities such as cytokine expression. For example, BSP can induce human umbilical vascular endothelial cells proliferation (Wang et al. 2006) and migration (Luo et al. 2010), possibly through up-regulation of the expression of vascular endothelial growth factor (Wang et al. 2006), a key growth factor to initiate angiogenesis (Bao et al. 2009). The aqueous extracts of *B. striata* containing BSP promoted the proliferation of fibroblasts (Liu et al. 2009), which are the main cells of dermis (Greaves et al. 2013). Moreover, an in vivo study showed that BSP could elevate the secretion of epidermal growth factor (Luo et al. 2010) that mediates re-epithelialisation (Greaves et al. 2013; Hardwicke et al. 2008).

Interestingly, BSP may play dual roles in inflammation. BSP can enhance the expression of tumour necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β) and inducible nitric oxide synthase (iNOS) in macrophages in vitro (Diao et al. 2008). However, another study showed that BSP supressed the production of TNF-α, iNOS and NO in vivo (Luo et al. 2010). Pro-inflammatory cytokines, such as TNF-α, play important roles in the inflammatory phase and epithelialisation of wound healing (Frank et al. 2003). However, they may interrupt normal cell proliferation in the tissue formation phase (Fràter-Schröder et al.

1987). Further exploration may be focused on whether and how BSP could control inflammation at an appropriate level, which will bring unique benefits to wound healing.

Attempts to use KGM for wound healing are also emerging. A film of a blend of KGM/chitosan when used for wound healing showed not only excellent liquid-containing properties, but also a strong antibiotic effect and a higher haemostatic efficiency contrasting gauze loaded with conventional agents (Fan et al. 2013). The blocking of mannose receptor using mannose did not significantly affect the stimulation but concanavalin A inhibited the stimulatory effect. This indicated that another receptor on the cell surface, but not the mannose receptor, mediated the stimulatory effect of KGM on fibroblast proliferation (Shahbuddin et al. 2013). Moreover, forming graft-conetworks composed of cross-linked KGM and poly(*N*-vinylpyrrolidinone-*co*-poly(ethyleneglycol)diacrylate could stimulate the migration of both fibroblasts and keratinocytes (Shahbuddin et al. 2014).

The possible mechanisms underlying the activities of both GM in wound healing is illustrated in Fig. 3. More similar investigations are expected, given the clear biological functions of these polysaccharides in wound healing.

Perspectives

These two GMs may not be the most common polysaccharides used for pharmaceutical purposes, but they have demonstrated great potential as promising biomaterials for drug delivery and wound dressing. Given their interesting physical and biological properties, KGM and BSP are expected to be used in broader applications. First, they could be used as hydrogels. Existing hydrogels have a three-dimensional polymer networks with versatile advantages as drug delivery vehicles and tissue engineering scaffolds. However, despite their ability to form hydrogels, there has hardly been any attempt to develop KGM- or BSP-based hydrogel scaffolds for three-dimensional cell culture and tissue engineering. In contrast, other polysaccharide polymers with similar properties have widely been used for stem cell cultivation and bone/cartilage regeneration (Gong et al. 2009; Wang et al. 2009). Second, both polysaccharides are convenient to conjugate with other molecules, providing many possibilities for modification. Technologies to fine-tune their properties by chemical modification, as well as to precisely control the materials sizes, are in high demand. Third, glucomannans are unique carbohydrate molecules with abundant mannose and glucose units that can be recognised by various cell receptors. For instance, the interaction between mannose and macrophage-mannose receptor (MMR, or CD206) (Matthijsen et al. 2009; Taylor and Drickamer 1993), or that between β-glucan and dectin-1 (Brown et al. 2002; Goodridge et al. 2011), may inspire new strategies for engineering GM materials for drug delivery and tissue regeneration. In particular, development of GM-based nanoparticles for targeted delivery of drugs to immune system, or for modulation of immune cell behaviour to enhance tissue regeneration, would be of immediate interest.

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