REVIEW

Bioactive natural compounds for the treatment of gastrointestinal disorders

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ABSTRACT

Many healthy subjects and patients are taking natural bioactive products for the prevention and treatment of multiple conditions, including gastrointestinal disorders. Based on current evidence, the scientific validity of the use of many of these commercial compounds by the general public is severely limited, with quality control and regulatory issues continuing to be a concern. Nevertheless, there is sufficient preliminary data to warrant further research of these products in order to identify novel compounds for potential clinical use in addition to performing formal randomized controlled clinical trials of the commercial preparations.

INTRODUCTION

Natural medicinal products have been used for millennia for the treatment of multiple ailments. Although many have been superseded by conventional pharmaceutical approaches, there is currently a resurgence in interest in the use of natural products by the general public, which forms the basis of a world-wide, multi-million dollar major commercial industry. In addition, the pharmaceutical industry continues to examine their potential as sources of novel medicinal compounds to identify novel growth factor, immunomodulatory and potential anti-microbial activity.

In contrast with most standard medicinal compounds, these products are often marketed and used by individuals in order to prevent, rather than to treat, disease. In addition, patients often begin to take such products in addition to physician-prescribed medication, especially if they feel only limited benefit from the conventional (as opposed to alternative or complementary) medical approach. Many patients, therefore, attend clinics already taking these preparations or asking for advice about their value. Although many of the claims made for such products are based on extremely limited scientific evidence, it is important that clinicians are aware of the major products available and the scientific evidence that exists regarding their potential biological activities. In this review, we discuss some of the main products with biological activity currently being used, focusing mainly on areas of interest with particular relevance for the gastroenterologist. In view of the extensive scope of this review, readers are referred throughout to appropriate focused specialist reviews for further details.

GLOSSARY OF TERMS

Naturopathic medicine is the use of therapies that are primarily natural, including clinical nutrition, homeopathy, botanical medicine, hydrotherapy and counselling. Food products providing major calorific contribution are usually termed macronutrients, whereas essential factors such as vitamins and minerals are termed micronutrients. Products with proven biological activity that originate from biological compounds are often described as bioactives, whereas the subgroup of products that bridge the gap between food products and drugs are also termed nutriceuticals or functional foods.

Key words: nutriceuticals, repair, ulceration.
Abbreviations: ChiFos, chicory fructo-oligosaccharides; EGF, epidermal growth factor; IL, interleukin.
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UNICELLULAR ORGANISMS: BACTERIA AND YEAST

Probiotics

Probiotics are living microorganisms that, following ingestion, form part of the colonic flora, at least temporarily, and are used with a view to improving the health and well being of the host. Various strains of probiotics, often in combination, are used which differ with regard to their metabolic and immunological activities but, unlike virulent organisms that tend to amplify inflammation, probiotics may down-regulate inflammation in the intestinal mucosa. A number of uses of probiotics in gastrointestinal diseases have been proposed, including modulation of gut mucosal immunity and the prevention and treatment of intestinal infections. Several trails of probiotic therapy for the treatment of ulcerative colitis have given encouraging results [1–3], although they appear less promising for the treatment of Crohn's disease [4]. Owing to many of the reported studies suffering from low patient numbers and/or using open, rather than a blinded, study protocols, further studies are required.

In addition to trials for inflammatory bowel disease, studies are ongoing examining the use of probiotics to prevent or treat infectious diarrhoea. Evidence in support of their value includes the finding that *Lactobacillus* strain GG shortened the duration of diarrhoea in hospitalized children from 2.5 days (placebo) to 1.4 days. [5]. For a more detailed review of the background and use of probiotics, readers are referred to the review by Shanahan [6].

Botulinum toxin

The use of the purified form of botulinum toxin from the anaerobic bacteria *Clostridium botulinum* now has an established place in clinical practice, due to its ability to cause temporary striated muscle paralysis. It is used extensively by neurologists for dystonic torticolis, blepharospasm, muscle spasm following stroke and by the cosmetic surgery industry to smooth facial wrinkles. In addition, gastroenterologists have been examining its role for the treatment of patients with idiopathic anal fissures where anal muscle spasm caused by the pain exacerbates the problem [7], and for the treatment of achalasia when botulinum toxin is injected directly into the endoscopically located sphincter region. Its use provides symptom relief for approx. 6 months in about two-thirds of cases with achalasia [8]. However, for both anal fissures and achalasia, its therapeutic value is limited by high recurrence rates [9,10].

MULTICELLULAR ORIGIN: PLANT SOURCES

In addition to being a source of vitamins, a major area of interest for the use of biologically active chemical components of plants, i.e. phytochemicals, is for cancer prevention. For example, several phytochemicals have been shown to reduce colonic aberrant crypt foci formation caused by administration of the carcinogen azoxymethane to rats [11]. The list of potential anti-carcinogenic phytochemicals under study is long, but includes dithiolthiones, glucosinolates and isothiocyanates (cruciferous vegetables), coumarins and limonene (citrus fruits), isoflavones inositol hexaphosphate, protease inhibitors and saponins (soybean), carotenoids (palm oil and yellow vegetables) and allium compounds (onion, garlic and leek). For a review of this area, see Drewnowski and Gomez-Carneros [12].

Although the major focus of phytochemical research has been on cancer prevention, several products of plant origin are being used and/or under study for a variety of other gastrointestinal problems and the better recognized of these are discussed below.

Prebiotics (including chicory roots) and symbiotics

Prebiotics are a collective term for non-digestible but fermentable dietary carbohydrates that may selectively stimulate growth of certain bacterial groups resident in the colon, such as bifidobacteria, lactobacilli and eubacteria, considered to be beneficial for the human host. Digestion-resistant short-chain carbohydrates are also referred to as non-digestible oligosaccharides [13] or low-digestible carbohydrates [14]. There is much interest currently in the commercial sector in adding prebiotic supplements, particularly inulin, fructo-oligosaccharides and soybean oligosaccharides, to food products to influence colonic flora, i.e. 'bifidogenic' effects. Prebiotics have a low energy value (< 9 kJ/g) and increase stool volumes, but caution has been shown in their use as fermentation and osmotic side effects, such as excessive flatus, bloating, abdominal cramps and diarrhoea, may occur in a dose-related manner. Increased fermentation of short-chain fatty acids in the colon may protect against development of colorectal cancer, and the use of prebiotics to influence this activity is therefore a major area of research [15]. Additional areas in which prebiotic therapy may be useful include prevention of intestinal infections and modulation of the intestinal immune response in inflammatory bowel disease.

An example of a prebiotic is Chicory fructo-oligosaccharides (ChiFos). Following ingestion, ChiFos reach the colon intact and acts as a prebiotic with bifidogenic effects [16]. The specificity of ChiFos for bifidobacteria is due to these bacteria secreting a β-fructosidase, allowing them to use fructo-oligosaccharides as metabolic substrates [17,18] as well as inhibiting other bacteria through acidification of the media. The potential use of ChiFos as sugar substitutes and fat replacers makes them of particular interest to the food industry.

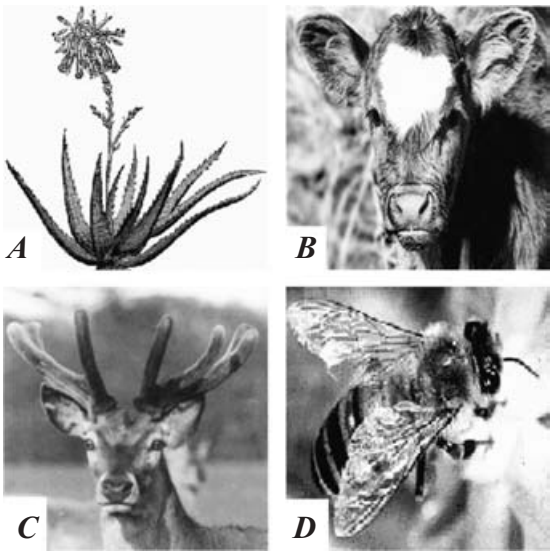

Figure 1 Sources of currently used bioactive products from diverse sources

(A) The *Aloe vera* plant, used in many medicinal and cosmetic products, contains a wide range of potentially bioactive products. (B) Bovine colostrum is a by-product of the commercial dairy industry and is a rich source of multiple growth factors. (C) Deer antler, with its overlying velvety covering, is commercially farmed and grows at a remarkable 1–2 cm per day. It is currently being studied for novel morphogenic and angiogenic factors. (D) Honey has been used as a medicinal product since before Roman times. Manuka honey is reputed to possess additional antibacterial activity compared with standard pasture honey.

Symbiotics refers to products in which a prebiotic and a probiotic are combined. The growth proliferation of the probiotic strain will be selectively promoted if it utilizes the prebiotic carbohydrate.

Aloe vera

Aloe vera has been used as a medicine since before Roman times (Figure 1A). It contains several potentially bioactive compounds, including salicylates, magnesium lactate, acemannan, lupeol, campestrol, β-sitosterol, γ-linolenic acid, aloctin A and anthraquinones. It is currently available as an ingredient in a number of healthcare products where both leaf exudate and gel are available. *Aloe vera* possesses multiple activities that may have beneficial effects for gastrointestinal disease, including anti-inflammatory, analgesic and pro-healing effects. For example, inflammation produced by application of croton oil to mouse ear or rat hind paw is decreased after topical application of aloe gel [19]. In addition, a component of *Aloe vera*, acemannan, has been reported to accelerate healing and reduce pain in aphthous stomatitis, [20] and prevent stress-induced gastric ulceration in rats [21]. The wound healing properties of *Aloe vera* are probably not solely a consequence of its anti-inflammatory action, as *in vivo* and *in vitro* studies suggest *Aloe vera* or mannin derivatives can stimulate collagen synthesis and fibroblast activity [22,23]. Clinical trials of *Aloe vera* in inflammatory bowel disease are ongoing.

Soyabean

Soya foods are the predominant source of dietary isoflavones and are also a rich source of trypsin inhibitor, phosphatidylinositol, saponins and sphingolipids, all of which have potential health benefits, including cancer prevention (breast, prostate and colon) and prevention of ischaemic heart disease and regulation of the host immune system [24,25]. Many of these applications are, however, at a preliminary stage and further research is required to substantiate these claims. Soya protein is currently used as part of milk feed substitutes for infants with cows' milk intolerance [26] and may also be beneficial in decreasing symptoms of the dumping syndrome in patients following vagotomy [27].

Turmeric

Curcumin (diferuoylmethane) is a yellow pigment in turmeric (*Curcuma longa*) and is used widely as a spice in Indian and Thai cuisine. Curcumin exhibits a number of pharmacological effects and its reported anti-inflammatory activity has been attributed to suppression of prostaglandin synthesis [28]. Preliminary reports suggest that tumeric and its extracts may be beneficial for a variety of gastrointestinal conditions, as tumeric root extract relieved pain from biliary dyskinesia in a placebo-controlled double-blinded study [29] and curcumin capsules improved endoscopic healing of peptic ulcers as well as improving symptoms of patients with non-ulcer dyspepsia [30]. This latter study was, however, performed using an open protocol and further blinded studies are required to support these findings.

Curcumin decreases proliferation of the colonic cancer cell line HT29 in a concentration- and time-dependent manner [31]. There is currently much interest in its potential as a chemopreventative agent for colorectal cancer, as curcumin possesses both cyclooxygenase-2 ('COX-2')-selective inhibitory [32] and pro-apoptotic activity [33]. The latter process possibly acts through the mitochondrial pathway involving caspase-8, BID cleavage, cytochrome *c* release and caspase-3 activation, with Bcl-2 and Bcl-x_L being critical negative regulators of curcumin-induced apoptosis [33].

Bael

The bael (*Aegle marmelos)* tree grows in tropical and subtropical countries. Various parts of the bael plant are used in Ayurveda and Unani medicine for treatment of a variety of diseases, including treatment of diarrhoea, dysentery and dyspeptic symptoms. In support of this idea, methanolic extracts of unripe fruit from *Aegle marmelos* decreased castor oil-induced diarrhoea in mice, possibly due to the presence of tannin and mucilaginous substances [34]. In addition, patients suffering from

diarrhoea-predominant irritable bowel syndrome showed significantly greater improvement in symptoms when given an indigenous preparation containing *Aegle marmelos* and *Bacopa monniere* compared with placebo [35].

Marmelosin, isolated from the bael plant, has been reported to have anti-helminthic and anti-bacterial activity. No positive effect was seen, however, in a controlled trial examining its efficacy in clinical improvement or bacteriological cure of patients with shigellosis [36]. Further gastroenterological interest in bael comes from the finding that oral administration of luvangetin, a pyranocoumarin isolated from the seeds of *Aegle marmelos*, protected against multiple models of gastric ulceration in rodents. Although the exact mechanism remains unclear, this protection was probably not mediated via prostaglandin pathways [37].

Garlic

Garlic derivatives are commonly used by the public for a variety of conditions, including as a cholesterol-lowering agent. In relation to the gastrointestinal tract, there is currently interest in its potential anti-cancer activity due to it containing the prebiotic fructo-oligosaccharide. In addition, ingestion of garlic results in the formation of diallyl disulphide from its organosulphur constituents, causing increased tissue activities of the phase II detoxification enzymes quinone reductase and glutathione transferase [38]. Diallyl disulphide has been shown to decrease oesophageal cancer development caused by *N*-nitrosomethylbenzylamine in rats [39].

In addition to its potential anti-cancer activity, aged garlic extract has been reported to possess immune-enhancing and antioxidant properties (for review, see [40]). Further studies are required, however, to confirm these actions, and it is important to note that excessive intake of garlic derivatives may be irritant, resulting in reddening of the gastric mucosa and loss of small intestinal epithelial cells [41].

Pine bark

Extracts of the bark of pine have been used in several parts of the world as traditional medicine. Pycnogenol® is a proprietary extract of the bark of the French maritime pine tree *Pinus maritime*. The extract is prepared by extraction of fresh pine bark with an aqueous solution of NaCl followed by ethylacetate. The resulting product is a mixture of at least 40 different molecules, mainly flavonoids, as monomers, such as catechin, epicatechin and taxifolin, as well as condensed polymers designated as procyanidins. These molecules have antioxidant properties and may also act as modulators of metabolic enzymes [42], resulting in altered macrophage function, including reduced nitric oxide production [42]. As a number of gastrointestinal diseases, such as Crohn's disease, have been associated with dysregulation of nitric oxide production, clinical trials of products containing pine bark extract could be of interest [43].

Dragon's blood (Sangre de grado)

Although less well studied, several other plant-derived extracts are of potential interest and are often derived from sources such as South American folklore products. One example of this is Dragon's blood (Sangre de grado). This viscous red tree sap is widely used by indigenous cultures of the Amazon river basin where it is considered to possess remarkable healing properties. Derived from several *Croton* species, Sangre de grado is widely available throughout the Amazon basin and is used orally in a dilute form for gastritis, gastric ulcer, intestinal infections and inflammation [44]. It has also been shown to heal experimental gastric ulcers induced by application of 80 % acetic acid in rats [44]. This product has not been researched adequately for its active components and biological properties to be determined.

MULTICELLULAR ORIGIN: ANIMAL SOURCES

In the commercial sector, particularly in countries with large dairy herds such as New Zealand, milk and other dairy-derived products are undergoing extensive investigation for novel potential bioactive constituents (Figure 1B). Some of the main products under scrutiny are described below.

Colostrum

Colostrum is the first milk produced after birth and is particularly rich in immunoglobulins, anti-microbial peptides (e.g. lactoferrin and lactoperoxidase) and other bioactive molecules, including growth factors. In combination with the milk that is subsequently produced, it is important for the nutrition, growth, development and immunological defence of the newborn infant. It is produced commercially as a by-product of the milk industry and is currently available in health food stores, where it is usually marketed as a general health-promoting agent. There is increasing evidence, however, that it may be useful for the specific treatment of both neonatal and adult gastrointestinal disease. For a detailed review of colostrum and immune function see Solomons [45] and for colostrum and growth factors see Playford et al. [46].

Colostrum contains multiple specific (antibody) and non-specific (e.g. lactoferrin) anti-microbial factors in addition to several cytokines, including interleukin (IL)-1β, IL-6, IL-10, tumour necrosis factor ('TNF')-α and granulocyte-, macrophage- and granulocyte/macrophage colony-stimulating factors. Natural bioactive substances in colostrum also include nucleosides and nucleotides [47]. Both the specific and non-specific constituents of colostrum may have relevance to immune modulatory

and anti-microbial activity when given to neonates or adults. Several reports support the potential of colostrum for the prevention and treatment of microbial infections [48] acting on the hosts general and specific immune function [49] as well as the microbe itself. For example, healthy volunteers given bovine colostrum responded to attenuated oral *Salmonella typhi* Ty21a vaccine administration with a greater increase in circulating specific IgA compared with controls [50]. However, not all trials have confirmed beneficial effects, for example, adjuvant hyperimmune bovine colostrum was ineffective in decreasing the stool frequency, duration or severity of childhood shigellosis [51].

Several studies suggest that administration of (usually bovine) colostrum, growth-factor-enriched colostrum or purified peptides derived from colostrum may be useful to treat a variety of gastrointestinal diseases. Administration of commercial colostral preparations have been shown to decrease non-steroidal anti-inflammatory-induced gut injury in rats, mice and humans [52,53] and to stimulate mucosal healing of patients with inflammatory bowel disease (Figure 2) [54]. Other gastrointestinal conditions for which colostrum-derived growth factors may be useful include chemotherapy-induced mucositis, necrotizing enterocolitis and short bowel syndrome [46].

The identity of the factor(s) in colostrum responsible for these biological actions are unclear. Multiple peptide growth factors are present in colostrum, including transforming growth factor ('TGF') α and β, insulin-like growth factor ('IGF') 1 and 2, epidermal growth factor (EGF) and granulocyte colony-stimulating factor ('G-CSF') [46]. More than one peptide is likely to be important, as synergistic activity between various factors in colostrum have been demonstrated. For example, co-administration of bovine lactoferrin with EGF resulted in synergistic activity in stimulating growth of the rat intestinal epithelial cell line IEC-18 [55]. However, two factors present in colostrum that are of particular interest for the treatment of gastrointestinal disease include transforming growth factor β [56] and EGF [57]. It is also important to note that there is marked variation in the relative abundance of the growth factor constituents across species (e.g. human colostrum has much higher concentrations of EGF than bovine colostrum) and when the colostrum changes to milk.

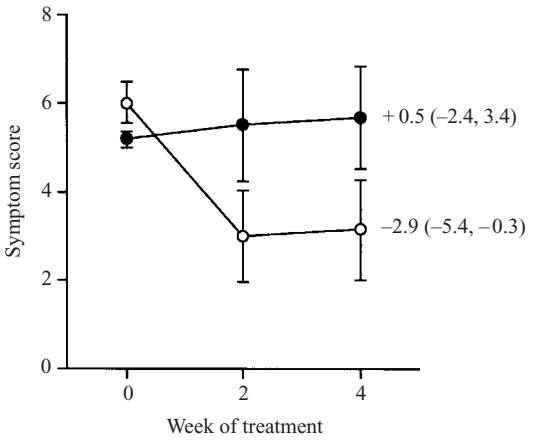

Figure 2 Colostrum therapy for the treatment of inflammatory bowel disease

Bovine colostrum is widely available in health food shops as a by-product of the milk industry. In a trial of patients with ulcerative colitis restricted to the left side of the colon, colostral enemas (○) were found to be superior to control (●) in a small randomized double-blinded study. Mean changes (95 % confidence intervals for the change) are shown. The symptom score is a well-validated scoring system score based on the assessment of patient well being (0–3), abdominal pain (0–2), rectal bleeding (0–3), temperature (0–2), anorexia/nausea (0–1), bowel frequency (0–3), stool consistency (0–2), abdominal tenderness (0–3), and presence of extra intestinal manifestations (0–1). All patients were required to have a minimum Powell–Tuck score of five to qualify for entry into the study. This Figure is reproduced from Z. Khan, C. Macdonald, A. C. Wicks, M. P. Holt, D. Floyd, S. Ghosh, N. Wright and R. J. Playford (2002) Use of the 'nutriceutical', bovine colostrum, for the treatment of distal colitis; results from initial study. Aliment Pharmacol. Ther. **16**, 1917–1922, with permission. © (2002) Blackwell Publishing.

Milk-derived products

Casein

The caseins are a family of phosphoproteins synthesized in the mammary gland in response to lactogenic hormones and other stimuli and secreted as large colloidal micelles. The American Dairy Science Association Committee on Nomenclature and Classification proposed bovine caseins be designated α_{s1}, $\alpha s2$, β and κ caseins [58], with α_{s1}-casein being the major protein fraction of bovine milk. Casein contains opiod-type peptides that can influence gut motility, decreasing gastric emptying in rats [59], in addition to possessing immune modulatory activity using *in vitro* [60] and *ex vivo* studies [61].

In addition to any specific activities present in casein, an important effect of casein ingestion may be to preserve activity and aid adsorption of other biologically active peptides by acting as a competitive substrate for pancreatic proteolytic enzymes. We have demonstrated this previously for EGF in humans [62], and this general mechanistic process has subsequently been shown to occur in preserving the stability and/or improving the absorption of other peptides, such as insulin-like growth factor 1 [63], in several species.

Whey

Whey is a by-product of cheese and casein manufacture and contains approx. 20 % of the original milk proteins. These proteins include α-lactalbumin, β-lactoglobulin, lactoferrin, lactoperoxidase, immunoglobulins, glycomacropeptide and a variety of growth factors, including the EGF-receptor ligand bettacellulin [64]. The biological

activities of some of these molecules may, however, only become apparent after acidification or partial digestion. Biological activities under investigation include immune modulation and anti-inflammatory and prohealing effects; for example, α-lactalbumin decreased gastric injury caused by ethanol in rats [65], although it is of note that the authors report that casein was not protective in this model. A small human study has also suggested a beneficial effect of whey in patients with chemical-induced corrosive injury [66].

Yogurt

Yogurt contains substantial amounts of live lactic acid bacteria and the beneficial effects of yogurt are postulated to be due to its probiotic contents, although direct effects may also occur due to its milk constituents. There is limited, mainly animal, data suggesting enhanced immune responsiveness following yoghurt administration. However, limitations in the experimental design of much of the published literature require there be many more rigorously controlled randomized double-blinded studies to examine this area further [67].

Deer antler velvet

Each spring, the antlers of deer grow at a remarkable rate of about 1–2 cm per day for about 120 days. Deer velvet has a long history in traditional Chinese medicine for treating kidney disease, strengthening the body and healing chronic wounds. Over the last few decades, however, commercial farming of deer antler has also emerged as a product for the Western dietary supplement market (Figure 1C).

Deer velvet products have been shown to induce proliferation and/or morphogenic change of a variety of cell lines, including fibroblasts and the neuronal cell line PC-12 [68]. The identity of the factors responsible for these changes are unclear, although individual factors of potential interest for bone morphogenesis have been identified [69]. In addition, deer antlers may provide novel immunomodulatory factors, as an ethyl alcohol extraction of antler has been shown to increase murine phagocytic activity [70]. The rapid rate of growth at the antler tip requires major remodelling and angiogenic production. There is therefore currently interest in the factors controlling such responses to develop novel anti-cancer (anti-angiogenic) products. We are not aware of trials of deer antler for specific gastrointestinal conditions.

MULTICELLULAR ORGANISMS: MARINE ORIGINS

Fish oil

Fish oil capsules are widely used as a general health supplement in addition to cardiovascular prophylaxis. The two major polyunsaturated fatty acids in fish oil are eicosapentaenoic and docosahexanenoic acids. Polyunsaturated fatty acids form a major constituent of animal cell membranes and eicosapentaenoic acid is also the substrate for eicosanoid production via the cyclooxygenase pathway for 3-series prostaglandins and the lipoxygenase pathway for 3-series thromboxanes [71]. Rats fed on diets containing high doses of fish oil have increased polyunsaturated fatty acid composition in constituents in the cell membrane of the stomach and duodenum, along with decreased prostanoid production [72], supporting the idea that dietary modification with fish oils may influence membrane fluidity and cellular function. Inflammatory and immune cells are also sensitive to change according to the fatty acid composition of the diet, leading to the possibility of a link between dietary polyunsaturated fatty acid intake, inflammation and immunity. For an excellent review on the general area of fish oils and immunity, see [73].

Fish oil preparations have been proposed as potential therapies for a number of gastrointestinal conditions. Several studies have reported a corticosteroid-sparing effect of gelatine-coated fish oil capsules for the treatment of ulcerative colitis [74–76], although in a direct comparison study, fish oil supplementation was less efficacious than the commonly used 5-amino-acid salicylic drug sulphasalazine [77]. Trials of fish oil therapy for the treatment of Crohn's disease have provided conflicting reports, with some [78], but not all [79], studies showing potential beneficial effects. Further trials appear warranted, although there is generally a requirement for more palatable formulations of n-3 fatty acids to improve patient compliance. There is also interest in the potential value of fish oils for the treatment of cancer cachexia for conditions such as pancreatic cancer [80].

Sponges and snails

This unusual source of bioactive compounds has been under investigation for many years, mainly in the area of development of novel anti-inflammatory drugs. The lead compound of marine origin with anti-inflammatory property has been manoalide isolated from the sponge and developed for its anti-inflammatory properties [81]. Manoalide has an unusual sesterterpenoid structure that antagonizes phorbol-induced inflammation but not that induced by arachidonic acid, suggesting that manoalide acts prior to the cyclooxygenase step in prostaglandin synthesis, possibly by inhibiting phospholipase A2. However, it also possesses other activities, such as acting as a calcium channel blocker [82].

The most promising of the marine anti-inflammatory agents to date is contignasterol, a novel steroid with 14b-stereochemistry isolated from the marine sponge *Petrosia contignata* [83]. This has been shown to decrease antigen-induced bronchial responsiveness in guinea-pigs [83], and the potential application of such anti-inflammatory drugs in gut inflammation may merit further exploration.

Sponges and snails, along with several marine fungi and bacteria, are under active investigation for the isolation of novel anti-microbial factors. Examples include the finding of a novel glycoside anti-fungal agent from the marine sponge *Siliquariaspongia japonica* [84] and an anti-microbial peptide obtained from the marine snail *Telescopium telescopium* that potently inhibits the growth of *Escherichia coli* [85].

MULTICELLULAR ORGANISMS OF INSECT ORIGIN

Honey

Honey has been used as a medicine since ancient times (Figure 1D). The high sugar content of honey makes it a very hyperosmolar preparation and this has been used to advantage as a topical preparation for skin burns and other superficial infections, acting as an anti-bacterial agent. For example, topical honey was shown to be effective in treating postoperative skin wounds in neonates that had failed to respond to antibiotic therapy [86]. Honey also has the advantage of acting as a lubricant between the damaged tissue and the overlying dressing, thereby facilitating changes of wound dressing without damaging the underlying granulation tissue. Additional specific anti-bacterial activities have been reported for honey and there has been a particular focus on honey derived from the manuka plant. It is important to note, however, that some studies have failed to show a major difference in anti-microbial activity of manuka honey when compared with standard pasture honey (for example, see [87].

Honey preparations have been proposed as potentially useful for many conditions of the gastrointestinal tract, including periodontal and other oral diseases [88], dyspepsia and as part of oral rehydration therapy. *In vitro* studies suggest that honey possesses bactericidal activity against *Helicobacter pylori* [89], although a clinical trial of manuka honey therapy to induce *Helicobacter* eradication failed to show a beneficial effect [90]. Honey may also be useful as a constituent of oral rehydration therapy, as a clinical trial in which honey was used in place of glucose for the treatment of infants and children admitted into hospital with gastroenteritis showed significantly decreased duration of diarrhoea in the honey-treated patients (58 h compared with 93 h [91]).

Royal jelly

Royal jelly is used by bees to induce development of larvae into the queen phenotype and is currently sold as a general health tonic. There is extremely limited evidence supporting any major therapeutic benefit of its use and it is of note that in susceptible subjects, ingestion of royal jelly can induce asthma and anaphylaxis [92].

COMMERCIAL VALIDITY OF CLAIMS FOR BIOLOGICAL ACTIVITY AND REGULATORY ISSUES

Virtually all of the bioactive compounds available commercially, including those discussed above, are taken as oral preparations. Although biological activity has often been demonstrated *in vitro*, it is important to appreciate that this does not equate to activity once ingested. For example, many peptide growth factors are susceptible to acid/pepsin and pancreatic proteolytic digestion and are, therefore, likely to be degraded to inactive forms [62] soon after ingestion. In addition, many of the receptor-binding sites, such as the EGF-receptor, are not accessible from the apical (lumenal) surface [93] and, therefore, even if they reach the small intestine intact, this does not result in receptor activation. Similarly, for non-peptide based compounds, formal pharmacokinetic and dose–response human studies have usually not been performed and yet, despite these limitations, many commercial preparations claim biological activity based solely on *in vitro* work. Furthermore, the major commercial market relates to subjects taking the product as a prophylactic against illness, rather than as a therapy, but there is minimal data supporting their value for such indications.

Much of the appeal of bioactive products is the perception that their natural origin equates to a 'healthier option'. However, it is important to note that toxicological injury has been caused by the use of some products, such as Chinese herbal remedies, in addition to inducing specific immunological allergic reactions [94]. In addition, current regulatory authority requirements for screening and post-marketing surveillance are much less stringent if a product is classified as a food supplement, rather than a drug, despite some of these compounds containing poorly identified factors with major biological activity. Additional problems include potential batch variation and quality control issues and these aspects are particularly relevant if the active ingredients of the products are poorly defined. In the U.K., many of the nutriceuticals, such as colostrum, are regulated by standard food hygiene regulatory mechanisms. In addition, the Medicines Control Agency has recognized the need for vigilance by incorporating adverse reactions reporting on unlicensed herbal remedies into their drug reaction monitoring function. Similar concerns have been raised in France, requesting that European-wide legislation should be introduced regarding the testing of bioactive products, including introducing formalized bacterial and chemical standards [95].

Further approaches that are currently under scrutiny are to alter the volume and nature of the components of bioactive plant and animal products. Examples include the production of genetically modified rice to provide additional vitamin A (golden rice) and using specific

promoters, such as that from the *β-lactoglobulin* gene, to cause cattle to produce milk containing additional peptides, including human homologues of growth factors, that may be beneficial for patient treatment. Interested readers are referred to the review by Dalyrymple and Garner [96]. These products are, however, a long way from the natural products envisaged by most users of alternative and complementary medicine.

In summary, many healthy subjects and patients are taking potentially bioactive products for the prevention and treatment of multiple conditions, including gastrointestinal disorders. Based on current evidence, however, the scientific validity of the use of many of these commercial products is severely limited, with quality control and regulatory issues continuing to be a concern. Nevertheless, this area does appear to have sufficient preliminary data to warrant further, scientifically valid, rigorously performed research to identify novel compounds for clinical use in addition to performing formal randomized controlled clinical trials.

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