Alginate as a Source of Dietary Fiber

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Alginate, an algal polysaccharide, is widely used in the food industry as a stabilizer, or as a thickening or emulsifying agent. As an indigestible polysaccharide, alginate may also be viewed as a source of dietary fiber. Previous work has suggested that dietary fibres may protect against the onset and continuation of a number of cardiovascular and gastrointestinal diseases. This article aims to examine what is currently understood about the fiber-like activities of alginate, particularly its effects on intestinal absorption and the colon, and therefore aims to gauge the potential use of alginate as a dietary supplement for the maintenance of normal health, or the alleviation of certain cardiovascular or gastrointestinal diseases.

Keywords colonic health, colonic microflora, glycaemic response, mucus

INTRODUCTION

Alginate is a polyuronic saccharide that is isolated from the cell walls of a number of brown seaweed species around the world, and it is produced as an extracellular matrix by certain bacteria (Stokke et al., 2000). Alginites have a number of large-scale industrial [e.g., as an ingredient in shoe polish and as an important factor in the dye industry and industrial separation of milk whey (Yamamoto et al., 1992; Jensen, 1993)] and medical uses [such as for cell microencapsulation (Uludag et al., 2000), as microsphere vectors for drug delivery (Skaugrud et al., 1999), for making dental impressions (Ertesvag and Valla, 1998) and as the active ingredient in absorbent dressings (Ingram et al., 1998; Bryan et al., 2001)]. However, more than six times the amount of income from these applications is generated worldwide by the use of seaweed and seaweed products in human nutrition (Jensen, 1993). In general, the use levels for alginites in food applications are cost-driven, and usually range between 0.5–1.5%. Propylene glycol alginites (PGA—used as stabilizers in low pH applications) have a wider variety of uses than alginites, but are used at much lower levels in these applications. Table 1 shows a number of common uses for alginate in the food industry.

Alginate biochemical and biophysical properties are, therefore, dependent on alginate molecular weight and M:G ratios. Further details of alginate structure are available elsewhere (Moe et al., 1995).

Dietary fiber (regarded in this article as dietary material that escapes digestion and/or absorption before reaching the colon) is generally accepted as being beneficial to both...
cardiovascular and colonic health, although a number of epidemiological studies have suggested that source and type of dietary fiber may be more important modulators of colonic health and disease (Bonithon-Kopp et al., 2000; Goodlad, 2001; Levi et al., 2001; Terry et al., 2001). Dietary fibers are known to have a number of physiological effects on the body, some of which are much more closely associated with health benefits than others.

### Reduction of Intestinal Absorption Rates and Systemic Effects

Viscous dietary fiber (classified chemically as “soluble” dietary fiber (Englyst et al., 1994)) intake has been previously shown in a number of clinical studies to lower the rate of small intestinal absorption of metabolizable nutrients, thereby reducing the glycaemic load on the body (Jenkins et al., 2000). In turn, this reduces the level of insulin response necessary. As a result of this decreased absorption rate, the likelihood of cardiovascular disease and onset of non-insulin-dependent diabetes mellitus (diabetes type II) or obesity may be diminished (Salmeron et al., 1997a; Salmeron et al., 1997b; Ludvig et al., 1999; Jenkins et al., 2002; Willett et al., 2002). Previous studies have also suggested that viscous fiber intake alleviates the symptoms in sufferers of cardiovascular disease and type II diabetes (Simpson et al., 1981; Jenkins et al., 2002).

### Reduction of Colonic Luminal Toxicity

Increased fiber intake leads to a decreased transit time (Lewis and Heaton, 1999) and increased stool bulk and water content (Blackwood et al., 2000; Munro, 2001). Dietary fibers have also been previously demonstrated to bind up potential mutagens that may occur in the colon (Ferguson and Harris, 1996; Harris et al., 1998; Karakaya and Kavas, 1999). All of these physiological effects of dietary fiber (i.e., bulking of luminal contents, reduced transit time and increased mutagen binding) lead to a reduction in colonic mucosal exposure to the wide range of potentially damaging agents of bacterial, dietary, and endogenous origin that may occur within the colon.

### Alteration of Colonic Microflora

Between $10^{13}$ and $10^{14}$ bacteria reside in the human colon (Roberton, 1993; Topping and Clifton, 2001). The microfloral content of the colon will be modulated by dietary fiber type occurring within the lumen. The identity of all the normal colonic microflora is not yet established. Although attempts are currently being studied to determine the diversity within this complex microbiota, classical microbiological methods, and therefore established views on the colonic microflora, may be somewhat inaccurate (Blaut et al., 2002). Anaerobic bacterial degradation of material entering the colon leads to the production of short-chain fatty acids (SCFA), which may be taken up and metabolized by the host. Recently much work has focused on the effects of SCFA on colonic well-being, with SCFA (especially butyrate) often touted as potential preventative and/or curative agents in inflammatory bowel diseases and colorectal cancer.

So far, only a handful of clinical studies have shown any direct beneficial effects of SCFA (administered in enemas) in colitis (Harig et al., 1989; Breuer et al., 1991; Scheppach et al.,

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**Table 1** Common uses of alginate in food products

<table>
<thead>
<tr>
<th>Application of alginate</th>
<th>% of total alginate food applications</th>
<th>Notes on application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premium beer foam stabilizer</td>
<td>21.2</td>
<td>PGA usage allows better head retention, and protects against foam-negative contaminants</td>
</tr>
<tr>
<td>Restructured foods</td>
<td>19.6</td>
<td>Use in reformation of food materials (e.g. onion rings, pimento pieces in olives). Endows food product with thermostability and desired consistency.</td>
</tr>
<tr>
<td>Further uses of PGA</td>
<td>18.9</td>
<td>PGA is acid stable and resists loss of viscosity. Has unique suspension and foaming properties. Wide range of applications including:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Soft drinks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Dressings/condiments</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Milk drinks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Sorbet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Ice cream</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Noodles/pasta</td>
</tr>
<tr>
<td>Bakery products</td>
<td>14.9</td>
<td>Provides bakery creams with freeze/thaw stability and reduced syneresis. Improves shelf life and moisture retention in bread and cake mixes. Allows cold solubility in instant flan preparations.</td>
</tr>
<tr>
<td>Fruit preserves</td>
<td>6.5</td>
<td>Commonly used as gelling, thickening, and stabilizing agents in jams, marmalades, and fruit sauces. Alginate-pectin gels are heat reversible and give a higher gel strength than either individual component.</td>
</tr>
<tr>
<td>Ice cream</td>
<td>3.8</td>
<td>Allows correct viscosity of ice cream, while avoiding crystallisation and shrinkage. Also secures heat shock resistance and allows homogenous melting without whey separation. Used in combination with other stabilizers for further effects (e.g., increased thickening and slow melting with guar/locust bean gum).</td>
</tr>
<tr>
<td>Other</td>
<td>15.1</td>
<td>Desserts (e.g., mousses, instant puddings, ripple syrups) Emulsions and sauces (e.g., low-fat mayonnaise, tomato ketchup, salad dressings, low fat spreads) Extruded foods (e.g., noodles and pasta)</td>
</tr>
</tbody>
</table>

Compiled by FMC biopolymer. All applications use alginate, unless otherwise stated. PGA = propylene glycol alginites.
Effects on Digestion Rates

A number of previous studies have reported that alginates may reduce the activity of certain digestive enzymes within the upper GI tract. In vitro determination of protease activity under physiological conditions has suggested that low concentrations (<0.1%) of alginate reduce pepsin activity by up to 80% (Sunderland et al., 2000); they also have a small inhibitory effect on trypsin activity (Hart J.L., Brownlee I.A., Dettmar, P.W. and Pearson J.P., unpublished work). These results are supported by the effects of higher concentrations of alginate on reducing proteolytic degradation of casein upon incubation in pepsin and/or pancreatic enzyme solutions (Manchon and Desantiblanquat, 1986; El Kossori et al., 2000). In comparison to other fibers in these in vitro studies, the inclusion of 33 mg of alginate in a solution containing 330 mg casein reduced peptic/tryptic digestion of the casein by similar levels (% inhibition as mean ± SD, 54.1 ± 1.3) as analogous quantities of gum arabic (52.5 ± 2.1), carrageenan (57.3 ± 2.6), and pectin (52.3 ± 4.5). Locust bean gum (47.2 ± 2.3) gave a significantly lower level of proteolytic inhibition than alginate. The pulp from prickly pear fruits (62.0 ± 2.5) gave significantly better protection against proteolysis than the above single fiber sources (El Kossori et al., 2000). Increased levels of alginate (i.e., 66 mg and 82.5 mg) added to casein solution did not lead to better proteolytic inhibition.

This inhibitory effect on proteases of alginates may be of benefit in reducing the heightened glycaemic index of mixed (i.e., protein, carbohydrate, and fat-containing meals) meals common in the Western world by reducing glycaemic load from amino acids. Previous work has reported that, although powdered seaweeds (1% w/v) completely inhibited amylase activity, extracted algal fibers (including alginates) had no effect (Bobin-Dubigeon et al., 1997). This suggests that seaweeds may contain a specific inhibitor of amylase that may increase a reduction in glycaemic response.

Effects on Blood Cholesterol Levels

A meta-analysis of 67 controlled trials suggested that pectin had the greatest effect in lowering total cholesterol levels per gram of 4 common viscous fiber sources (reduction in cholesterol of 70 µM/L plasma/g fiber, compared to 37 µM/L/g oat products, 28 µM/L/g psyllium and 26 µM/L/g guar gum). These effects appeared to be almost entirely due to a reduction in LDL cholesterol, rather than HDL cholesterol (Brown et al., 1999). This style of analysis does not account for variations in the study populations used, and currently no single study has adequately compared the cholesterol-lowering effects of dietary fiber types to each other within the same population. Also, relatively few studies have considered the effects of alginates in lowering cholesterol.

Alginates (7.5 g/d, M/G 1.5) supplementation of a low fiber diet has previously been shown to more than double (140% increase) mean fatty acid excretion in the digesta of a small cohort (n = 6) of human ileostomy patients (Sandberg et al., 1994). It must be noted, however, that 4 of the 6 patients had only a 50% or less increase in fatty acid excretion, while the much higher fatty acid release in the other 2 patients may have accounted for this apparently large rise.
Animal model studies have also demonstrated that the presence of alginate in the small intestinal lumen decreases uptake of fats and reduces plasma cholesterol under zero cholesterol (Seal and Mathers, 1996; Seal and Mathers, 2001), low fat (Ito and Tsuchiya, 1972; Jimenez-Escrig and Sanchez-Muniz, 2000) and high fat diets (Nishide et al., 1993; Suzuki et al., 1993b; Jimenez-Escrig and Sanchez-Muniz, 2000). These effects are likely to be due to the increased levels of faecal bile and cholesterol excretion that have previously been reported (Kimura et al., 1996; Seal and Mathers, 2001); they could be of benefit in reducing blood cholesterol levels in the general population.

Levels of 1% and 3% Na-alginate were shown to have similar hypocholesteremic effects (mean reduction in plasma cholesterol from fiber-free controls of 8.5% and 20.5%, respectively) to those of the algal polysaccharide funoran (7.3% and 20.9%), rather than carrageenan (14.6% and 29.9%) (Ito and Tsuchiya, 1972; Jimenez-Escrig and Sanchez-Muniz, 2000). These effects are likely to be due to the increased levels of faecal bile and cholesterol excretion that have previously been reported (Kimura et al., 1996; Seal and Mathers, 2001); they could be of benefit in reducing blood cholesterol levels in the general population.

CONCLUSIONS ON INTESTINAL UPTAKE/SYSTEMIC EFFECTS OF ALGINATE

These effects of alginate on glucose/cholesterol uptake would suggest that the inclusion of alginate in the diet may reduce the likelihood of the onset of diabetes Type II (especially in high risk populations) and/or obesity, and possibly cardiovascular disease, as well as reduce systemic risk factors in patients with these diseases. Furthermore, animal studies have shown that alginate inclusion in the diet may reduce hypertension in a high fat, high sodium diet (Ren et al., 1994; Jimenez-Escrig and Sanchez-Muniz, 2000). The level of reduction of plasma glucose/cholesterol seen with alginate appears to approximate those seen with other types of viscous algal polysaccharides in animal models. This effect of alginate in lowering plasma glucose/cholesterol has been attributed to its reduction in intestinal absorption and its prolongation of gastric emptying (also resulting in increased satiety). Further effects on lowering postprandial energy uptake rates can be envisaged due to the inhibitory effect of alginate on gastrointestinal proteases.

Neither inhibition of proteolytic activity or a reduction in plasma glucose/cholesterol uptake are unique properties of alginate in viscous fiber terms. However, the comparison of alginate to other dietary fibers in these terms is not easy due to the limited number of studies carried out. Although an increased level of small intestinal sterol excretion is noted with alginate (Sandberg et al., 1994), no data as to its effects on lowering total plasma cholesterol are available in humans. No direct comparison between glycaemic responses in the presence of alginate or other fiber types is possible past those made in Wolf et al., (2002) due to the massive variety of test meals and/or diets used in this type of study.
Previously, it has been suggested that alginate may be much more palatable than similar levels of other viscous fibers due to its unique gelation properties (Wolf et al., 2002). Unlike many other polysaccharide gums, which give a slimy and unpleasant mouth feel, alginate can be given at relatively low viscosity in liquid form. Once the alginate comes into contact with acid in the stomach, it will become a gel, leading to prolonged gastric emptying and a considerably slower rate of intestinal absorption than would be seen under the initial viscosity of the ingested alginate. This factor would suggest that alginate may be clinically more useful in reducing blood cholesterol and postprandial glycaemia than other viscous fiber types. However, further tests are necessary to evaluate algatines role in combating and/or preventing such conditions as obesity and Type II diabetes.

As with other viscous fibers, the inclusion of high levels of alginate in the diet have been linked to a reduced bioavailability of certain beneficial dietary components, including β-carotene (Riedl et al., 1999), and minerals, such as calcium (Boscher et al., 2001), iron, chromium, and cobalt (Harmuth-Hoene and Schlenz, 1980). This reduced nutrient and mineral absorption might suggest that the inclusion of high levels of alginate in the diet of the elderly, pregnant women, and infants may outweigh any potential health benefits.

Reduction of Colonic Luminal Toxicity

Bulking of Colonic Contents

Any method by which dietary constituents can reduce the potential toxicity of the colonic luminal contents. Intake of 175–200 mg kg body weight−1 of alginate by male volunteers (n = 5) has previously been shown to increase stool wet and dry weight, but not decrease whole gut transit time (Anderson et al., 1991). Similar bulking of luminal products have also been reported in pigs fed a diet containing 5% alginate (Hoebler et al., 2000), and this effect was reported to be higher in the colon than other seaweed dietary fibres (i.e., cellulose, xylan, or carrageenan) of the same concentration. Stool bulking will act to effectively dilute out any luminal, mucosally aggressive agents in the colon.

Adsorption of Toxins Found within the Colon

Alginates have been reported to adsorb a range of potential food and chemical mutagens, thereby not only lowering colonic exposure to these agents, but also to the rest of the body (Nishiyama et al., 1991; Nishiyama et al., 1992; Maruyama and Yamamoto, 1993; Ikegami et al., 1994; Sugiyama et al., 1999; Aozasa et al., 2001). The data pertaining to these effects will, therefore, be looked at more closely.

*In vitro* experimentation allows measurement of the levels of specific toxins, mutagens, or carcogens bound to fibres in solution. In pH 7.6 aqueous buffer, 5mg/mL alginic acid adsorbed dioxin isomers (toxins found in food and water) better than a wide range of other fiber types (i.e., glucomannan, gum karaya, lignin, chitin, cellulose, mannan, and xylan), but not as well as others (i.e., locust bean gum and pectin) at the same concentration (Aozasa et al., 2001). Further *in vitro* work has also shown that alginic acid and Ca-alginate bind around twenty times as much of the heterocyclic amine food mutagens Trp-P-1 and Glu-P-1 as defatted corn fiber (Nishiyama et al., 1991). Alginic acid showed similar adsorption characteristics for these mutagens as pectin. Further *in vivo* studies suggested that this action of alginates was brought about by binding the amine mutagens via their carboxylic groups (Nishiyama et al., 1992). Sodium alginate showed extremely low binding levels (<0.5%) for the carcinogen N-nitrosodimethylamine. Similarly low levels of this carcinogen were bound by cellulose, fucoidan, carrageenan, and agar (Maruyama and Yamamoto, 1993).

Within animal studies, a basal chow containing 5% sodium alginate reduced accumulation of toxic pentachlorobenzenes (given as single bolus in food) in rats by similar levels as guar gum and λ-carrageenan over a 7 d period (Ikegami et al., 1994). The same level of dietary alginate reduced D-galactosamine induced liver injury in rats, although this effect was modest by comparison other fiber types (e.g., cellulose, glucomannan, chitin, chitosan, and hemicellulose) (Sugiyama et al., 1999).

One of the factors believed to be important in colorectal carcinogenesis is luminal bile acid content (Owen, 1997; Ochsenkuhn et al., 1999; Debruyne et al., 2001). The increased excretion of bile acids reported in animal models may, therefore, initially be seen as a protective factor (Kimura et al., 1996; Seal and Mathers, 2001). However, earlier work has suggested that the inclusion of 5% alginate in rat diet gave rise to an increased biliary output (Ikegami et al., 1984). This would imply that, although alginate may act to increase whole body cholesterol metabolism, it will not necessarily prevent bile-induced damage to the colon.

It has been suggested that secondary bile acids are more damaging to the colon than primary bile acids. Therefore, increased binding of secondary bile acids may help prevent mucosal damage occurring in the colon. Table 2 shows cited values for bile acid binding by various dietary fibers, including alginate. Alginate binds a similar level of primary bile acids (i.e., total cholate and chenodeoxycholate binding capacity) and secondary bile acids (i.e., deoxycholate) as other algal polysaccharides (Wang et al., 2001), but significantly lower levels of secondary bile acids than another polyuronate, pectin (Camire et al., 1993).

CONCLUSIONS ON REDUCTION OF COLONIC LUMINAL TOXICITY BY ALGINATES

Alginates, much like other fiber types that are not fully fermented in the colon, increase stool wet and dry weight. They bind bile acids more strongly than cellulose, but this effect is only modest compared to that of pectin. A number of studies have suggested that alginates could bind up a wide range of other damaging agents from the GI lumen, thereby lowering colonic and systemic exposure to these moieties. These studies
Table 2  Bile acid binding properties of a range of dietary fibers

<table>
<thead>
<tr>
<th>Fiber</th>
<th>Cholate</th>
<th>Chenodeoxycholate</th>
<th>Deoxycholate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV alginate</td>
<td>26</td>
<td>56</td>
<td>168</td>
<td>(Wang et al., 2001)</td>
</tr>
<tr>
<td>HV alginate</td>
<td>113</td>
<td>35</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>Agar</td>
<td>57</td>
<td>86</td>
<td>183</td>
<td></td>
</tr>
<tr>
<td>Carrageenan</td>
<td>36</td>
<td>90</td>
<td>184</td>
<td></td>
</tr>
<tr>
<td>Cellulose</td>
<td>6.25</td>
<td>0</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Wheat bran</td>
<td>9</td>
<td>61</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Lignin</td>
<td>138</td>
<td>159</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Pectin</td>
<td>73.4</td>
<td>—</td>
<td>999.5</td>
<td></td>
</tr>
<tr>
<td>Cellulose</td>
<td>0</td>
<td>—</td>
<td>0.2</td>
<td>(Camire et al., 1993)</td>
</tr>
<tr>
<td>Wheat bran</td>
<td>119.3</td>
<td>—</td>
<td>237.7</td>
<td></td>
</tr>
</tbody>
</table>

LV = low viscosity, HV = high viscosity. *These studies used bile acids conjugated to taurine rather than basic salts. All tests were carried out at approximately neutral pH for various lengths of time (10 min for Camire et al. (1993), 1 h for Vahouny et al. (1980) and 2 h for Wang et al. (2001)).

also suggest that these effects are not exclusive to alginates, as other fiber types have similar effects.

Although alginate has the potential to reduce the exposure of the colonic lumen to certain damaging agents, it is unsure whether this effect will reduce disease risk within the normal population.

**Alteration of Colonic Microflora**

Previous studies have reported the bacterial degradation of, and short-chain fatty acid production from, alginates (Suzuki et al., 1993a; Michel et al., 1996; Kuda et al., 1998). However, relatively few models have considered the effects of alginate inclusion on the bacterial microflora, and the potential effects of this on the host, or how alginate structure may effect its degradation. This will be briefly reviewed below.

Upon incubation in human faecal microflora, alginate degradation does not show signs of SCFA and gas production until after 6 h (Michel et al., 1996). Although over 80% of alginate was degraded in 24 h incubation with faecal inoculum, levels of SCFA release were significantly lower than this (Michel et al., 1996). This could suggest that alginites are increasing the numbers of aerobes in the inoculum, therefore reducing the levels of measured SCFA released (due to the aerobic metabolism of alginate/SCFA), and the potential effects of this on the host, or how alginate structure may effect its degradation. This will be briefly reviewed below.

In the experimental set-up of Michel et al. (1996), mannosuronate was slowly fermented, suggesting that human-derived microflora do not metabolize this sugar well. In the rat model of Suzuki et al. (1993a), as alginate fermentability increased (i.e., as smaller molecular weight fragments of alginate recovered from faeces), the M:G ratio of recovered alginate fell. This suggests that natural alginites of different M_r will have different fermentation patterns.

In the experimental set-up of Michel et al. (1996), mannosuronate was slowly fermented, suggesting that human-derived microflora do not metabolize this sugar well. In the rat model of Suzuki et al. (1993a), as alginate fermentability increased (i.e., as smaller molecular weight fragments of alginate recovered from faeces), the M:G ratio of recovered alginate fell. This suggests that natural alginites of different M_r will have different fermentation patterns.

Table 3  Cited production of SCFA derived from fermentation of alginates by human faecal inocula

<table>
<thead>
<tr>
<th>Study</th>
<th>Acetate</th>
<th>Propionate</th>
<th>Butyrate</th>
<th>Lactate</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michel et al. (1996)</td>
<td>43.4</td>
<td>7.4</td>
<td>2.93</td>
<td>—</td>
<td>0.54</td>
</tr>
<tr>
<td>Kuda et al. (1998)</td>
<td>36.2</td>
<td>16.6</td>
<td>16.6</td>
<td>1</td>
<td>—</td>
</tr>
</tbody>
</table>
CONCLUSIONS ON ALGINATES’ EFFECTS ON THE COLONIC MICROFLORA

From the above evidence, it seems indubitable that alginates have an effect on the colonic microflora, in terms of populations of species and the quantities of short-chain fatty acids produced. Whether these effects are truly beneficial to the host, as with the effects of many other dietary fiber types, is not clear. The work of Terada et al. (1995) does suggest a beneficial effect of alginate in lowering levels of putrefaction by the colonic microflora. Once the beneficial and detrimental effects of the colonic microfloral populations and their metabolites on the host are more clearly demarcated, it will be easier to draw conclusions from the above works.

Direct Effects on Colonic Mucosa

As alginates are hydrocolloids that escape full bacterial fermentation, they are expected to greatly increase stool water content and bulk, as has been previously demonstrated (Anderson et al., 1991). They also appear to beneficially alter the colonic microflora (Terada et al., 1995) by increasing bifidobacterial numbers and reducing bacterial toxin levels in the colonic lumen. These factors may be extrapolated to benefits for colonic health and colonic mucosal integrity, but the direct effects of alginate on the colonic mucosa has rarely been tested.

Although reduction of luminal aggression is of benefit to colonic health, a strengthening of colonic mucosal barrier function will also reduce colonocyte exposure to luminal aggression. The primary factor in protection of the colonic mucosa is the colonic mucus barrier that lines the entire colon. Colonic mucus layer thickness and integrity (Pullan et al., 1994; Strugala et al., 2001), factors vital to colonic mucus barrier function, may be reduced in colonic disease.

A previous study, where low levels (25 µg in 1 mL saline) of sodium alginate were directly instilled into a vascularily perfused rat colon for 30 min, showed that the presence of alginate in the colon increased total colonic mucin output by approximately 140% (Barcelo et al., 2000) compared to saline (control) solutions. Cellulose, pectin, and arabic gum did not cause a significant increase in total colonic mucin output vs. controls. Within the same model, Ulvan (25 µg/mL), a sulphated algal polysaccharide, elevated mucin output (by 190%), as did the isotonic SCFA solutions 5 mM butyrate (130%) and 100 mM acetate (160%), or the sugars glucuronic (210%) and galacturonic (110%) acids (25 µg/mL).

Although this work suggests that total mucin production by the colon is elevated by the presence of alginate, it did not directly measure the colonic mucus barrier (instead measuring goblet cell numbers and luminal mucin content); therefore, it was unable to give any information as to the its thickness and protective function. We, therefore, decided to test the effects of dietary alginate on colonic mucus barrier dynamics and to further compare these to the effects of other dietary fibers, so that alginate efficacy as a dietary fiber could be evaluated.

As the colonic mucus layer is altered in colonic mucosal diseases, such as IBDs and colorectal cancer (see above), we believe that the colonic mucus barrier represents a “window” of colonic health. Histological techniques will lead to underestimation of in vivo mucus layer thickness (Strugala et al., 2003), because tissue handling and use of dehydrating fixatives will damage the mucus layer and only allow a snapshot of mucus integrity. It is, therefore, necessary to study the effects of dietary fibers, or other colonic luminal agents, using a suitable in vivo method.

Further from this, we also hoped to densitometrically measure and compare the colonic mucosal blood content of rats fed these dietary fibers as an additional index of colonic mucosal health.

MEASURING THE EFFECTS OF ALGINATES AND OTHER DIETARY FIBRES ON COLONIC MUCUS BARRIER DYNAMICS AND MUCOSAL BLOOD CONTENT

Methods

All experimental procedures carried out were approved by UK Home Office under the Animals (Scientific Procedures) Act, 1986.
Table 4  Fibers types used in dietary feeding study

<table>
<thead>
<tr>
<th>Diet</th>
<th>Total fibre content 1</th>
<th>Soluble:insoluble 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (Wheat bran)</td>
<td>18.82</td>
<td>0.34</td>
</tr>
<tr>
<td>Fibre-deficient</td>
<td>0.27</td>
<td>n/a</td>
</tr>
<tr>
<td>1% alginate</td>
<td>18.49</td>
<td>0.40</td>
</tr>
<tr>
<td>5% alginate</td>
<td>17.22</td>
<td>0.83</td>
</tr>
<tr>
<td>Pectin (from apple)</td>
<td>12.32</td>
<td>20.89</td>
</tr>
<tr>
<td>Cellulose</td>
<td>15.28</td>
<td>0.04</td>
</tr>
</tbody>
</table>

1Total fiber content and the ratio of soluble:insoluble fiber were determined by a previously described chemical method (Englyst et al., 1994). n/a = not applicable. All diets were produced by adding fiber to the same basal diet (23.2% rice starch, 20% Ca-caseinate, 32.5% sucrose, 5% soya oil and 5% vitamin/mineral mix), so that there was no variation between dietary constituents between groups. Instead of 14.3% fiber, the fiber-deficient diet contained extra rice starch. There was no significant difference in the weight of feed eaten by the rats within each dietary group (p > .05 by one-way ANOVA).

Animals and Diets

Groups of 10 male Wistar rats were housed in individual cages at 24 d-old and fed one of the 6 diets shown in Table 4. All diets, except the fiber-deficient, were produced to contain c. 15% dietary fibre (SDS, UK). As wheat bran is the fiber normally included in rodent diets, this diet was selected as a positive control. To produce both alginate diets (1% and 5%), a feed containing c.15% alginate (M, c. 400 kDa, M:G ratio 0.45, supplied by FMC Biopolymer, Norway) was mixed with the control (wheat bran) diet to give two diets that contained 1% and 5% alginate, but that still had a total fiber content of around 15%. Diets were all produced from the same basal diet containing 23.2% rice starch, 20% Ca-caseinate, 32.5% sucrose, 5% soya oil, and 5% vitamin/mineral mix), so that there was no variation of dietary constituents (except fiber) between groups. The fiber-deficient diet contained extra rice starch instead of fibre.

Feeding took place over an 8-wk period. During this time, rats were kept in a 12 h light-dark cycle at constant temperature and humidity and allowed free access to food and water. Rodent health and food/water intake were measured throughout this feeding period. At the end of the feeding period, rats were fasted overnight (15 h) in order to empty the colon of luminal contents before being anaesthetized.

Measurement of Mucus Layer Dynamics

The surgical procedure used here is described elsewhere (Holm and Flemstrom, 1990; Sababi et al., 1995; Atuma et al., 2001; Strugala et al., 2003). Briefly, rats were anaesthetized by administration of 0.26 mL/g body weight Inactin (Thiobutabarbital sodium, Sigma, UK) intraperitoneally. Body temperature, breathing rate, and blood pressure were monitored and controlled throughout the procedure. Laparotomy was performed, and the colon was opened by microelectrocautery c.1 cm distal to the caecum. The colon was carefully placed over a special viewing chamber, lit from above and below. The chamber was filled with 0.9% saline solution, and the mucosa was left to equilibrate for 30 min. The mucosa was then observed via trinocular microscope (Olympus, SZ-CTV).

A drop of charcoal in 0.9% saline was placed into the mucosal fluid. The carbon particles sank and demarcated the luminal surface of the mucus barrier. Mucus thickness was measured by carefully advancing a microprobe tip width of c. 2 µm attached to a micromanipulator (Mitutoyo, Japan) from the luminal surface of the mucus to the mucosal surface.

Measurements were made every 10 min in triplicate at constant sites on the mucosa. First, the maximal mucus thickness was assessed by measurement of the mucus layer over 60 min. After this, the loosely adherent mucus layer was removed by suction, leaving behind the firmly adherent gel, and mucus thickness measurements continued as the mucus layer replenishment occurred. If the mucus barrier reached its maximal thickness level over 3 consecutive readings, partial removal was repeated and replenishment rate once again assessed. Mucus thickness measurements were taken over a total time (excluding equilibration period) of 6 h.

Measurement of Mucosal Blood Content (Colonic IHB)

Throughout the mucus thickness measurement period, mucosal microphotographs were taken by digital camera (Olympus Camedia, C-3030) every 30 min and also after the initial partial removal of the mucus layer by suction.

Measurement of mucosal blood content was completed by densitometric analysis of these images, using the methods of Ishiguro et al., (2001). Briefly, this method allows for the measurement of mucosal redness caused by hemoglobin, and it expresses this as a unitless index of haemoglobin, or colonic IHB (Ishiguro et al., 2001). This measurement is dependent on the redness:greenness ratio of the image.

Results

Effect of Alginate on Maximal Mucus Thickness

Maximal mucus thicknesses for all 6 dietary groups are shown below in Table 5 and Figure 1. Of the 6 diets tested, 1% alginate gave the highest mean maximal mucus thickness (p < 0.01); this was calculated using a unpaired t-test analysis with Welch’s correction. The 5% alginate diet gave a colonic mucus layer that was approximately 25% thinner than the 1% alginate diet, but was significantly higher than pectin, fiber-deficient and cellulose groups.

Effect of Alginate on Mucus Layer Replenishment

The 1% alginate diet gave a significantly higher mucus replenishment rate over time compared to all other diets, including the wheat bran control (p < 0.0001, assessed using a, paired t-test of the data presented in Figure 2). 5 percent alginate also
Table 5  Effect of diet on indices of colonic health

<table>
<thead>
<tr>
<th>Diet</th>
<th>Mean index of colonic mucosal health ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximal mucus thickness (µm)</td>
</tr>
<tr>
<td>Control (Wheat bran)</td>
<td>660 ± 37&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fiber-deficient</td>
<td>429 ± 19&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>1% alginate</td>
<td>763 ± 56&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>5% alginate</td>
<td>555 ± 13&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pectin</td>
<td>476 ± 25&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cellulose</td>
<td>440 ± 16&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Values in same column that share superscripts are not significantly different (p < 0.05) from each other compared using one-way t-test (see text for details). ND = not determined. Maximal mucus thickness values represent the mean (±SEM) maximal thickness for the entire dietary group (n = 10 rats) as assessed every 10 min over the first hour. Mucus replenishment rate is the mean (±SEM) total mucus output divided by total time (5 h) for each group. Colonic IHB is the mean IHB (±SEM) over the entire time course for each dietary group.

gave a significantly higher mucus replenishment rate than pectin, cellulose, and fiber deficient diets, but not the wheat bran control. All diets gave a significantly different rate of replenishment from each other (see Table 5) with the order 1% alginate > control > 5% alginate > pectin > fibre-deficient > cellulose.

Effect of Alginate on Colonic IHB

The mean colonic IHB did not change over time for each dietary group (data not shown). Therefore, the total mean colonic IHB (for each time point, for each rat in the study) was compared by one-way, unpaired t-test with Welch's correction. Rats fed on the 1% alginate diet showed a less reddened colonic mucosa than all other dietary groups. Rats fed 5% alginate also had a lower colonic IHB than control (wheat bran) rats. Cellulose alone gave a significantly increased in vivo colonic mucosal reddening. Results are displayed in Table 5.

CONCLUSIONS ON DIRECT EFFECTS OF ALGINATE ON COLONIC MUCOSA

Inclusion of low levels (i.e., 1%) of alginate within the diet benefit all indices of colonic mucosal health tested here. Inclusion of higher levels of alginate (i.e., 5%), however, only reduce mucosal reddening (compared to wheat bran controls), while also appearing to reduce the benefits to the dynamics of the colonic mucus barrier (i.e., maximal barrier thickness and mucus replenishment rate) seen after feeding 1% alginate. Due to its effects on the colonic mucus barrier, inclusion of low levels of alginate (i.e., 1% or less) in the diet may be beneficial in alleviating the histopathological symptoms seen in ulcerative colitis (i.e., a thinner, discontinuous mucus layer). Five percent dietary alginate, due to its reduction in mucus barrier potential and compared to 1% alginate, may eventually cause increased mucosal damage by luminal contents. Therefore, a low level of alginate inclusion in the diet seems appropriate for colonic protection. It must be noted that, compared to the effects of pectin, cellulose, or fibre-deficient diets, 5% alginate was beneficial to colonic health and protection.

The mode of action of alginate in reducing mucosal reddening is not fully understood. By reducing wound-healing time (Del Buono et al., 2001; Dunne et al., 2002), alginates would also be expected to reduce mucosal bleeding and/or inflammation (see below). Previous work has suggested that alginates may elevate the immune response (Otterlei et al., 1991, 1993; Lahaye and Kaeffer, 1997; Son et al., 2001; Peddie et al., 2002). This
would be expected to reduce the likelihood of intestinal infection, resulting in reduced intramucosal damage and, therefore, reddening.

Alginates have previously been demonstrated to have a synergistic, intermolecular interaction with gastric mucins (Taylor, C., Allen, A., Dettmar, P.W., and Pearson, J.P., unpublished work) by in vitro rheological studies. It is, therefore, likely that they will have a similar synergism with colonic mucins. Putatively, this could be expected to increase the rate of colonic mucus removal by shear in vivo. An increased “mechanical challenge” on the colon by dietary fiber has previously been suggested as a factor in increasing the number of mucus producing goblet cells in the colon (Enss et al., 1994), and a similar effect may be brought about here. This increase in goblet cell numbers would be expected to result in a thicker in vivo maximal mucus layer, which was secreted faster. However, in our study, goblet cell numbers were not assessed, so this mode of action is speculative.

Further research in this field will focus on the effects of alginate structure on its alteration of colonic mucus barrier dynamics. Lower levels of alginate inclusion will be tested. It is also important to study the effect of alginate inclusion into otherwise fiber deficient diets, thus allowing an in vivo test of alginate’s potential as a simple dietary fiber supplement in fibre deficient diets.

It is possible that the effects demonstrated here may be a general benefit of fiber types that are hydrocolloids and not fully fermentable in the bowel. Similar results have been demonstrated using this methodology for diets containing ispaghula husk as a source of dietary fiber (Brownlee et al., 2002), and previous work has suggested an increase in colon mucus production and goblet cell numbers may be caused by another water soluble, seaweed derived fiber, Ulvan (Barcelo et al., 2000).

Further Benefits of Alginates to the Gastrointestinal Tract

Outside of the effects beneficial to health previously discussed, alginate intakes has been suggested to have further benefits to the gastrointestinal tract. The effects are discussed below.

Wound Healing

Recent studies have suggested that certain alginates may enhance repair of mucosal damage in the GI tract in vivo and in vitro. Male Sprague Dawley rats fed an 8 mg dose of an M-rich alginate prior to gastric lesion by indomethacin (20 mg/kg) injection and restraint showed approximately half the level of macroscopic damage seen in untreated individuals (Del Buono et al., 2001). This level of damage reduction was similar to rats administered 50 μg/kg of the known cytoprotective agent, epidermal growth factor (EGF). A G-rich alginate did not reduce levels of gastric damage. The same M-rich alginate caused cell migration (similar to EGF) in esophageal and gastric cell lines, whereas the G-rich alginate did not (Dunne et al., 2002). A modified alginate containing almost exclusively M-blocks (>95%) did not cause cell migration within this study, suggesting a necessity for both M and G-blocks to have this effect.

Hemostatic wound dressings containing alginates as the active component are commonly used for skin lesions. Their efficacy on reducing bleeding and aiding wound healing have also been assessed on buccal and rectal mucosa. The direct adherence of calcium alginate leads to formation of a gel over the wound. Exchange of calcium ions from the alginate gel with sodium from the plasma is believed to stimulate platelet activation and clotting at the wound site, thereby aiding hemostasis (Matthew et al., 1994). This effect may also reduce tissue granulation upon wound healing (Ingram et al., 1998).

In a study on oral mucosa wound healing in dogs, alginate containing gauze significantly increased haemostasis within a 2 mm deep surgical wound (Matthew et al., 1994), although histological analysis suggested no benefits to wound healing with alginate at the time points tested (1, 4, 12, and 24 wk). Alginate containing dressings did not cause a reduction in hemorrhage in the rectal tissues of post-operative haemorrhoidectomy patients (Ingram et al., 1998).

The effect of alginates on wound healing of intestinal mucosa has not yet been ascertained. Any mucosal protection that alginate may provide in the stomach (Del Buono et al., 2001) will not necessarily be mirrored by similar effects throughout the GI tract.

Immunostimulation

Alginates have previously been shown to stimulate interleukin and TNF-α production by isolated human monocytes (Otterlei et al., 1991) in vitro. The presence of the membrane-bound CD14 receptor on macrophages has been shown to be necessary for this stimulatory actions of alginates, and it is the same mechanism by which bacterial lipopolysaccharides are sensed (Espevik et al., 1993). Intrapertioneal injection of alginates caused an increased immune response in fish (Peddie et al., 2002) and mice (Son et al., 2001) in vivo. These immunostimulatory activities appear to be heightened with increased mannuronate content of the alginate (Otterlei et al., 1993). β-glucans have also been shown to stimulate immune responses (Roubroeks et al., 2000; Son et al., 2001).

An increased protein turnover (i.e., retention of newly synthesized proteins was three times higher than that of non-alginate fed controls) was seen in turbot larvae fed a high mannuronate alginate compared to larvae fed the same feed without alginate (Conceicao et al., 2001). Pigs fed high mannuronate alginate within their diet (1.25%) were shown to put on weight faster than non-alginate-fed animals (Gaserod and Dessen, 2003). Both of these factors would suggest that the alginate-fed animals were generally more healthy than animals fed the same feed without alginate. In the study outlined by Gaserod and Dessen (2003), the oxidative burst of isolated phagocytes from the alginate-fed
pigs was significantly higher than that of control pigs (after 4 wk feeding), as was the level of circulating monocytes and lymphocytes (after 6 wk feeding). Therefore, the alginate-fed pigs appeared to have a greater number of immune cells that were more responsive. Hypothetically, this immunostimulatory effect could become detrimental with higher levels of alginate intake. However, this is unlikely in human nutrition terms, as alginate is not used at high levels within foods and drinks.

Recent reviews have suggested a number of dietary fibers and prebiotics to also be immunostimulatory (Vanderhoof, 1998; Schley and Field, 2002). This action is attributed to either the alteration they cause in the colonic microflora, or the alteration in SCFA production by the microflora. A direct effect of fiber on immunostimulation cannot necessarily be discounted, as low levels of fibers will be sampled by gut-associated lymphoid tissues and presented to the immune system. Other fibers may also have direct stimulatory effects on immune cells that are similar to the effect of alginate on isolated macrophages, as reported by Otterlei et al. (1991).

CONCLUSIONS ON FURTHER BENEFITS OF ALGINATES TO THE GASTROINTESTINAL TRACT

The hypothesis that alginites may aid gastrointestinal wound healing is new, and this is witnessed by the small amount of work studied in this area. Further studies need to be done to test the efficacy of alginate in wound healing throughout the GI tract and to compare the effects of alginites on GI wound healing to other types of dietary fibers (i.e., are these effects specific to alginites, or merely a function of large polysaccharides/viscous moieties). It must be noted that other types of naturally-occurring alginates, or merely a function of large polysaccharides/viscous moieties). It must be noted that other types of naturally-occurring polysaccharides have previously been used in topical wound dressings (Koide, 1998; Lloyd et al., 1998); therefore, they also have the potential to aid GI wound healing.

Evidence exists, both from in vitro and in vivo models, that alginites with high M-content cause stimulation of the immune system. Whether this will occur through dietary intake of alginate is currently unclear.

The potential GI wound-healing and immunostimulatory capabilities of alginate have initially been studied due to non-food uses of alginate (as an anti-reflux therapy and to encapsulate living cells for implantation, respectively). These properties of other types of dietary fiber are, therefore, not as well characterized as those of alginate. This makes comparison of alginate to other fiber in these contexts very difficult, but also highlights areas that require future study in the field of dietary fiber research.

SUMMARY

Evidence suggests that the intake of dietary alginites results in a number of potentially beneficial physiological effects, such as reduced intestinal absorption, increased satiety, reduced damaging potential of GI luminal contents, modulation of colonic microflora, and elevation of colonic barrier function. Alginites have all these properties, whereas other fiber types have previously been reported to have some but not all of these effects. Similar effects have also been noted for other dietary fibers. A direct comparison of the physiological effects of alginate to those of other dietary fibers is not always possible, since relatively few studies have considered the potential of alginate as a dietary fiber. Further studies on the dietary fiber properties are necessary to allow this.

Due to the gelation of alginate in the presence of acid or calcium, it may, unlike other hydrocolloids, be taken in relatively large and initially low viscosity doses without the reported poor palatability of other viscous fibers (Murray et al., 1999; Wolf et al., 2002). Because of this, the administered dosages of alginate that can have the relevant, physiological effects on the reduction of glycaemic response, alteration of the colonic microflora, and reduction of mucosal aggression by the luminal contents, as well as increase colonic mucosal barrier function and colonic health, should be possible. Furthermore, alginites have a number of novel mechanisms of gastrointestinal protection for dietary fibers, such as mucosal wound healing and immunostimulation from their ingestion. These unique actions for dietary polysaccharides may give alginites gastrointestinal and systemic health properties not associated with any other dietary fiber, furthering their uses as a functional food component.

A wide range of alginites, with varying structural properties that govern their physiological actions are available worldwide. Once the effects of these structural properties on physiological parameters are fully elucidated, it may be possible to produce functional alginites for intestinal and cardiovascular health.

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