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Review

Biological effects of gum arabic: A review of some recent research

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ABSTRACT

Gum arabic (GA) is a branched-chain, complex polysaccharide, either neutral or slightly acidic, found as a mixed calcium, magnesium and potassium salt of a polysaccharidic acid. The backbone is composed of 1,3-linked β-D-galactopyranosyl units. The side chains are composed of two to five 1,3-linked β-D-galactopyranosyl units, joined to the main chain by 1,6-linkages. Pharmacologically, GA has been claimed to act as an anti-oxidant, and to protect against experimental hepatic-, renal- and cardiac toxicities in rats. These reports could not be confirmed by others. GA has been claimed to alleviate the adverse effects of chronic renal failure in humans. This could not be corroborated experimentally in rats. Reports on the effects of GA on lipid metabolism in humans and rats are at variance, but mostly suggest that GA ingestion can reduce plasma cholesterol concentrations in rats. GA has proabsorptive properties and can be used in diarrhoea. It enhances dental remineralization, and has some antimicrobial activity, suggesting a possible use in dentistry. GA has been shown to have an adverse effect on electrolyte balance and vitamin D in mice, and to cause hypersensitivity in humans. More studies are needed before the pharmacological properties of GA can be utilized in therapy.

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1. Introduction

Gum arabic (GA, E-Number 414) is an edible, dried, gummy exudate from the stems and branches of *Acacia senegal* and *A. seyal* that is rich in non-viscous soluble fiber (Williams and Phillips, 2000). It is defined by the FAO/WHO Joint Expert Committee for Food Additives (JECFA) as 'a dried exudation obtained from the stems of *A. senegal* (L.) Willdenow or closely related species of *Acacia* (family Leguminosae)' (FAO, 1999).

In 1982 JECFA classified GA as 'ADI not specified' (FAO, 1982). However, as a result of subsequent research, the specifications for GA have been revised on several occasions (FAO, 1986, 1990, 1999; WHO, 1990a,b).

GA has wide industrial uses as a stabilizer, thickening agent and emulsifier, mainly in the food industry (e.g. in soft drinks syrup, gummy candies and marshmallows), but also in the textile, pottery, lithography, cosmetics and pharmaceutical industries (Verbeken et al., 2003). It has a complex chemical composition (see below).

In folk medicine, GA has been reported to be used internally for the treatment of inflammation of the intestinal mucosa, and externally to cover inflamed surfaces (Gamal el-din et al., 2003). Despite the fact that GA is widely used as a vehicle for drugs in experimental physiological and pharmacological experiments, and is assumed to be an "inert" substance, some recent reports have claimed that GA possesses anti-oxidant, nephroprotectant and other effects (Rehman et al., 2001; Gamal el-din et al., 2003; Ali et al., 2008). Clinically, it has been tried in patients with chronic renal failure, and it was claimed that it helps reduce urea and creatinine plasma concentrations and reduces the need for dialysis from 3 to 2 times per week (Suliman et al., 2000). These findings are not universally accepted and their confirmation, validity, reliability and mode of action await further studies.

The present article attempts to collate some recent published data on the chemical, pharmacological and toxicological properties of GA.

2. Chemistry

The chemical composition of GA is complex and numerous papers have been published on this subject (for example, the review of Islam et al., 1997 and papers cited therein). It is not the intention of this current review to give a comprehensive report on the chemistry of the gum, but to give a summary of the principle findings.

GA is a branched-chain, complex polysaccharide, either neutral or slightly acidic, found as a mixed calcium, magnesium and potassium salt of a polysaccharidic acid (arabic acid). The backbone is composed of 1,3-linked β-D-galactopyranosyl units. The side chains are composed of two to five 1,3-linked β-D-galactopyranosyl units, joined to the main chain by 1,6-linkages. Both the main and the side chains contain units of α-L-arabinofuranosyl, α-L-rhamnopyranosyl, β-D-glucuronopyranosyl and 4-*O*-methyl-β-D-glucuronopyranosyl, the last two mostly as end units (Anderson and Stoddart, 1996; Islam et al., 1997; Verbeken et al., 2003). Idris et al. (1998) reported GA to be comprised of 39–42% galactose, 24–27% arabinose, 12–16% rhamnose, 15–16% glucuronic acid, 1.5–2.6% protein, 0.22–0.39% nitrogen, and 12.5–16.0% moisture.

The chemical composition of GA can vary with its source, the age of the trees from which it was obtained, climatic conditions and soil environment (Al-Assaf et al., 2005; Anderson et al., 1968; Idris et al., 1998; Islam et al., 1997; Karamalla et al., 1998; Verbeken et al., 2003). GA from *A. senegal* var. *karensis* has almost double the weight average molecular weight of *A. senegal* var. *senegal* (Al-Assaf et al., 2005).

GA is a highly heterogeneous material, but was separated into three major fractions by hydrophobic affinity chromatography (Randall et al., 1989). Most of the gum (88.4% of total), an arabinogalactan (AG), had a very low protein content (0.35%) and a molecular mass of 3.8×10^5 Da [from gel permeation chromatography (GPC) data; $2.79\% \times 10^5$ Da from light scattering]. The second fraction (10.4% of total), an arabinogalactan-protein complex (AGP), contained 11.8% protein and had a molecular mass of 1.45×10^6 Daltons (both methods). The third fraction (1.2% of total gum), referred to as a low molecular weight glycoprotein (GP), had a protein content of 47.3%, and a molecular mass of 2.5×10^5 Da (GPC data). Ray et al. (1995) fractionated GA by both hydrophobic affinity chromatography and GPC; their results were in broad agreement with those of Randall et al. (1989). The major amino acids present in the protein of AG and AGP were hydroxyproline, serine and proline, whereas in GP, aspartic acid was the most abundant (Islam et al., 1997).

A wattle blossom model was proposed for describing the structure of the AGP complex. It was postulated that the high molecular weight fraction of the gum is composed of large carbohydrate blocks with a molecular mass of approximately 2.5×10^5 Da; these are attached covalently to a polypeptide chain (Fincher et al., 1983; Connolly et al., 1987, 1988). An alternative model was suggested by Qi et al. (1991), but more recent studies have indicated that the molecules of the AGP complex have a globular structure, which supports the wattle blossom model (Verbeken et al., 2003, and references quoted therein).

Osman et al. (1993) fractionated GA by hydrophobic interaction chromatography to yield four fractions, all of which had a similar carbohydrate composition, but differed in their content of protein, amino acid composition and molecular mass distribution. All four fractions reacted with an array of anti-arabinogalactan-protein monoclonal antibodies via anti-carbohydrate epitopes and were precipitated by Yariv's reagent, which indicated that all four fractions were AGPs. It was shown that at least one protein was unique to each fraction.

Enzyme-linked immunosorbent assays (ELISAs) have been developed to differentiate between GA and the gums of other *Acacia* species, including *A. seyal*. Polyclonal antibodies raised against GA in rabbits readily differentiated between the various *Acacia* species, indicating significant structural differences between the species (from Islam et al., 1997).

^{13}C NMR spectroscopy has been shown to be a powerful analytical method for the unambiguous identification of GA; samples adulterated with other gums are readily detected using this technique (Anderson et al., 1991). Al-Assaf et al. (2005) found that analysis of GA using GPC coupled to a multi-angle laser light scattering detector, a refractive index detector and an UV detector set at 214 nm provided a useful 'fingerprint' for the rapid evaluation of GA for specific applications. The method was able to assess protein content and its distribution in the various gum components.

GA is primarily indigestible to both humans and animals. It is not degraded in the small intestine, but fermented in the large intestine by microorganisms to short-chain fatty acids, particularly propionic acid (Phillips, 1998; Kishimoto et al., 2006). Such degradation products are absorbed in the human colon and subsequently utilized energetically in metabolism (Phillips, 1998). In an experiment using an enrichment culture of pig cecal bacteria, Kishimoto et al. (2006) showed that a *Prevotella ruminicola*-like bacterium was the predominant organism that was most likely to be responsible for the fermentation of GA to propionate.

3. Pharmacological properties

3.1. GA as an anti-oxidant

The purported action of GA as an antioxidant has led to the publication of a series of articles by the same group claiming a

protective effect of GA against experimental gentamicin and cisplatin nephrotoxicity (Al-Majed et al., 2002, 2003), doxorubicin cardiotoxicity (Abd-allah et al., 2002) in rats, and acetaminophen hepatotoxicity (Gamal el-din et al., 2003) in mice. All of these studies were based on the assumption that GA has strong anti-oxidant properties, and a major mechanism for the induction of these toxicities is the generation of free radicals (Ali and Al Moundhri, 2006; Hinson et al., 2004). However, Ali et al. (2003) reported that treatment of rats with GA produced only slight palliation of gentamicin nephrotoxicity, a result that does not confirm the work of Al-Majed et al. (2002).

Using a lipid model system, Trommer and Neubert (2005) studied eight different polysaccharidic compounds (including GA) for their antioxidant and lipid peroxidation lowering effects *in vitro*. It was found that GA protected against lipid peroxidation in skin in a dose-dependent manner. More recently, however, Cindoruk et al. (2007) reported that GA was ineffective in ameliorating hepatocelluar damage in cholestasis induced by fenofibrate in rats.

It has also been reported by Ali (2004) that administration of GA at concentrations of 2.5%, 5.0% and 10.0% in the drinking water for eight consecutive days to rats did not significantly alter either the concentrations of the free radical scavengers, reduced glutathione (GSH), ascorbic acid (AA), and superoxide dismutase (SOD), or lipid peroxidation. This finding seems to suggest that there is no evidence that GA has a strong anti-oxidant action. It is difficult to explain the claimed hepato-, nephro- and cardio-palliative and protective effects of GA reported by Al-Majed et al. (2002, 2003) and Abd-allah et al. (2002), through an antioxidant mechanism, if GA lacks an appreciable antioxidant action.

3.2. Effect of GA on renal function

Either end stage renal failure or end stage renal disease requires renal replacement therapy (RRT) in the form of either dialysis or renal transplantation for survival. However, provision of RRT requires expert teams, working in specialized units, which makes therapy of patients with renal failure expensive. Maintenance peritoneal dialysis and hemodialysis sustain the lives of approximately 250,000 uremic patients in developing countries (Friedman, 1996). The number of end-stage renal disease patients requiring RRT has increased dramatically throughout the world during the last decades (Locatelli et al., 2006).The cost of treating uraemia represents a growing demand on the health care systems of both rich, developed and poor, developing countries, the last being affected most. The literature is replete with publications on the impact of nutrition on kidney disease (Younes et al., 2006; Lacson et al., 2007). Most dietary attempts to treat chronic renal failure (CRF) and to decrease uremia use a protein restriction regimen (Fouque et al., 2006; Chaturvedi and Jones, 2007). An alternative dietetic approach has relatively recently been proposed, based on fermentable carbohydrate (FC) supplementation of the diet (Winchester and Salsburgh, 2004). This has been claimed to result in a similar urea-lowering effect by increasing urea nitrogen (N) excretion in stools, with a concomitant decrease in the total N excreted in urine of adults (Lukichev et al., 1992; Bliss et al., 1996; Ali et al., 2008) and children (Al Mosawi, 2002, 2004, 2007). Some of these papers will be discussed below.

Based on laboratory data (e.g. Younes et al., 1995), extraction, modification, and recycling of nitrogenous wastes by the gastrointestinal tract is a potentially low-cost means of substituting for missing renal function. Multiple approaches to the bowel as a "substitute kidney" have been attempted. Direct removal of nitrogen-containing compounds by an external gut fistula, gastric, ileal, or colonic gavage (dialysis), or induced diarrhea extract water and urea, but only minimal amounts of larger molecules, such as creatinine (Friedman, 1996).

Binding of nitrogen compounds to inert, orally administered sorbents, such as either charcoal or oxystarch has been used in experimental uremia (Fukagawa, 2006; Iwasaki et al., 2006). Modification of nitrogen compounds by ingesting enzymes derived from either soil bacteria or packaged in artificial cells has also been attempted (Winchester, 2002). Evidence indicates that strains of bacteria can be induced to synthesize enzymes that recycle urea and other nitrogen compounds retained by uremic patients. Verification of the safety, usefulness and reliability of bowel substitution in renal failure will, if proven in controlled clinical trials, accelerate development of a practical regimen to extend patients' longevity where no other means are possible (Friedman, 1996; Winchester et al., 2003).

The study of Matsumoto et al. (2006) examined the potential role of butyrate in modifying the generation of the pro-fibrotic cytokine transforming growth factor-beta (TGFbeta1) by renal epithelial cells. Following 8 weeks of dietary supplementation with 25 g/day of a special type of GA (SUPERGUM), there was a twofold increase in serum butyrate ($n = 7$, $P = 0.03$). *In vitro* work demonstrated that exposure of renal epithelial cells to elevated concentrations of butyrate suppressed both basal and stimulated TGF-beta1 synthesis. The action of butyrate was mediated by suppression of the extracellular, signal-regulated, kinase/mitogen-activated, protein kinase signaling pathway. In addition, butyrate exposures reduced the response of renal epithelial cells to TGF-beta1, as assessed by luciferase activity of a TGF-beta-responsive reporter construct. Attenuation of TGF-beta1 signaling was associated with reduced 114 phosphorylation of Smad 3 and decreased trafficking of TGF-beta1 receptors into signaling, non-lipid, raft-associated membrane fractions. These data demonstrated that dietary supplementation with "SUPER GUM" (a naturally processed polysaccharide exudate from *A. senegal*) increased serum butyrate, which, at least *in vitro*, has beneficial effects on renal pro-fibrotic cytokine generation (Matsumoto et al., 2006).

More recently, Nasir (2007), in a thesis studying the effect of GA on renal functions in healthy mice, claimed that it not only increased fecal weight consistent with the action of dietary fibers, but also showed binding of free water, which resulted in reduction of intestinal fluid absorption and thus of urine volume. This was paralleled by an increase in ADH secretion. GA also bound intestinal Na^+, which was again reflected by reduced renal excretion. These findings are at variance with earlier findings that GA actually enhances water and Na^+ absorption in a rat model of chronic-osmotic diarrhea by improving oral rehydration (Teichberg et al., 1999a,b; Wapnir et al., 1997). This difference, according to Nasir (2007), might be related to the fact that she studied the effect of GA in healthy mice, and that the water-holding capacity of dietary fibers may have opposite consequences in intact intestine and during diarrhea.

One of the unexplained findings of Nasir (2007) is that GA treatment was associated with an increased 24 h-creatinine clearance in healthy mice. The exact mechanism for this remains unclear, since it represents a remote effect of GA on the kidney, which requires one or more humoral factors. It is well known that GA is fermented by intestinal bacteria leading to formation of various degradation products, such as short-chain fatty acids (Bliss et al., 1996). In a recent study, serum butyrate concentrations were increased following treatment with GA in healthy subjects (Matsumoto et al., 2006) and this may have a role in the claimed salutatory effect on creatinine clearance and GFR. In contrast, in an experimental model of chronic renal failure CRF (rat kidney remnant model), Ali et al. (2004) showed that treatment of rats with GA at doses of 3 or 6 g/100 mL in the drinking water for five consecutive weeks was not effective in either reversing the decrease in body weight or the increases in creatinine and urea observed 2 weeks after the surgical induction of the CRF. These results do

not support the notion of a beneficial effect of GA in experimental CRF, as was reported in patients in two centers in the USA (Bliss et al., 1996). Whether that lack of effect was related to the severity of the CRF, inadequate dosage, species difference, or other reasons is unknown.

Recently, a report from Sudan assessed the effect of GA on the concentration of certain metabolites in the sera of patients with CRF on a low-protein diet (Ali et al., 2008). GA was given at an oral dose of 50 g/day for 3 months, with or without supplementing the diet with ferrous sulfate (200 mg/day) and folic acid (5 mg/day). Serum creatinine, urea, phosphate and uric acid concentrations were reported to be significantly reduced by GA, while the treatment significantly increased that of serum calcium. No explanations for these results have been offered, and the inclusion of iron and folic acid supplements has not been justified, although it was concluded that GA could alleviate "adverse effects of CRF".

3.3. Effect of GA on blood glucose concentration

Wadood et al. (1989) gave powdered seeds of *Acacia arabica* orally to normal rabbits and rabbits with allaoxan–induced diabetes. It was found that the powder (at doses of 2, 3 and 4 mg/kg) significantly reduced the blood glucose concentration of normal, but not diabetic rabbits. The authors concluded, albeit without experimental evidence, that *A. arabica* initiated the release of insulin from pancreatic β cells of normal rabbits. Previously, experiments were carried out *in vitro* and in normal human subjects to evaluate alternative food-grade viscous polysaccharides as agents for reducing postprandial hyperglycemia and to assess the relationship between the *in vitro* and *in vivo* performance of the polysaccharides (Edwards et al., 1987).

Mixtures of different types of gum (not including GA) have been shown to inhibit glucose movement *in vitro*, and lower postprandial blood glucose and plasma insulin in human subjects when incorporated in a drink containing 50 g glucose (Edwards et al., 1987; Torsdottir et al., 1989). Infusion of meals containing starch showed that a decrease in the digestion rate of starch in the upper small intestine accounted for part of the effect of viscosity on glycemic response, whereas the main effect of gum was apparently to slow gastric emptying (Leclère et al., 1994).

3.4. Effect of GA on the gastrointestinal tract

3.4.1. Intestinal absorption

The small intestine is the major site of electrolytes and organic non-electrolytes absorption in the gastrointestinal tract (GIT) through various mechanisms operating at the cellular and molecular levels (Wapnir and Teichberg, 2002). Simultaneous intestinal secretion is a physiological phenomenon also tightly controlled by mechanisms. This maintains within the intestinal lumen a state of fluidity, dilution, and solubilization indispensable to the normal intestinal function of digestion and absorption. The net effects of these mechanisms maintain the normal mammalian small intestine in an absorptive mode. However, under certain circumstances, secretion forces exceed absorption and a net secretory condition ensues leading to diarrhea and dehydration. Diarrheal disease is a major cause of morbidity and mortality, especially in the pediatric age group (Thapar and Sanderson, 2004). It has been shown that GA improves small intestinal absorption of sodium in normal rats (Codipilly and Wapnir, 2004; Wapnir et al., 1996) and of sodium and water in two animal models of diarrheal disease (Wapnir et al., 1997). In normal male juvenile rats, addition of 5 and 10 g/L of GA increased the rates of sodium removal from the intestinal lumen perfused with oral rehydration solutions (ORS) containing either 60 mM or 90 mM sodium. Although GA tended to facilitate bidirectional fluid movement in these experiments, net water absorption was unaffected (Wapnir et al., 1996). The higher concentration of GA was also associated with expansion of the basolateral intercellular space. Experimental diarrhea was induced in rats by either one week of drinking a cathartic (magnesium citrate-phenolphthalein) solution to produce chronic osmotic-secretory effects or by jejunal perfusion of theophylline to induce jejunal secretion. Addition of GA to the jejunal ORS-perfusate resulted in roughly a twofold increase in absorption of sodium, potassium and water in the chronic osmotic-secretory diarrhea model, and neutralized theophylline induced abolition of net sodium and potassium absorption, in addition to reversing water and glucose malabsorption (Wapnir et al., 1997). The observed expansion of the basolateral intercellular spaces between villus absorptive epithelial cells and the lamina propria induced by GA perfusion was considered a reflection of the enhanced water and sodium reabsorption. GA added to an ORS also reduced chloride, and sodium secretion in rats perfused under anesthesia with cholera toxin in the jejunum (Turvill et al., 2000). The positive effects of the GA on fluids and electrolyte absorption observed in jejunal perfusion studies were also reported in rats recovering from chronic osmotic diarrhea induced by cathartic agents (Teichberg et al., 1999a,b). Free living rats drinking the GA-supplemented ORS *ad libitum* showed accelerated recovery in comparison to those receiving either water or ORS without gum. Recovery parameters included greater enhancement of weight gain, food and fluid intake, and a lower fecal output in rats whose ORS contained GA. This increase was evident after 4 h of recovery and persisted for 24 h. The authors ascribed the weight gain to the increased fluid intake and solid food consumption. However, no ready explanation for the persistent increased solid food intake was offered. The relative decrease of fecal output noted was ascribed to the increased fluid absorption – a feature that was also observed with GA in acute jejunal perfusion studies (Wapnir et al., 1996, 1997). The previous data suggest that GA is equally effective when consumed orally as when directly introduced post-stomach, as in intestinal perfusion studies (Wapnir et al., 1996, 1997; Teichberg et al., 1999a,b; Rehman et al., 2000, 2001, 2003; Wingertzahn et al., 2001). Indeed, orally administered GA added to an isotonic electrolyte-glucose-zinc solution resulted in a higher blood concentration of zinc achieved after 15 min and throughout 3 h. There was also a significant time effect for sodium and water (Ibrahim et al., 2004). Investigating intestinal transport effects of GA was extended to involve other solutes such as glutamate and non nutrient (pharmacological) agents. GA containing solutions, also orally administered, resulted in a faster rate of absorption for glutamate under normal physiological conditions, and for the pharmacological agent acetaminophen during intestinal dysfunction induced by theophylline (Codipilly and Wapnir, 2004). Various mechanism(s) have been proposed to account for the proabsorptive effects of GA on intestinal water and electrolytes under normal conditions and more so in conditions of diarrheal illness (Codipilly et al., 2006). GA is a soluble fiber with moderate emulsifying properties (Menzies et al., 1996; Phillips, 1998) that may result in greater accessibility of electrolytes and associated water to the microvillous membrane. This was probably reflected in the increased lumen-to-serosa water influx noted with GA administration in the chronic osmotic-secretory diarrhea model (Wapnir et al., 1997). However, this simple effect of GA on membrane accessibility was not supported by the evidence in theophylline-induced secretory diarrhea. In these animals the events were complex in that the net increments in absorption were the algebraic sum of small positive changes in lumen-to-serosa influx and decreases in serosa-to-lumen efflux. This prompted further research for alternative answers. Additional work indicated that GA enhanced absorption of the solutes transported by diffusion (via transcellular and/or

transjunctional transport pathways) and does not act via sodium dependent mechanisms (Wingertzahn et al., 2001). Other evidence shows that GA may exert its proabsorptive effects by modulating the levels of the free radical nitric oxide (NO) in the upper intestine, either by scavenging NO produced in the enterocyte and diffusing into the lumen (Wingertzahn et al., 1998), or by inhibiting inducible NO synthase (Rehman et al., 2004). This antioxidant capability of GA was demonstrable both *in vivo* and *in vitro*, with the observed scavenging effect being more significant than NO synthase inhibition. NO alters water and electrolyte transport through activation of guanylate cyclase (Mourad et al., 1999). This upregulates the synthesis of cGMP, a potent activator of intestinal secretion. Removal of NO from the intestinal lumen either by scavenging or by inhibiting synthesis may therefore be partially responsible for the antisecretory effects of GA. Earlier experiments have indicated that the beneficial proabsorptive effects of GA might derive from regulation of NO-dependent gating of the membrane basolateral potassium channels (Rehman et al., 2001), and from its capability of enhancing intestinal paracellular transport (Rehman et al., 2003). In a recent publication, Wapnir et al. (2008) extended their investigations on the mechanisms of action of GA to the molecular level. Their goal was to determine whether GA could be associated with modulation of NF kB expression in a model of intestinal dysfunction induced by the cathartic agents phenolphthalein and magnesium citrate, both known to increase local production of NO (Izzo et al., 1998). They also questioned whether this would be associated with reduction of the inflammatory response caused by cathartics (evidenced by intestinal mucosa cytokine production and gene expression). NF kB is a nuclear transcription factor which upregulates the expression of inducible NO synthase (Ahn and Aggarwal, 2005), the key controller of tissue NO concentration. It may also regulate the synthesis of pro-inflammatory cytokines, which in turn can upregulate inducible NOS (Karrasch and Jobin, 2008). Wapnir and colleagues (2008) reported that addition of GA to the cathartic solution reduced NF kB expression towards values associated with control animals that received tap water only. Interestingly, this was not paralleled by down regulation of pro-inflammatory cytokine expression in the small intestinal mucosa. The authors argued that cathartic-induced intestinal dysfunction does not behave as a typical inflammatory phenomenon, such as clinical and experimental sepsis, and therefore these results were not unexpected.

3.4.2. Degradation of GA in the intestines

It has been reported that GA is not degraded in the stomach and small intestine, but undergoes complete fermentation within the cecum of rats (McLeanRoss et al., 1984; Walter et al., 1988; Phillips 1998), and humans (Phillips, 1998). Such fermentation promotes bacterial proliferation (May et al., 1994), and the larger bacterial mass induces increased production of short chain fatty acids (SCFAs) linked with enlargement of the cecum (Younes et al., 1995). Indeed incorporation of GAa into fiber-free diets resulted in increased weight of the cecal wall or increased proliferation of cecal epithelial cells (Howard et al., 1995). Hypertrophy of the cecum enlarges the cecal absorptive mucosa and increases cecal blood flow (Tulung et al., 1987). The major SCFAs produced are acetate, propionate and butyrate (Kishimoto et al., 2006), with propionate production most stimulated by GA (Tulung et al., 1987; Annison et al., 1994; May et al., 1994). Kishimoto et al. (2006) showed that a *Prevotella ruminicola*-like bacterium was the predominant organism that is most likely responsible for fermentation of GA to propionate (Kishimoto et al., 2006). This specific bacterium was isolated from an enrichment culture of pig cecal bacteria, and, therefore extrapolation of such results to the human colon has to await further studies. However, it is of relevance that this bacterium is a common member of the intestinal microbiota of the human large intestine (Benno et al., 1989).

Short chain fatty acids have considerable effects on intestinal and liver metabolism as either fuels or metabolic effectors. Propionate produced by bacterial fermentation from GA is the major SCFA metabolized by the liver (Moundras et al., 1994), particularly as a gluconeogenic substrate. It is utilized at a faster rate than amino acids, thus reducing amino acids deamination and luminal ammonia generation. Bacterial growth within the large intestinal lumen requires a nitrogen source (Younes et al., 1995) and GA fermentation provides the energy for bacteria to uptake ammonia as a nitrogen source. In addition, proprionate is also known to reduce ureogenesis from ammonium chloride in hepatocytes (Wyatt et al., 1986; Kishimoto et al., 2006). The decrease in luminal ammonia concentration may enhance diffusion of urea down its concentration gradient from the blood into the lumen. As such, nitrogen is trapped for elimination in the faeces.

3.5. Effects of GA on lipid metabolism

The effects of GA on lipid metabolism are variable. GA increased cholesterol biosynthesis in rats fed a cholesterol-containing diet, but had no effect in rats on a cholesterol-free diet (Kelly and Tsai, 1978). Ross et al. (1983) and Sharma (1985) reported reductions of total serum cholesterol by 6% and 10.4%, respectively when subjects received 25 g/day and 30 g/day of GA for periods of 21 and 30 days. The decrease was confined to LDL and VLDL cholesterol only, with no effect on HDL and triglycerides. In another study, Mee and Gee (1997) used a combination of fibers derived from GA and apples individually known to have potential hypercholesterolemic properties (Ross et al., 1983; Sharma, 1985; Sicart and Sablé-Amplis 1987) for 6 weeks. Although the levels of fiber supplementations used in this study were modest compared to previous studies, there was a significant cholesterol-lowering effect. Total cholesterol dropped by 10% and LDL by 14%, with no significant change in either HDL or triglyceride concentration. The authors ascribed the exaggerated outcome to the concerted effects of the two fibers. In contrast, consumption of GA at a dose of 15 g/day for 4 weeks by normal (Haskell et al., 1992) or hypercholesterolemic subjects (Jensen et al., 1993) had no significant effect on plasma lipids. In rats, the results were as contradictory. Topping et al. (1985) has shown that plasma cholesterol concentrations were unaffected by feeding GA, but plasma triacylglycerols were significantly lower than in controls. In another study (Annison et al., 1995), GA was fed to rats replacing cellulose in purified diets supplemented with cholesterol and cholic acid. No significant effects of increasing concentrations of GA were found on the concentrations of either plasma or liver cholesterol when compared to levels found in rats that consumed control diet containing cellulose alone. Plasma triacylglycerol concentrations were, however, higher in rats fed GA, whereas liver triacylglycerols were lower.

Various mechanisms have been proposed to explain the hypocholesterolemic effect of GA (Kelley and Tsai, 1978; Moundras et al., 1994; Annison et al., 1995; Tiss et al., 2001). Some studies have suggested that the viscosity of fermentable dietary fibers contribute substantially to the lipid lowering effects in animals and humans (Gallaher et al., 1993; Superko et al., 1988; Moundras et al., 1994), whereas another suggests that this property does not relate to plasma lipids (Evans et al., 1992). The mechanism most clearly implicated is related to increased fecal bile acid and neutral sterol excretion or a modification of lipid digestion and absorption (Eastwood, 1992; Moundras et al., 1994). Dietary fibers are believed to either bind or sequester bile acids, diminishing their active reabsorption in the ileum and leading to their excretion in the feces. This consequently results in promoting diversion of cholesterol to bile acid synthesis, in addition to inducing

increased numbers of lipoprotein receptors in the liver and decreased plasma cholesterol concentration (Trustwell and Beynen, 1992). Furthermore, GA has a high cation-binding capacity, particularly for calcium (Ca^{2+}). Degradation of GA in the cecum releases the sequestered bile acids and the acidic pH generated during the fermentation process renders them insoluble. The bound calcium is also released and forms insoluble complexes with bile acids, thereby promoting their excretion (Moundras et al., 1994). Moundras et al. (1994) investigated the plasma cholesterol-lowering effect of different polysaccharides in rats. Bile acid excretion was found essential in the cholesterol lowering effect of soluble fibers, and this was connected with induction of key enzymes of cholesterol metabolism (i.e. HMG CoA reductase and cholesterol 7α-hydroxylase). In this study, GA was neither as potent in affecting fecal bile acid excretion and lowering plasma cholesterol concentrations nor was it as capable of inducing key enzymes of cholesterol metabolism when compared to the other polysaccharides (guar gum or β-cyclodextrin). The same group investigated whether the amount and type of SCFA metabolized in the liver could directly influence lipid metabolism and reinforce the effects of bile acid losses induced by dietary fiber. A negative correlation was found between portal propionate and plasma cholesterol concentrations. In support, several studies proposed that propionate could limit the induction of key enzymes of cholesterol metabolism (Chen et al., 1984; Illman et al., 1988, Wright et al., 1990). However, in another experiment, addition of propionate failed to affect these enzymes (Levrat et al., 1994). At the level of modifying lipid digestion and absorption, Pasquier et al. (1996), mimicking pH conditions prevailing in the stomach, evaluated the effects of several soluble fibers, including GA, on dietary fat emulsification and lipolysis *in vitro*. The authors proposed that the smaller the emulsion droplet size and thereby surface area generated in the presence of viscous fiber, the lower the extent of lipolysis. GA strongly inhibited lipolysis at pH 5.4 after 30 min, but without having any effect on emulsion droplet size. Inhibition of lipolysis in this study was attributed to possible strong interaction of the protein moiety of GA with the available droplet (lipid/water) interface (where gastric lipase acts), blocking it or preventing the release of the non-esterified fatty acids generated at the droplet surface.

3.6. The effect of GA on tooth mineralization

Dental caries occur when tooth enamel is lost due to an imbalance of the demineralization and remineralization phases, and prevention can be achieved when the remineralization phase is enhanced (Aoba, 2004). Several agents have been used for that purpose, including fluoride (Cheng et al., 2007). Recently, it has been shown, using histopathological methods, that GA has the ability to enhance remineralization (Onishi et al., 2008), probably by supporting other remineralization activities. This supporting role was ascribed to the rich content of Ca^{2+}, Mg^{2+}, and K^{+} salts of polysaccharides in GA, and to the effect of the gum on the metabolism of Ca^{2+} and possibly phosphate. It is also known that GA contains cyanogenetic glycosides and several different types of enzymes (such as oxidases, peroxidases and pectinases) that exhibit antimicrobial properties against certain organisms such as *Prophyromonas gingivalis* and *Prevotella intermedia* (Clark et al., 1993).

3.7. Effect of GA on hepatic macrophages

Macrophages play an important role in the regulation of immunological process in rats. Mochida et al. (1996) studied the effect of GA on macrophage activation by their ability to produce superoxide anions *in vitro*, and found that GA suppresses macrophage activation *in vitro*. This confirms an earlier report that GA is capable of almost completely blocking the macrophage function (Fujiwara et al., 1995; Mochida et al., 1990). The authors inferred that such effects of GA would merit consideration in the therapy for chronic liver disease, as deranged function of Kupffer cells and hepatic macrophages occurs in this disease and is involved in its complications, such as endotoxemia.

4. Adverse effects and toxicity of GA

Historically, the first case of an occupational sensitization to GA in a candy factory was reported more than seven decades ago. That was followed by a number of reports of GA causing contact dermatitis and asthma (e.g. Ilchyshyn and Smith, 1985). In all these reports, the offending allergen has not been identified. However, in 1998, a carbohydrate specific IgE was identified in a chocolate confectioner with cough and dyspnea (Fötisch et al., 1998). More recently, Sander et al. (2006) found that sensitization to GA carbohydrate structures occurs casually in atopic patients with pollen sensitization without obvious exposure to GA, and that allergy to GA is mediated preferentially by IgE antibodies directed to polypeptide chains of GA.

Doi et al. (2006) studied the subchronic toxicity of a new type of GA (SUPER GUM [Acacia (sen) SUPER GUM]), a naturally processed polysaccharide exudate from *A. senegal*, when given to both sexes of F344 rats at dietary levels of 0 (control), 1.25%, 2.5%, and 5.0% (10 rats/sex/group). During the study, the treatment had no effect on clinical signs, survival, body weights, food and water consumption, urinalysis, ophthalmology, hematology, and blood biochemistry, and no gross pathological or histopathological alterations. Increased relative cecum (filled) weights, evident in both sexes of the 5.0% group and females of the 1.25% and 2.5% groups, were considered to be a physiological adaptation. It was concluded that, at least, up to a dietary level of 5.0%, SUPER GUM (equivalent to 3117 mg/kg body weights/day for males, and 3296 mg/kg body weights/day for females) caused no adverse effect. This confirms earlier reports that documented the safety of GA (Anderson, 1986). The safety of GA (5, 10, 20 or 40 g in water for 4 weeks) has recently been confirmed in healthy men (Calame et al., 2008).

GA (10% in the drinking water) for either 3 or 14 days decreased urinary excretion of inorganic phosphate and increased that of calcium (Ca^{2+}) and magnesium (Mg^{2+}), and also decreased plasma concentrations of 1,25-dihydroxy vitamin D in healthy mice (Nasir et al., 2008). The magnitude of these metabolic disturbances in mice with renal insufficiency has not been determined, but is expected to be more pronounced.

5. Conclusions

GA is a non-digestible food ingredient that has found many applications in the food and pharmaceutical industries. The gums claimed therapeutic usefulness in hepatic and renal failure awaits further verification in animal models and humans. No significant adverse or toxic actions have been associated with the use of GA.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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