Role of Glucomannans in Immunology

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ABSTRACT- Glucomannans play a much broader role in human health then providing dietary fibre. They are biologically active molecules and can when added to the body imitate innate molecules found in different organs including surface carbohydrates on cells. This review considers the immunological role of exogenous glucomannans within animals and man.

GENERAL

The diet includes 'exogenous' carbohydrates which provide the body with energy, dietary fibre and fermentation derivatives of the fibre. The exogenous carbohydrates can influence the innate immune responses of the body (1). The ingested carbohydrates incorporate many different types of sugars and sugar ratios. These include the glucomannans. Glucomannans are biologically active carbohydrates comprising mainly mannose and glucose (2). In nature, these polysaccharides form part of the hemi-cellulose component of some plant cell walls. The glucomannans have been consumed for centuries either for food uses directly, or health therapies – particularly *Amorphophallus konjac* glucomannan (3-9) and *Aloe vera* (10, 11).

Carbohydrates are considered often to be biologically 'neutral' but do in fact play a critical role in immune recognition (12). They can be recognised by the T cells (T-lymphocytes) or participate in T cell stimulation within T cell antigenic determinants (epitopes) (13). Interactions between carbohydrate specific antigens and T cells and consequently the implications of these interactions can modulate immune responses (14). The development of some forms of preventative therapies, such as the current focus on the design of novel vaccines, rely on carbohydrates (15).

Mannans in general and glucomannans especially exhibit therapeutic benefits for wound healing and burns; either systemically or topically (16-18). Glucomannans stimulate fibroblast growth factor(s) and the activity and proliferation of cells. This in turn stimulates collagen production and secretion at wound or burn sites (16, 19).

This review is novel in that no many updates in this area; hence this is a comprehensive update on the role of glucomannans in immunology. In fact this review focusses on the role of ingested glucomannans in immunology and explores the possibilities of their usage as a therapeutic tool for stimulating the healing wounds and burns through systemic or topical applications. It is recognised that the body produces cell recognition carbohydrates that contain mannose residues although the *de novo* synthesis is outside the scope of this review. Evidences from a number of sources are highlighted in Table 1.

SITE OF ACTIVITY AND ACTIONS

Gut

Non-starch (and starch) polysaccharides are consumed from various plant sources in the human diet. Monosaccharide units from within these plant structures exist in many different bonding sequences. These sequences affect the properties of the carbohydrates.

Dietary fibre (as a nutritional group) has been defined slightly differently among different organisations/institutions. For example, by the American Association of Cereal Chemists (AACC) (20), as 'edible parts of plants or analogous carbohydrates that are resistant to digestion and absorption in the human small intestine with complete or partial fermentation in the large intestine. Dietary fibre includes polysaccharides, oligosaccharides, lignin [not a carbohydrate], and associated plant substances.

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Dietary fibres promote beneficial physiological effects including laxation, and/or blood cholesterol attenuation and/or blood glucose attenuation'. Dietary fibre has been defined by the Institute of Medicine, Washington DC (21) as: 'Dietary fibre consists of nondigestible carbohydrates and lignin that are intrinsic and intact in plants. Functional fibre consists of isolated, nondigestible carbohydrates that have beneficial physiological effects in humans. Total fibre is the sum of dietary fibre and functional fibre'. Furthermore, The Codex Alimentarius Commission (CAC) (22) has defined dietary fibre as 'carbohydrate polymers with greater than ten monomeric units, which are not hydrolysed by the endogenous enzymes in the small intestine of humans'.

Dietary fibre has been reported widely to have an effect on the immune response in the gut (18, 23-26). These effects are mediated by the gut-associated lymphoid tissue (GALT) system (27, 28). The GALT system includes the: tonsils (aero-digestive tract); small 'aggregates' in the oesophagus; Peyers patches (small intestine); lymphoid 'aggregates' in the appendix and large intestine; some patches of lymphoid tissue in the stomach and; in the lamina propria (connective tissue) of the gut. Systemic immune effects originating from the gut (such as these induced by glucomannan) are mediated *via* the GALT system (29).

Dietary fibre oligosaccharides and polysaccharides include both (i) insoluble (e.g. from high fibre breakfast cereals, wholemeal breads and pasta, brown rice and other whole grains, vegetables, potatoes with skins, nuts and seeds) and (ii) soluble (e.g. from oats, barley, rye, bananas, apples, beans and pulses, root vegetables like carrots and potatoes) forms. It is reported often that the insoluble forms are less biologically active in the gut than the soluble forms as the latter form gut active viscous structures (Table 2). The insoluble (cellulose, hemicellulose and non-carbohydrate lignin molecules) and soluble (pectins, gums and mucilages) have been reviewed in some details by (30).

When dietary fibre is transported to the large intestine after ingestion, it is fermented by the endogenous microflora. The mechanisms by which fermentable dietary fibres work with respect to immune responses have not yet been established fully, although a number of hypotheses by different people have been proposed. These include: modulation of the intestinal microflora causing 'immune-enhancing' effects on lactic acid bacteria in contact with immune cells in the intestine; the production of short chain fatty acids (SCFAs) from the fibre fermentation/degradation and/or; by changes to mucin production (29, 31); interaction with the carbohydrate specific receptors (fimbrae or pili) of pathogens, inhibiting their attachment to epithelial cells (32) and; receptors on immune cells (33).

Horvath et al. (34) conducted a double-blind, placebo-controlled, randomised trial on the efficacy of glucomannan for abdominal pain-related functional gastrointestinal disorders in children. The authors concluded that glucomannan at 2.52g/d dose was not different from the placebo (maltodextrin) at the same dose in achieving therapeutic effects. Onakpoya et al. (35) discussed the efficacy of glucomannan supplementation in overweight and obesity individuals. The authors found that eight out of nine randomised controlled trials there was no significant difference in weight loss between the glucomannan and the placebo groups. Furthermore, Keithley et al. (36) evaluated clinical trial data concerning glucomannan supplements for weight loss in overweight and moderately obese adults. Participants received 1.33g of either glucomannan or a placebo three times per day for eight weeks. The authors reported that glucomannan supplements were well tolerated but did not promote weight loss or alter body composition, hunger/fullness, or lipid and glucose parameters. More recently, Ho et al. (37) conducted another systematic review and meta-analysis of randomised controlled trials on the effect of konjac glucomannan on LDL cholesterol, non-HDL cholesterol and apolipoprotein B. The authors reported that in twelve studies (n = 370), 8 in adults and 4 in children, met the inclusion criteria, konjac glucomannan at ~3 g/d significantly lowered LDL and non-HDL cholesterol concentration, while six trials suggested no impact on apolipoprotein B.

Glucomannan (native, with a molecular weight of 0.5-2 million Daltons) in the diet may prevent the development of allergic rhinitis-like symptoms associated with an increase of plasma immunoglobulin E (IgE) and G (IgG) according to work with mice (23, 24, 38, 39). Hydrolysed (depolymerised) glucomannans can also induce positive immune effects in mice when consumed (18). In addition, glucomannans more generally have also been shown to 'stimulate' the immune system and improve infection resistance in fish and dogs (26, 40). Zhang et al. (41) concluded from work using *Schizothorax prenanti* fish that oxidised konjac glucomannan not only promoted growth but also improved the 'immune status' of the fish. Oxidised konjac glucomannan (OKGM) and low-molecular-weight oxidised konjac

glucomannan (L-OKGM) can 'up-regulate' immune related gene expression and enhance disease resistance in *S. prenanti* although the L-OKGM have higher immunomodulatory activity (42). In addition, beneficial effects of oxidised konjac glucomannan in fish have been shown to extend to the intestinal morphology and microbial flora of the *S. prenanti* (43). Khalaji et al. (44) reported that mannan-oligosaccharides increase the immune response of birds too especially broiler chicks.

Onitake et al. (45) reported that colonic inflammation can be improved by the administration (consumption) of glucomannan. Both interleukin-4 (IL-4) and (IL-13), the critical inflammatory cytokines in oxazolone (OXA)-induced colitis derived from mononuclear cells from the *Lamina propria* of the colon, can be suppressed by glucomannan administration. Furthermore, a similar study investigating the 'protective' effects of konjac glucomannan (and inulin) on colitis in a dextran sodium sulphate-induced murine study showed that it may prevent colitis-related symptoms (46). Oral administration of pulverised konjac glucomannan prevents the elevation of plasma IgE by suppressing IgE class switching in B cells and/or the commitment development of naive lymphocytes to both T-helper type 1 (Th1) and T-helper type 2 (Th2) (23).

Similarly to consuming konjac (*Amorphophallus konjac*) glucomannan in some respects, consuming *Aloe vera* has shown beneficial health effects such as promoting the growth of lactobacilli such as *L. acidophilus*, *L. plantarum*, *L. casei* (in the colon) which may play a critical role in immune response (47) while reducing the growth of *C. albicans* (48). There are about seventy five potentially active constituents of *Aloe vera*, including glucomannans, where the glucomannans play a key role in, for example, healing (49) - see below. Bałan et al. (50) reported that oral administration of *Aloe vera* stimulated cell-mediated immunity and antibody production in mice. Kocik et al. (51) reported that feeding mice with *Aloe vera* gel diminished L-1 sarcoma-induced early neovascular response and tumour growth. The 'acemannan' in *Aloe vera* is made of predominantly galactomannan with acetylated mannose residues according to (52). However, more accurately, acemannan is in fact a molecule with a glucomannan backbone β-(1-4) linked with acetylated residues and some residues α-(1-6) linked to galactose (53). The ratio of mannose:glucose can range from 3:1 to 22:1. The molecular weight ranges from around 30-1000K Daltons (53).

Wounds

Apart from generalised topical effects of carbohydrates on skin (below), the consumption of specific oligosaccharides improves the wound healing process (54). For example, ingesting depolymerised konjac glucomannan can prevent atopic diseases by suppressing IgE production in mice and hence prevent the occurrence of dermatitis (18). Al-Ghazzewi et al. (55) reported that the consumption of depolymerised konjac glucomannan can accelerate wound healing (in mice) due to a range of systemic physiological effects.

Wound healing is a complex process and includes three phases: thrombosis (clotting) and inflammation; proliferation and formation of new tissue and; tissue retrieval (56). Specific exogenous carbohydrates, especially mannans, are associated with aspects of skin health and wound-healing (57, 58). In particular, glucomannans have been reported to promote accumulation of (at the wound site) fibroblasts and stimulate the production of collagen (19, 59, 60). Shahbuddin et al. (61) reported that konjac glucomannan has the ability to stimulate/induce fibroblast metabolites and the migration of both fibroblasts and keratinocytes. The glucomannan molecules also stimulate fibroblast growth factor and the activity and proliferation of the regenerative cells, which in turn improve collagen production and secretion, leading to accelerated wound improvement (16).

Herbal wound healing therapies have been discussed by many authors in the literature (for example, Krishnan (62). These therapies often contain mannans although the therapies are not always promoted on that basis. For example, the acemannans isolated from *Aloe vera* leaves, have been utilised for wound care historically and have been shown to promote healing and reduce radiation induced skin reactions (10, 63-65). Sánchez-Machado (66) reported that *Aloe vera* possesses numerous activities some of which are due to the presence of polysaccharides or acemannans. The acemannans are a major polysaccharide component in *Aloe vera* extracts and have been studied widely. They are reported to stimulate wound healing and tissue regeneration by inducing cell proliferation and stimulating Vascular Endothelial Growth Factor (VEGF) and type I collagen synthesis (67). This activity may in part be attributed to the location of the acetyl groups in the acemannan. Chokboribal et al. (68) reported that deacetylated acemannan showed a reduction in the expression of VEGF and type I collagen expression in fibroblasts. The extent of healing benefits of *Aloe vera* may/may not,

therefore, be due solely to the acemannan fraction as the active component of the extracts in view of the molecular complexity of the extracts.

In a study on *Aloe vera* in conjunction with human primary epidermal keratinocytes (HPEK) using flow cytometry and gene expression analysis, Moriyama et al. (69) reported an increase of cell surface expression of β1-α 6-, β4-integrin, and E-cadherin in HPEK treated with *Aloe vera* gel which may result in the cell migration and wound healing. The gel also influenced cell cycle progression and gene expression of differentiation markers in HPEK, suggesting a role of *Aloe ve*ra towards improving keratinocyte function. Hamman (53) reported that *Aloe vera* gel extracts have the ability to promote both wound healing and immunomodulatory responses. The gel extract containing acemannan has also been shown to increase epithelialisation and healing in wounds of dogs (70). In human studies, Avijgan (71) discussed the case of 53-year-old patient with a large ulcer on their lower leg. Throughout the wound, epidermal and dermal layers were involved, with granulation tissue exhibiting necrosis. Treatment including antibiotics, topical antiseptics, surgical debridement and skin grafting, all failed to improve the status of the wound. However, a dressing containing *Aloe vera* extract gel was applied twice daily, whereupon observations were made twice weekly. After three weeks there was a decrease in wound exudates and visible inflammation, together with a reduction in ulcer size. Further observations showed that after six weeks, the ulcer was healed fully.

Garcia-Orue et al. (72) studied the effects of 'nanofibrous' dressings containing recombinant human epidermal growth factor (rhEGF) and *Aloe vera* extract on wound healing. They demonstrated *in vitro* that the membranes improved fibroblast proliferation at the wound site. Furthermore, these membranes accelerated significantly wound closure and re-epithelisation in an *in vivo* full thickness wound healing assay carried out on db/db mice. The wound healing property of *Aloe vera* gel has been attributed by some to the content of mannose-6-phosphate (73). It has been reported also that the wound-healing capacity may be attributed partially due to presence of mannose-6-phosphate, glucomannan, and gibberellin, a growth hormone (74). The acemannan content of glucomannan containing products influence collagen composition (more type III) and increase collagen cross linking for wound contraction (75). It also increases the synthesis of hyaluronic acid and dermatan sulphate in the granulation tissue of a healing wound (76). Chantarawaratit et al. (67) discussed the polysaccharide roles in *Aloe vera* extracts relating to promoting the proliferation of fibroblasts and the production of hyaluronic acid and hydroxyproline in fibroblasts; which may contribute in forming the extracellular matrix of the wound. More recently, Hashemi et al. (77) reported that the glucomannan affects fibroblast growth factor and stimulates the activity and proliferation of these cells and in turn improves collagen production and secretion.

Yadav et al. (78) studied the activity of *Aloe barbadensis* on wound healing in rats. The authors found that wound healing was accelerated by increased collagen synthesis. This was in agreement with earlier study by Oryan and colleagues (79). Mendonça et al. (80) investigated the effects of topical applications of *Aloe vera* gel with or without 'microcurrent' on the healing of surgical-induced wounds in Wister rats. The authors reported that wound healing accelerated in the group treated with *Aloe vera* compared to the control.

An oral dosage of *Aloe vera* mucilage by rats with diabetes type-II has been shown to accelerate healing of skin wounds. This suggests that the treatment enhances the expression of vascular endothelial growth factor (VEGF) and transforming growth factor (TGF) β-1 in/around the wound. The TGF-β1 may stimulate fibroblasts to support the extracellular matrix at the wound site (81). Dermal applications of *Aloe vera* mucilage in wounds of rats have been reported to accelerate healing as well as thrombosis and contraction of the wound site (79). Jia et al (82) reported that topical applications of *Aloe vera* mucilage led to enhanced healing of wounds in both desert rats and rabbits. In general, *Aloe vera* contains a range of phytochemicals such as pyrocatechol, saponin, acemannan, β-mannan, anthraquinone, C-glycosides, diethylhexylphth-alate, bradykininase, oleic acid, phytol, and magnesium lactate along with water-soluble polysaccharides like glucomannan (75, 83-85). In addition to these components, vitamins (vitamin E and C) and amino acids do exist and may well play important role in acceleration of wound healing (77, 86). It has been reported that acemannan may promote skin wound healing *in vivo* partly through activating protein kinase B (PKB) or AKT which refer to the AK mouse thymoma/mammalian target of rapamycin (mTOR)-mediated protein translation mechanism; which may represent an alternative intervention/ therapy for a cutaneous wound (87).

There are many types of collagen but often they are classified into five main types: Type 1 in

skin, tendons, vascular, organs and bone; Type 2 in cartilage; Type 3 in reticular fibres; Type 4 in basement membranes and; Type 5 in skin, hair and placentas. Heggers et al. (88) reported that mannan rich *Aloe vera* gel not only increases the collagen content of a wound but also changes the collagen profile (more type III). This is associated with an increase the degree of collagen cross linking. Consequently this can accelerate wound contraction and increase the breaking strength of local scar tissue. An increased synthesis of hyaluronic acid and dermatan sulphate in the granulation tissue of a healing wound when using *Aloe vera* has also been reported (76). These authors applied topical *Aloe vera* extract on wounded diabetic rats and reported that it enhanced the process of healing due to an influence on phases associated with inflammation, fibroplasia, collagen synthesis and maturation and wound contraction (88). Other hypothesises relating to how glucomannans work in wounds tend to focus on the role of acemannan as a potent macrophage-activating agent (stimulating the release of fibrogenic cytokines) (63, 90). Growth factors may bind directly to acemannan, leading to enhanced stability and prolonging of their stimulation of granulation tissue (65). In a study on mice implanted with murine sarcoma cells, mannan (acemannan) from *Aloe vera* stimulated the synthesis and release of interleukin-1 (IL-1) and tumour necrosis factor from macrophages, which in turn initiated an immune effect that resulted in necrosis and regression of the cancerous cells (91). Furthermore, Pugh and colleagues (83) reported that *Aloeride* (a high molecular weight polysaccharide, 4 to 7 million Da) derived from *Aloe vera* possess immunostimulatory properties which can induce the expression of the mRNAs encoding tumour necrosis factor-alpha (TNF-α) and interleukin-1-beta (IL-1β).

Lectins and acemannan have shown inhibitory activity on the growth of tumour cells in animals, possibly through an activation of macrophages (92). Akev et al. (93) reported that the main lectin of the *Aloe vera* gel, aloctin 1, has the ability to prevent tumour development in mice; probably by activating the immune system. Lectin-like substances from the leaves of *Aloe vera* and *Aloe saponaria* have haemoagglutinating properties and are able to promote the growth of normal human cells in culture but inhibit tumour cell growth (94, 95).

Another mechanism by which mannans accelerate wound healing is by interacting with growth hormones which then interact with growth factor receptors on the fibroblast. This stimulates fibroblast activity and proliferation, leading to enhanced healing with an increase in collagen synthesis (19, 96).

Huang et al. (97) investigated the effects of calcium hydroxide within konjac glucomannan based films as wound dressings (in animal studies). The authors found that their films promoted effectively the contractility of wounds, especially at the early stages of healing. Histological observations showed that these films improved considerably granulation tissue and epithelial coverage (developed by seven and fourteen days of treatment). Fan et al. (98) discussed the use of chitosan/konjac glucomannan (CS/KGM) films embedded with antibiotic as a haemostatic wound dressing as another wound care option. Vetvicka and Vetvickova (99) reported that yeast-derived insoluble β (1-3)-D-glucans inhibited strongly adipogenesis, accelerated wound healing and lowered skin irritation. In addition to konjac glucomannan, other sources of glucomannan may become beneficial in wound therapy. Wang et al. (100) reported that two plant-derived glucomannans; konjac glucomannan and the polysaccharide of *Bletilla striata* have emerged as new sources for development of bioactive materials for pharmaceutical applications including wound healing dressings. Glucomannan from *B. striata* polysaccharides is a major bioactive component not only capable of promoting wound healing, but also show good performance as a kind of promising natural biomaterials (101). He et al. (102) conducted a study on collagen-konjac glucomannan-chondroitin sulphate blend to restore skin traumatism and reported on its ability to accelerate the restoration of the skin from trauma sites.

Burns

Burns can be caused by many factors and glucomannans can interact with these different types of wounds.

Sunburn

Skin exposure to ultraviolet B (UVB) radiation has a destructive effect on keratinocytes by causing DNA damage that can subsequently lead to malignant transformation (103). Herbal cosmeceuticals are often used in sunscreens as a barrier to protect skin from the harmful UV rays (104).

In general, the mannans exhibit significant therapeutic properties on skin (17, 32, 55, 105, 106). However, very little literature evidence is available regarding the use of glucomannans for burn therapy. *Aloe vera* gel has been reported to

relieve thermal burns and sunburn (107). Kuhn and Winston (108) reported that *Aloe vera* gel can help to heal burns and reduce burn pain, especially first and second-degree burns (sunburns and scalds). The efficacious components have not been defined exactly. The leaves and inner gel of the *Aloe vera* plant do in fact contain numerous components that have the potential to ease sunburn and minor cuts (109). However, in contradiction to some reports, Puvabanditsin and Vongtongsri (110) studied the efficacy of *Aloe vera* cream for the prevention and treatment of sunburn and suntan on twenty volunteers. The authors showed that the cream had no sunburn protection and no efficacy in sunburn treatment when compared to a placebo therapy.

Accidental burns

Topical treatment with *Aloe vera* has been shown to decrease healing time and to be more effective for first and second-degree burns compared with third-degree (111). This opinion has been supported by Maenthaisong et al. (10) who reported that *Aloe vera* gel might be an effective intervention to be used in burn wound healing situations for first to second degree burns. Shahzad and Ahmed (17) compared the efficacy of *Aloe vera* gel with 1% silver sulphadiazine cream as a burn dressing for the treatment of both superficial and partial thickness burns. The authors reported that patients treated with the *Aloe vera* gel experienced faster healing and better pain relief than patients treated with the silver sulphadiazine. *In vivo* analysis of burn injuries demonstrates that *Aloe vera* gel acts as an inhibitor of thromboxane A2, which is a mediator of progressive tissue damage (73). It was reported that *in vivo*, *Aloe vera* gel used in the treatment of chronic ulcers stimulates and accelerates skin burn healing (112-114).

Applied radiation

Radiation damage of skin by UV and γ-radiation can be prevented by *Aloe vera* (63). Early studies have reported healing of radiation ulcers in two patients treated with *Aloe vera* containing cream (115, 116, 117). Twenty-seven patients with partial thickness burns were treated with *Aloe vera* gel in a placebo-controlled study (118). The gel-treated burn lesions healed significantly faster (12 days) than the burns treated with petroleum jelly gauze (18 days). As discussed above, *Aloe vera* contains many physiologically active substances, some of these have effective anti-inflammatory, immunomodulatory and wound-healing effects (119). It has been reported that the topical application of *Aloe vera* gel extract to the skin of UV-irradiated mice improved UV-induced immune suppression (120). A further study by Strickland et al. (121) reported that glucomannan oligosaccharide from *Aloe vera* inhibits loss of skin immunocompetency induced by ultraviolet radiation. More recently, the use of *Aloe vera* for the treatment of radiation specific injuries has been reported (106, 108, 122). de Freitas Cuba et al. (106) assessed the topical efficacy of *Aloe vera* on the healing characteristics of induced oral lesions of rats subjected to radiation. The authors concluded that the inflammatory response and healing of the lesions was reduced by the *Aloe vera*. Atiba et al. (123) reported that application of *Aloe vera* gel to rats exposed to radiation was able to improve the acute radiation-delayed wound healing by increasing the transforming growth factor (TGF-β-1) and basic fibroblast growth factor (bFGF) production.

There are a number of clinical reports that have found *Aloe vera* gel is not effective for the treatment of radiation induced burns. For example, in a randomised radiation therapy study of seventy patients that received either *Aloe vera* gel or no treatment (control), there was no significant difference (124). Similarly, for a trial of two hundred and twenty five patients receiving radiotherapy, *Aloe vera* gel applied until two weeks after the end of the radiotherapy was not significantly efficient in reducing the treatment-related side effects, compared with an alternative aqueous cream as a control (125). This may suggest that the *Aloe vera* polysaccharides (if the active components) in some formulations are not stable, throughout processing/storage where degradation occurs due to heat, acid or enzymes (53). Hence, it might be that processing of such materials should be standardised to preserve the natural biological activities (126, 127). The compositional variations among commercial *Aloe vera* products have been reported by Bozzi et al. (128) who studied the authenticity of commercial *Aloe vera* gel powders from several leading suppliers. The authors found that the samples as analysed were very inconsistent and in some cases extremely poor quality. They reported that only three out of nine products contained 'satisfactory' amounts of acemannan (~10% w/w) while the remaining samples showed very low amounts; some of which only contained about 1% w/w acemannan.

Infections

Glucomannans from different sources are used widely to formulate cosmetic products with skin

repairing and conditioning activity. The pharmaceutical industry has focussed on using these materials for the manufacture of various topical products such as ointments and gel preparations (102, 129). These glucomannan polysaccharides have the unique characteristics of being good moisturisers, re-epithelising, immune modulating and anti-inflammatory agents (53). These beneficial health roles of glucomannans, especially those from konjac and *Aloe vera* are reflected for example in their ability to accelerating wound healing (as discussed above) when applied topically (2, 10, 11, 55, 125, 130-132). Thompson (133) reported that topical applications of *Aloe vera* derived allantoin gel stimulated fibroblast activity and collagen proliferation. Furthermore, Heggers et al. (134) found that topical applications of *Aloe vera* gel re-established vascularity of burn tissues of guinea pigs, although no specific constituents were identified.

Mannan-rich carbohydrates play prominent roles in immune responses to infections (135). The biological activities of mannans in mammals include inducing macrophage activity and the stimulation of T cells, which exert potent immune stimulating activity with significant action against infectious diseases. Zheng et al. (136) reported that oxidised konjac glucomannans trigger immune responses against *Aeromonas hydrophila* infection in fish. Various studies have pointed out that konjac glucomannan hydrolysates combined with probiotics reduce pathogenic bacterial and fungal growth such as for *Staphylococcus aureus*, *Salmonella typhimurium, Listeria monocytogens, Escherichia coli* (137, 138) and *Candida albicans* (139). The antimicrobial properties of *Aloe vera* facilitate the healing of burns/wounds. Das et al. (140) reported that *Aloe vera* polysaccharides inhibit the growth of *Candida paraprilosis, Candida krusei* and *Candida albicans*. Furthermore, Kitamoto et al. (141) have discussed the bactericidal effects of konjac solutions on food poisoning bacteria. The konjac glucomannan was found to inactivate *Escherichia coli*, enterohemorrhagic *Escherichia coli* O157:H7 and *Escherichia coli* O26:H9, *Salmonella enteritidis*, *Vibrio parahemolyticus* and *Staphylococcus aureus*. The authors also found that treatment with konjac solutions was also effective in reducing counts of spore-forming bacteria (*Bacillus subtilis*, *Bacillus cereus*, *Clostridium perfringens*, and *Clostridium botulinum* type E and type A).

It has been reported that *Aloe vera* polysaccharides may inhibit of HIV-1 virus infections (142). The polysaccharides interact with cell-surface receptors on fibroblasts, stimulating them, activating their growth and replication.

Al-Ghazzewi and Tester (143) discussed the synbiotic ability of probiotic bacteria and hydrolysed konjac glucomannan towards inhibiting acne-inducing bacteria (*Propioni-bacterium acnes*) proliferation. Bateni et al. (105) studied the effect of konjac glucomannan hydrolysates on skin health, specifically towards reducing acne vulgaris presence in female volunteers. The authors reported that they found significant improvement of skin health for all patients. The pre/probiotic mediated effects towards reducing acne symptoms may be *via* inhibiting the production of pro-inflammatory cytokines (144, 145). These seem to act as mediators for initiating acne lesions (146).

In other topical applications, a trial (*in vivo*) was conducted towards the use of konjac glucomannan hydrolysate applied within as pesseries to the vaginas of patients suffering from vaginal infections (147). The authors reported on the improvement of vaginal health. Overall, topical applications enhance skin natural defence barriers due to mucosal adherence and modulation of mucosal immune function (148-150).

Aloe vera gel is used often in the cosmetic industry in creams, soaps, suntan lotions and cleansers where it is claimed to be a beneficial therapy for skin conditions (151). It may prevent dandruff and help control fungal infections such as alopecia (152). Silva et al. (153) reported that chitosan/*Aloe vera* based formulations have antibacterial activity. Kon and Rai (154) reported that glucomannans (especially from *Aloe vera*) possess antimicrobial activities against a range of pathogens, including *Salmonella typhimurium*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Mycobacterium tuberculosis*, *Escherichia coli* and *Aspergillus flavus*.

The antagonistic property of *Aloe vera* leaves against several pathogens has been discussed by Lorenzetti et al. (155) who found that some fractions were effective against *Staphylococcus aureus*, *Salmonella*, *Streptococcus*, *Staphylococcus* and *Corynebacterium* Glucomannan is beneficial for reducing wound infections and thus accelerates the healing process. This process occurs by directly stimulating macrophage and fibroblast activity (73, 156, 157). Cellini et al. (158) reported that *Aloe vera* gel inhibited the strains of *Helicobacter pylori* and attributed this to the polysaccharides present in the gel exerting an anti-adhesive effect.

Glucomannans in general and especially depolymerised konjac glucomannans are able to exert a positive impact on skin health by reducing infections (105). They also promote accumulation of fibroblasts and stimulate the production of collagen in skin wounds (19, 59, 61).

CELL RECOGNITION

Cell recognition is an active and on-going process giving rise to a specific physiological response. Cell adhesion is a form of recognition and is mediated by molecular groups having specific binding properties (159, 160). To initiate an immune response against infections, antigens must recognise and react to infectious threats. This recognition occurs by interaction of surface receptors on the antigen attached cells with corresponding surface molecules on the infectious agents (161). Usually complex carbohydrate residues coat the surfaces of cells and have the potential to carry the information required for cell-cell recognition (162).

Lectins are proteins which are able to recognise and bind to specific carbohydrates. Mannose works very often on cells as a lectin binding substrate (163-165). These residues are often binding sites for pathogens too. By applying carbohydrates to the body that mimic these residues it is possible to prevent bacteria such as *Escherichia coli* from attaching to the tissue mucosa and thus reduce infection. Some infecting bacteria carry specific forms of lectins which are able to recognise and bind to the unique sequences of mannans on the tissue. Ofek et al. (166) reported that mannose-specific adherence is indicative of the presence on the bacterial surface of adhesins (lectins within structural projections) often called pili or fimbriae that bind the organisms to mannose residues on both epithelial and phagocytic cells. A schematic illustration of this process is shown in Figure 1. It has been reported that mannose-binding lectins may play a key role in determining host susceptibility and variability of responses to infection, pathogenesis and progression of disease in HIV patients (168) and neutropenia (167). It also plays a critical role in the innate immunity against infections caused by yeasts by increasing uptake by polymorphonuclear cells (169).

The mammalian immune system has both innate and acquired components, which cooperate to protect the host against microbial infections (170-173). The innate immune system is the first line of host defence and is mediated by phagocytes which include including macrophages and dendritic cells. Acquired immunity is involved in the late phase of infection with the generation of immunological memory.

The mucosal surfaces of the intestinal tract are exposed to pathogens and beneficial commensal microbiota and represent the first barrier of defence from ingested antigens and pathogens (174). In addition, they maintain the intestinal immune homeostasis. Recognition or differentiation of commensal from pathogenic microbiota is sensed (within the body) by the innate immune system unique molecular patterns expressed by pathogens, referred to as pathogen-associated molecular patterns (PAMPs), through germline-encoded pattern-recognition receptors (PRRs) including toll-like receptors and cytoplasmic receptors (170, 175-177). These will trigger a cascade of molecular events that will lead to a protective response against the infective agents.

The main source of PAMPs that are recognised by the immune system in the case of *Candida albicans* is the cell wall polysaccharides (178). The fungal pathogen *Candida albicans* has a multi-layered cell wall composed of an outer layer of proteins glycosylated with N- or O- linked mannosyl residues and an inner component of β-glucans and chitin (179). As the polysaccharides are on the outer surface of the fungal cell wall, they are the first point of contact between the fungus and the host immune system (180). Cell-surface mannan was found to participate in the adhesion to the epithelial cells, recognition by innate immune receptors and development of pathogenicity (181).

OVERVIEW

Glucomannans are biologically active molecules which can provide a number of therapeutic benefits in the body- including these related to the immunological system. These benefits may be topically focussed or as a consequence of ingestion. As the roles of carbohydrates are understood more fully in the body it is anticipated carbohydrate therapy will grow more rapidly with targeted therapies.

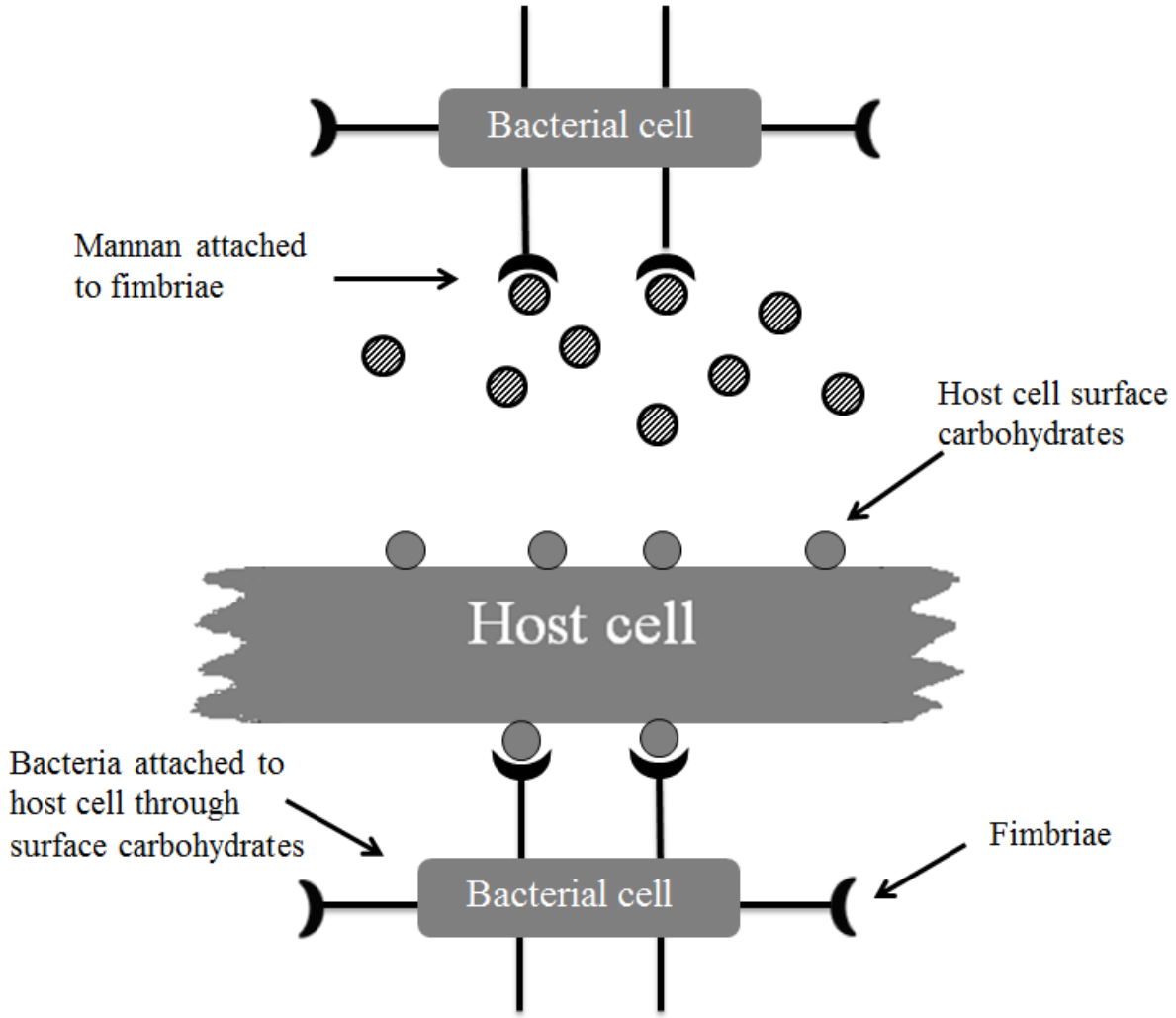

Figure 1. A schematic illustration of mannan attached to bacterial cell fimbriae to prevent bacteria from binding to host cell surface carbohydrates (Modified from Tester and Al-Ghazzewi (132)).

Table 1. Clinical trials on the topical use of konjac glucomannan and *Aloe vera* (Adapted from Grundmann (182)).

Preparation	Dose/Duration	Subject	Design	Results	Reference
Spray contains 5% konjac glucomannan hydrolysates	2 times/d/ every 20 d for 6 w	Acne vulgaris	R, N=26	Significant improvement of skin health; reduction of acne	Bateni et al. (105)
Nystatin vs Konjac glucomannan hydrolysate pessaries	3 capsules/d for 1w, 200mg capsules /2 times a week for 30 d	Vaginal infection	R, DB, N=26	Improvement of vaginal health recovery	Tester et al. (147)
Aloe extract (0.5% in hydrophilic cream or gel)	3 times/d to herpetic lesions/ 2 w	Genital herpes	R, DB, PC, PG, N=120	Aloe cream and gel were effective in reducing healing time. Aloe cream was more effective than gel	Syed et al. (183)
Aloe vera gel (contains 70% of aloe mucilage)	2 times/d to erosive and ulcerative lesions/ 8 w	Lichen planus	R, DB, PC, SC, N=54	Lesions were reduced.	Choonhakarn et al. (184)
Aloe vera gel	2 times/d to erosive and ulcerative lesions/ 8 w	Lichen planus	R, DB, PC, SC, N=34	Lesions were reduced.	Rajar et al. (185)

Aloe extract (0.5% in hydrophilic cream)	3 times/d to lesions/ 4 w	Psoriasis vulgaris	R, PC, PG, N=60	Psoriatic plaques were reduced and biopsies presented with reduced inflammation and parakeratosis.	Syed et al. (186)
Aloe vera (98% aloe leaf gel)	2 times/d to left or right arm/ 4 w	Psoriasis vulgaris	DB, R, PC, SC, IC, N=40	Placebo was more effective than aloe gel at early but not at later stage.	Paulsen et al. (187)
Aloe vera cream (70% aloe mucilage) compared to 0.1% triamcinolone acetonide cream	2 times/d to affected area/ 8 w	Psoriasis vulgaris	DB, R, SC, N=80	*Aloe vera* cream was as effective in reducing psoriatic plaque as triamcinolone acetonide cream with reduction in psoriasis area.	Choonhakarn et al. (188)
A 97.5% aloe gel compared to 0.25% prednicarbate and 1% hydrocortisone in placebo gel	Occlusive bandage for 2 d/2 w	UV-induced erythema	R, DB, PC, SC, N=40	Reduction of erythema by aloe gel compared to 1% hydrocortisone but after 2 days, 1% hydrocortisone cream was more effective.	Reuter et al. (189)
Aloe emulsion (30% crude extract)	2 times/d to affected areas/ 4-6 w	Seborrheic dermatitis	DB, R, PC, N=44	Recovery higher in aloe group vs. placebo with decrease in scaliness and pruritus in aloe group	Vardy et al. (190)
A 98% aloe gel and aqueous cream as placebo	3 times/d to affected area/ period of treatment and 2 w post-treatment	Radiation-induced dermatitis	R, DB, PC, MC, N=225	No differences in severity of itching, erythema, or moist desquamation, but aqueous cream was better in reducing moderate pain and dry desquamation.	Heggie et al. (125)
Pure aloe gel with mild soap or mild soap alone, patients could use prescribed skin care products	6-8 times/d to irradiated area/ Duration of treatment	Radiation-induced dermatitis	R, SB, SC, N=70	Delayed onset of skin changes with aloe gel.	Olsen et al. (191)
A 98% pure, aloe gel with added inert gel, patients could use hydrocortisone cream	2 times/d to irradiated area/ Duration of treatment	Radiation-induced dermatitis	R, DB, PC, N=191	No significant improvement.	Williams et al. (192)
Dermal wound gel, standard treatment as control	Wound dressing every 8 h until granulation thereafter every 12 h to complete healing	Surgical wounds	R, SC, N=21	Delay in wound healing for aloe gel group compared to standard treatment	Schmidt et al. (193)
Patch containing acemannan hydrogel, compared to clindamycin.	*Aloe vera* patch applied to surgery site/ 7 d post-surgery	Alveolar osteitis	R, N=1,194	Lower incident of alveolar osteitis and symptoms in patch group compared to clindamycin.	Poor et al. (194)
Dried aloe which converts to a gel upon contact with skin moisture	Wearing glove with aloe gel for 8h/d/ 30 d, 30 d rest, 10 days	Xerosis	PB, SC, N=29	Improvement for treated hand vs. untreated hand..	West and Zhu (195)
Use of 0.1%, 0.25%, or 0.5% of freeze-dried 200:1 concentrate aloe gel in hydrophilic cream	Single application and 2 times/ d / Short (0-3h) and long-term (2 w)	Moisturiser	R, SB, PC, N=20	Short-term increase in water content of the stratum corneum for 0.25 and 0.5% aloe at 1, 2, and 3h after application. Long-term increase in water content for *Aloe vera* creams after 1 and 2 weeks.	Dal'Belo et al. (196)

Abbreviation Key: IC – interpatient control, PB – partially blinded, SC – single-center, MC – multi-center, R – randomized, DB – double-blinded, PC – placebo-controlled, SB – single-blinded, PG – parallel group

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Table 2. Classification of dietary fibre oligosaccharides and polysaccharides according to their water solubility (Adapted from Dhingra et al. (30)).

Feature	Fibre component	Description	Main sources
Water insoluble fibre (Less fermented- i.e. less biologically active in the gut than soluble fibre)	Cellulose	Main structural units of plant cell wall. Soluble in concentrated acid but not in alkali.	Plants (vegetables, sugar beet, various brans)
	Hemicellulose	Cell wall polysaccharides contain a backbone of β-1, 4 glucosidic linkages. Soluble in dilute alkali.	Cereal grains
	Lignin	Non-carbohydrate cell wall component. Complex cross-linked phenyl propane polymer. Resists bacterial degradation.	Woody plants
Water soluble fibre (Fermented- i.e. more biologically active in the gut than insoluble fibre)	Pectin	Cell wall units with D-galacturonic acid as main components. Generally water soluble and gel forming.	Fruits, vegetables, legumes, sugar beet, potato
	Gums	Secreted at the site of plant injury by special secretary cell. Food and pharmaceutical use.	Leguminous seed plants (guar, locust bean), seaweed extracts (carrageenan, alginates), microbial gums (xanthan, gellan)
	Mucilages	Synthesised by plants and prevent desiccation of seed endosperm. Food industry use, hydrophilic, stabiliser.	Plant extracts (gum acacia, gum karaya, gum tragacanth)