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Inflammatory bowel disease - A peek into the bacterial community shift and algae-based 'biotic' approach to combat the disease

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ABSTRACT

Background: Inflammatory bowel disease (IBD) was regarded as a problem of the industrialised nations. However, with the popularity and convenience connected to ultra-processed food, fast food and restaurant dining, and due to the lack of appropriate strategies to avoid foodborne microbes, the disease started to emerge in other parts of the world also. Bacterial imbalance, intestinal permeability, and the associated dysbiosis-caused polarization of immune components to their pro-inflammatory phenotypes are implicated in the development of IBD. Now IBD is reported in children too, indicating the urgent need to take actions by finding diet components that can stall the proliferation of undesirable bacteria in our intestine.

Scope and approach: We present algae as a novel source for prebiotics to combat IBD. We first give an overview of IBD and the associated microbes. Next, we describe the unhealthy diet-induced microbes that are also connected to the disease and the foodborne microbes that are implicated in IBD. Then, we reveal the advantages of 'biotic' approaches such as using probiotic bacteria like bifidobacteria and lactobacilli and prebiotics from microalgae and macroalgae as well as a synbiotic strategy to combat IBD. In the end, we give suggestions for assessment of selected probiotics and prebiotics to counter pathogens or stimulate the growth of good bacteria in the intestine.

Key findings and conclusions: Dietary intervention, as a 'biotic' route, employing probiotics and bioactive compounds with prebiotic potential, and a combination of the two may provide a future path to control IBD because such strategies could thwart the proliferation of pathogens and development of intestinal dysbiosis.

1. Introduction

Inflammatory bowel disease (IBD) is an umbrella term for intestinal ailments including ulcerative colitis (UC) and Crohn's disease (CD), which cause digestive disorders and inflammation in the gastrointestinal tract. IBD arises from the interaction between genetic and environmental factors which affect the homeostasis of the immune system. Some of the symptoms of CD and UC include diarrhoea, abdominal pain, rectal bleeding, and weight loss. In addition, IBD patients experience emotional burden, which can affect the quality of life and ability to work. Both, CD and UC, may occur in adolescents and adults, irrespective of their gender. Previously, children were diagnosed with IBD when they were in the age range 11–16. In recent years, clinical practitioners have indicated an alarming observation; children younger than 10 years are also suffering from this disease, those between 5 and 10 years of age have a more severe disease course than adolescents, suggesting a greater disease burden in this age group (Ashton et al., 2017). The high incidence rate recorded during the last decades have made IBD a worldwide concern; more than 6 million of the global population are affected by the disease (Hammer & Langholz, 2020). This increase has traditionally been associated with western industrialised countries, and these nations are currently experiencing a stabilising incidence resulting in high prevalence rates. For example, compounded prevalence is witnessed in countries like the US, Norway, Sweden and Portugal (Kaplan & Windsor, 2021). On the other hand, newly industrialised countries in Eastern Europe and Asia have reported a drastically rising incidence of the malady. In Africa where we find sporadic cases, IBD is in the emergence stage, while developing nations like India are experiencing an accelerated incidence stage although the prevalence is low (Kaplan & Windsor, 2021). An additional aspect of IBD is the high economic

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burden associated with the disease. In Europe, annual direct health care costs (approximately €3500/CD patient and €2000/UC patient) have shifted from those connected to hospitalisation and surgery to drug-related expenditures (Zhao, Peng, et al., 2021). Medical treatments including mesalazine and corticosteroids, biological therapies such as anti-integrin and anti-inflammatory cytokine therapies (e.g. anti-Tumor Necrosis Factor, TNF-α) or knowledge of risk factors to arrive at preventative approaches, have not produced the desired outcome for IBD patients (Einwächter, 2019; Jairath & Feagan, 2020). Lack of response to medical treatments and adverse effects of current IBD management strategies point to the need for novel approaches to tackle the illness.

It is now known that gut microbiota plays a key role in the pathogenesis of IBD. One important environmental factor that affects the gut microbiota is diet, and individuals consuming western diet rich in sugar, fat and protein is susceptible to the disease. Hence, there is an urgent need to find alternative natural, healthy food-based interventions to tackle this debilitating malaise. Novel functional food ingredients, which can act as prebiotics/probiotics/antibiotics, can prevent or mitigate the pathogenesis of IBD and its symptoms, thereby helping the patients to regain their normal health status and well-being.

2. Microbes associated with IBD

UC and CD are two issues associated with microbial dysbiosis in the gastrointestinal tract (Fig. 1), and the highest bacterial concentrations are found in the distal ileum and colon, the two sites that are implicated in the disease (Gionchetti et al., 2006). Many studies have reported that the composition of enteric microbes is altered in IBD patients. For example, *Bacteroides*, adherent/invasive *Escherichia coli* and Enterococci were noted as the dominant species (Khan et al., 2019). In addition, *Staphylococcus aureus* and *Clostridium difficile* infections are also common in IBD patients. Another bacterium that can cause mucosal inflammation in UC patients is *Fusobacterium varium* (Ohkusa et al., 2003), and the prevalence of *F. nucleatum* indicates the disease severity in IBD patients (Strauss et al., 2011). Moreover, two bacterial families that have a higher abundance in IBD patients are *Pasturellaceae* and *Veillonellaceae* (Zheng & Wen, 2021). Now children are also suffering from CD, and the relative abundance of *Prevotella*, *Eubacterium*, *Odoribacter*, *Akkermansia*, *Roseburia*, *Parabacteroides*, *Alistipes*, *Coprococcus*, *Dorea*, and *Ruminococcus* will be lower in such patients, and those of *Escherichia*, *Klebsiella*, *Enterococcus* and *Veillonella* will be higher (Lewis et al., 2015). Researchers are slowly revealing the connection between the oral and gut microbiome too; for example, IBD patients can have a higher abundance of the saliva-derived pathobionts, *Haemophilus parainfluenzae*, *Veillonella* and *Klebsiella*; the latter can evoke Th1 responses and the eventual inflammation in the gut (Elmaghrawy et al., 2021). It is known that intestinal inflammation characteristics can be mitigated by 17 strains of Clostridia that helps in creating a TGF-β-rich environment and proliferation of T_{reg} cells (Atarashi et al., 2013). Hence, manipulating the microbial architecture to direct the immune cells to evoke anti-inflammatory responses effectively is the key to curing certain diseases. Such manoeuvring through dietary interventions could be an ideal approach to benefit the patients suffering from IBD.

2.1. Diet-induced proliferation of microbes

The gut homeostasis in IBD patients can be disturbed and the published articles have shed light on elements linked to bacteria and host, i.e., aberrations in host intestinal permeability as well as shift in commensal bacteria and their metabolite production. A change in mucus layer composition and alteration in adhesion molecules at the inter-epithelial spaces are also implicated in IBD (Michielan & DInca, 2015). *Ruminococcus gnavus* and *R. torques* are mucolytic bacteria, and the expression of MUC2 (mucin) will be higher in IBD patients, and the viscoelastic properties of the mucus layer will be altered due to improper sulfation and glycosylation (Png et al., 2010). In such a situation, pathogenic bacteria like *Citrobacter rodentium* could pass through the mucus and access the epithelium to cause colitis (Desai et al., 2016). Furthermore, the bacterial families, *Coriobacteriaceae*, *Provotellaceae*, *Veillonellaceae*, *Pseudomonadaceae*, *Streptococcaceae* and *Burkholderiaceae* had higher abundance in the UC and CD patients, and most of these bacteria did not have a good abundance correlation with other commensal bacteria (Alam et al., 2020). Dysbiosis in IBD patients could also be due to a reduction in the key butyrate producers, namely *Clostridium coccoides*, *C. leptum*, *Faecalibacterium prausnitzii* and *Bifidobacterium* in the intestine of the patients (Prosberg et al., 2016; Wang et al., 2014). Regarding the secondary bile acids produced by commensal bacteria, their levels are low in IBD patients (Yang et al., 2021). Sulfate-reducing bacteria belonging to the genus *Desulfovibrio* are associated with UC patients, and these bacteria produce hydrogen sulphide, H_2S (Gibson et al., 1991). Diet is the main factor that plays a key role in these outcomes. Nevertheless, other environmental factors, including geographic location, and genetic factors can have a synergistic effect. The significant effect of diet could be due to the antigens that directly encounter the commensal bacteria in the intestine. Dietary antigens that predominate in the gut lumen can cause undesirable consequences through the alteration of microbiota (Chapman-Kiddell et al., 2010). Exposure to certain food components can lead to microbial imbalance, which may have a bearing on the intestinal barrier and pro-inflammatory status that may initiate the development of IBD

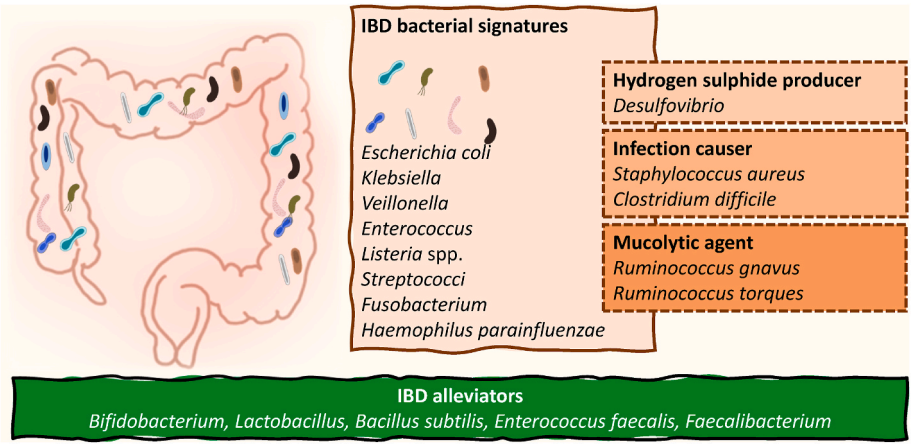

Fig. 1. Bacteria that are implicated in the development of inflammatory bowel disease (IBD). It is known that certain genera of bacteria increase their abundance to enhance the pathogenesis. On the other hand, some others cause infection during IBD. Few other bacteria produce hydrogen sulphide or degrade the mucus layer, resulting in a leaky gut. On the other hand, lactic acid and short chain fatty acid producing bacteria can possibly alleviate the symptoms of IBD.

(Ruemmele, 2016).

2.1.1. High-fat diet caused alterations

A food regime rich in protein and lipid and low in fibre is an intestinal health risk. A higher ratio of diet-derived n-6/n-3 polyunsaturated fatty acids, PUFAs (Scaioli et al., 2017) and high intake of *trans*-unsaturated fats can increase the incidence of UC (Ananthakrishnan et al., 2014). Risk of developing CD and UC increases with high intake of total fats, omega-6 fatty acids, and meat (Hou et al., 2011). High-fat diet is known to trigger the growth of bacteria belonging to the genera *Bacteroides*, *Escherichia*, *Klebsiella*, *Parasutterella*, and *Staphylococcus* (Singh et al., 2020) that are implicated in the development of IBD. Fat-rich western diets may lead to reduced diversity and lower production of short-chain fatty acids, SCFAs (Wang et al., 2014). Fatty food intake can also impair bile acid metabolism. Bile acid homeostasis is important to avoid IBD (Ticho et al., 2019). High bile salt hydrolase activity that facilitates the deconjugation of bile acids, is exhibited by beneficial bacteria belonging to *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, *Bacteroides* and *Clostridium* (Ferrell & Chiang, 2021). Clostridiales have 7a/b-dehydroxylation enzymes such as BaiB, BaiCD, BaiA2, BaiE, BaiF, and BaiH that could convert primary bile acids to their secondary forms (Funabashi et al., 2020). There are several bile-acid receptors including nuclear receptors (farnesoid X receptor, FXR; vitamin D receptor, VDR; pregnane X receptor, PXR; constitutive androstane receptor, CAR) and G protein-coupled receptors (Takeda G protein-coupled receptor, TGR5; sphingosine-1-phosphate receptor 2, S1PR2; muscarinic acetylcholine receptor M3, M3R) (Ticho et al., 2019). Ablation of bile acid-activated receptors can lead to the polarization of T cells and macrophages to their pro-inflammatory phenotypes (Fiorucci et al., 2021). Activation of bile acid activated receptors such as FXR and TGR5, which are highly expressed in the intestine and immune cells such as macrophages, dendritic cells and natural killer T cells have important functions to maintain tolerogenic immune phenotypes during intestinal inflammation (Fiorucci et al., 2018). It is reported that saturated milk fat can favour the bloom of *Bilophila wadsworthia*, evoke Th1 immune response (pro-inflammatory), bile acid conjugation with taurine and the subsequent increase in sulphur (Devkota et al., 2012).

While fatty food increases the *Firmicutes*-to-*Bacteroidetes* (F/B) ratio and *Oscillibacter* species, a carbohydrate diet increases the abundance of succinate-utilizing bacteria such as *Dialister succinatiphilus* and succinate-producing bacteria of the family *Prevotellaceae*, *Veillonellaceae*, and *Erysipelotrichaceae* (Nakayama et al., 2017). Succinate-consuming *Phascolarctobacterium faecium*, butyrate-producing *Agathobaculum butyriciproducens*, and bile acid-converting *Clostridium citroneae* (Watanabe et al., 2012) and members of the clostridial cluster can stall the development of intestinal inflammation. Furthermore, *Lactobacillus*, *Bifidobacterium*, and *Faecalibacterium* can stimulate anti-inflammatory cytokines and suppress inflammatory cytokines (Llopis et al., 2009; Okada et al., 2009; Sokol et al., 2008). In addition, the phylum *Actinobacteria* can inhibit nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha phosphorylation by lipopolysaccharides, LPS (Okada et al., 2009). Since *Bifidobacterium* and *Lactobacillus* were found to increase during the active IBD phase, caution should be exercised in the application of these bacteria during the active phase of the disease (Wang et al., 2014). Thus, fatty food can stimulate the bloom of undesirable bacterial species that generate unwanted bacterial metabolites, evoke pro-inflammatory responses, and stymie the production SCFAs which are much desired by the intestinal epithelial cells for maintaining homeostasis (Fig. 2).

2.1.2. Animal protein-rich food induced alterations

Animal protein diet, especially meat-based products can increase the risk of IBD (Jantchou et al., 2010). Animal protein fermentation by intestinal bacteria can also lead to the production of SCFAs. However, consumption of food rich in protein and low in carbohydrate will reduce the total SCFAs and fermentation of undigested protein produces, among

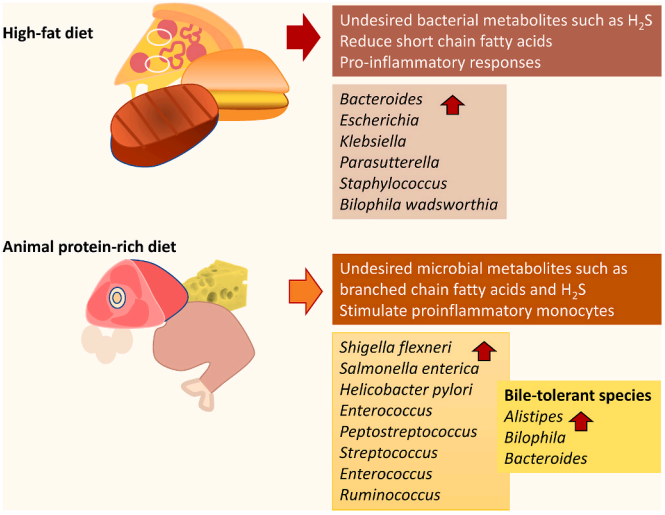

Fig. 2. Imbalance in nutrient uptake can have an effect on human health. Fat-rich and protein-rich food can adversely affect the bacterial communities in the intestine and cause the release of undesired bacterial metabolites that evoke proinflammatory responses.

others, branched-chain fatty acids (i.e., isobutyrate, isovalerate, and 2-methylbutyrate), ammonia, phenolic and indolic compounds, biogenic amines, H_2S, and nitric oxide that contribute to the development of IBD (Gilbert et al., 2018). These products can alter cell proliferation, cell viability, transepithelial resistance, paracellular permeability and lower H_2S detoxification (Gilbert et al., 2018). Branched-chain fatty acids are fermentation products of branched-chain amino acids, and high concentrations of branched-chain fatty acids can increase oxidative stress and inflammation (Zhenyukh et al., 2017). *Shigella flexneri*, *Streptococcus pneumoniae*, *Salmonella enterica*, *Helicobacter pylori* increase their virulence by feeding on polyamines, another product of protein fermentation by bacteria (Wu et al., 2011). Furthermore, *Firmicutes* and *Ruminococcus* species of the *Blautia* genus were abundant in individuals who consumed more animal proteins (Bolte et al., 2021). It was also observed that consumption of fast food increased the abundance of *Blautia*, *Lachnospiraceae*, *Clostridium bolteae*, *Coprobacillus*, *Ruminococccus gnavus*, *Parabacteroides johnsonii* and *L. sakei* (Bolte et al., 2021). Animal protein-rich diets can induce inflammation, not through adaptive immune responses, but by increasing Ly-6C^{high} pro-inflammatory monocytes, based on an observation in the colon of mice (Kostovcikova et al., 2019). *Enterococcus*, *Streptococcus* and *Peptostreptococcus* that were linked to IBD were abundant in mice that consumed animal protein diets (Kostovcikova et al., 2019). Furthermore, bile-tolerant microorganisms (*Alistipes*, *Bilophila* and *Bacteroides*) were noted to be abundant in individuals consuming animal-based diets (David et al., 2014), and all these bacteria are usually linked to chronic inflammation. Fibre-free diet increased the abundance of mucin-degraders such as *Akkermansia muciniphila* and *Bacteroides caccae*, and *Desulfovibrio piger* (Desai et al., 2016). A study employing data from 296 Caucasian adults listed the bacteria that were altered differently in women and men; five servings/day of ultra-processed food can increase the abundance of genera such as *Acidaminococcus*, *Butyrivibrio*, *Gemmiger*, *Shigella*, *Anaerofilum*, *Parabacteroides*, *Bifidobacterium* in women and *Granulicatella*, *Blautia* in men (Cuevas-Sierra et al., 2021). These findings indicate that fermentation of protein-rich diet and consumption of ultra-processed food can increase the levels of unwanted microbial metabolites such as branched chain fatty acids and H_2S, stimulate proinflammatory monocytes and promote the proliferation of bile-tolerant bacteria (Fig. 2).

2.2. Potential foodborne pathogens

Recurrent food poisoning can lead to a slew of undesirable physiological events in the intestine and increase the risk of IBD occurrence. As stated previously, both genetic and environmental factors could have their specific impact on the microbial communities and the intestinal immune system, thereby affecting the progression of IBD. Hence, environmental factors such as foodborne opportunistic bacteria that can be the root cause of recurrent food poisoning should be considered while devising strategies to avoid the disturbance of intestinal homeostasis. Cumulative effect of low level infections caused by many foodborne bacteria such as *Salmonella* and *Campylobacter* can lead to the emergence of IBD (Hutchinson, 2009). These pathogens could accelerate molecular aging and cause deficiency of important enzymes such as alkaline phosphatase in the intestine, which can lead to inflammation (Yang et al., 2017). Furthermore, evidence suggests that the foodborne pathogens can break the physical barrier in the intestine, paving the way for the development of IBD (Zhang et al., 2014). Hence, future studies that investigate the possibilities of preventing IBD should focus on combating foodborne pathogens too. It will be ideal to find bioactive compounds including those from algae that can stall the proliferation of these pathogens. Antimicrobial (bacteriostatic and bactericidal) and prebiotic algal ingredients could positively impact the gut health and delay or prevent the development of IBD.

2.2.1. Bacillus cereus

Bacillus cereus commonly found in soil poses several challenges in food production and safety. The spores of this Gram-positive, rod-shaped, facultative anaerobe that survive the food manufacturing process will be present in cereal products like breads as well as in dairy products like milk and cream and result in "ropiness" of such food products. This type of food spoilage caused by *B. cereus* accounts for 16–20% of the reported annual food poisoning incidences (Jessberger et al., 2020). Bioactive components from food ingredients including those from algae can counter the action of foodborne pathogens. In this context, micro and macroalgae extracts can be exploited for their antibacterial activities against *B. cereus* as there is some evidence that algal extracts can inhibit this pathogen. For example, the antibacterial activity of crude extracts obtained (using solvents like petroleum ether, chloroform, acetone, and ethanol) from the brown seaweed *Sargassum wightti* were assessed previously using the agar well diffusion, minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) methods. The crude petroleum ether extract that showed inhibitory activity against *B. cereus* (Venugopal et al., 2014). Furthermore, fucoxanthin, extracted with chloroform and methanol, from the seaweeds *Turbinaria triquetra, Ulva lactuca,* and *Laurencia obtusa* displayed inhibitory activity against *B. cereus* (Shannon et al., 2021).

2.2.2. Listeria innocua and Listeria monocytogenes

Listeria monocytogenes is a Gram-positive, facultative bacterium found often in food-processing facilities and ready-made meals. Miranda-Bautista et al. (2014) concluded that IBD patients are susceptible to more frequent and serious *L. monocytogenes* infection compared with the general population. *Listeria innocua* is a model organism for *L. monocytogenes* due to the challenges associated with carrying out large-scale experiments with the latter in research pilot plants (Mohan et al., 2019). Martelli et al. (2020) selected five species of seaweeds and microalgae that are already approved as foods, to examine the efficacy of the algal extracts *in vitro* using the agar well diffusion and in situ microbial challenge test towards *L. monocytogenes*. They identified a polyphenolic extract from *Himanthalia elongata* and an extract from *Arthrospira platensis*; while the former inhibited the growth of this bacterium the latter displayed the greatest zones of inhibition.

2.2.3. Escherichia coli

E. coli, one of the 30 members of the bacterial family *Enterobacteriaceae*, is a coliform bacterium and there are 6 types of *Escherichia* species (*E. adecaroxylate, E. blattae, E. fergusonii, E. hermannii* and *E. vulneris)*. It is a Gram-negative, non-spore-forming, facultative, anaerobic, rod-shaped, mesophilic bacterium. *E. coli* is often used as an indicator of food hygiene as it marks faecal contamination in foods and drinking water. The brown seaweeds such as *Ecklonia bicyclis*, *Laminaria japonica*, *Sargassum fusiforme* and *Undaria pinnatifida* contain baicalein (Vlaisavljević et al., 2021) that has antibacterial activities. Furthermore, phlorotannin extracts from the brown seaweeds, *Ascophyllum nodosum* and *Fucus serratus* were found to have excellent antibacterial activity against *E. coli* O157, *Salmonella agona*, and *Streptococcus suis* without harming pig intestinal cells (Ford et al., 2020).

2.2.4. Cronobacter (Enterobacter) sakazakii

Cronobacter sakazakii is a Gram-negative, rod-shaped, opportunistic pathogenic bacterium that can cause different diseases. Although it is found in infant formula and baby food, *C. sakazakii* is considered a threat to all age groups as it can cause different illnesses such as meningitis, bacteraemia, sepsis, and necrotizing enterocolitis. Several natural plant extracts exhibit antibacterial activity against *C. sakazakii* but the activity of algal extracts against this bacterium is yet to be demonstrated clearly (Polat Yemiş & Delaquis, 2020).

2.2.5. Salmonella enterica

S. enterica, a flagellate, Gram-negative bacterium which is present in all environments enters the digestive tract through contaminated food and water. Repeated exposures to *Salmonella* elevate endogenous neuraminidase activity, and the subsequent reduction in intestinal alkaline phosphatase reduces the ability of the intestine to detoxify the lipopolysaccharide endotoxin released by commensal bacteria (Yang et al., 2017). The linear (1 → 3)-β-glucans, proteins and glycosides in *Pavlova lutheri* and *P. gyrans* can serve as anti-adhesive agents because these compounds can act together and bind to *Salmonella enterica* sv. Typhimurium (Machado et al., 2020).

2.2.6. Campylobacter jejuni and Campylobacter concisus

Campylobacter are Gram-negative, mainly spiral-shaped bacteria and 17 species are reported under this genus. *Campylobacter jejuni* (subsp. *jejuni*), *C. concisus*, *C. coli*, *C. lari* and *C. upsaliensis* cause diseases in humans. *Campylobacter* can be found in food animals including shellfish, and they enter the intestine when we consume undercooked meat products, raw or contaminated milk and water. *C. concisus* with acquired zonula occludens toxin (zot) gene can cause a defect in intestinal barrier function and trigger the development of IBD (Zhang et al., 2014). Lactobacilli and bifidobacteria can competitively exclude *C. jejuni* because of their ability to produce acetic acid and lactic acid (Wagner et al., 2009). Phenolic compounds have antibacterial activity and such compounds in macroalgae should be tested for the antagonistic activity towards *Campylobacter*.

3. Panacea for intestinal inflammation

Commensal bacteria can impact the host immunity in multiple ways and can improve the host health through different mechanisms. Probiotic organisms like bifidobacteria and lactobacilli can be established in the intestine to regulate inflammatory responses that lead to pain and discomfort in IBD patients. The abundance of probiotic organisms in the intestine can be increased through the application of prebiotics such as oligosaccharides and polyphenols (e.g., phlorotannins) that are abundant in seaweeds. Such a strategy will also favour the growth of other beneficial bacteria or counter pathobionts or support intestinal homeostasis. Here, the aim is to discover the efficacy of single or multiple bacterial species (as probiotics) and bioactive components from algae (as prebiotics) for IBD treatment.

3.1. Probiotics to combat IBD

Probiotics are mostly derived from the natural microbiota of healthy organisms. They must have Generally Regarded As Safe (GRAS) status for human use and must survive the manufacturing process, which is a challenge as these bacteria are often derived from anaerobic environments. The most common probiotic bacteria are lactobacilli, lactococci, bifidobacteria, enterococci, streptococci as well as yeasts such as *Saccharomyces bouldarii.* To be clinically beneficial, their efficacy must be established through in-depth investigations because the intended effects may be elicited only by some strains. Probiotics as IBD prophylactics is conceived based on the role of intestinal bacteria in the pathogenesis of the disease (Gionchetti et al., 2006).

3.1.1. Lactobacilli, bifidobacteria, Streptococcus thermophilus, Bifidobacterium animalis and Enterococcus faecium

Lactobacillus acidophilus was found to regulate μ-opioid and cannaboid receptors in colonic epithelial cell lines and in the colonic epithelium in pre-treated rats and mice (Rousseaux et al., 2007), indicating their efficacy in reducing pain. Furthermore, *L. paracasei* was found to reduce abdominal pain and mucosal inflammation in an antibiotic-induced murine model of visceral hypersensitivity (Verdú et al., 2006). *L. reuterii* can also reduce diarrhoea in IBD patients (Verdú et al., 2006). Some *Lactobacillus* strains are effective in preserving the proteins at the tight and adherens junctions (Laval et al., 2015). *L. plantarum* was found to modulate the pro-inflammatory and anti-inflammatory cytokines favourably to control diseases (Zhao, Peng, et al., 2021). *Lactobacillus* GG was found to be capable of inducing and sustaining remission in the case of CD patients (Schultz et al., 2004). Consumption of *Lactobacillus reuteri*, *L. acidophilus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, and *B. animalis* ssp. *lactis*, once a day by both UC and CD patients indicated the therapeutic potential of the probiotics (Dore et al., 2020).

As for strategies that exploited the interaction of probiotics with prebiotics, intracolonic single-dose administration of *Bifidobacterium animalis* subsp. *lactis* and xyloglucan for 6 weeks helped in mucosal healing and resolving the colonic symptoms in UC patients (Bozkurt & Kara, 2020). Consumption of Symprove™ (Symprove Ltd, Farnham, Surrey UK) that contained *Lactobacillus rhamnosus* NCIMB 30174, *Lactobacillus plantarum* NCIMB 30173, *Lactobacillus acidophilus* NCIMB 30175 and *Enterococcus faecium* NCIMB 30176 in a water-based suspension of barley extract, every day in the morning in empty stomach, for 4 weeks helped in the reducing the fecal calprotectin in only UC patients, not in CD patients (Bjarnason et al., 2019). A recent review has informed the effect of probiotics (the species mentioned above) alone and in combination with prebiotics in IBD patients (Selvamani et al., 2022). Therefore, it is suggested that probiotic-prebiotic synergy should also be targeted to control intestinal inflammation.

3.2. Prebiotics for synergy with probiotics to combat IBD

Prebiotics can be defined as non-digestible fibres that resist digestion in the human small intestine and enter the colon where they are fermented by intestinal bacteria to impart health benefits that go above and beyond basic human nutrition (Slavin, 2013). Several studies have demonstrated the benefits of prebiotics for IBD. Oligosaccharides are the best-known prebiotics (Slavin, 2013). Consumption of dietary fibres including oligosaccharides can help maintain the abundance of dominant bacteria to establish a healthy intestinal microecosystem (Cheng et al., 2017). Inulin and oligofructose, lactulose and resistant starch were reported to meet all the characteristics of prebiotics, but galactooligosaccharides (GOS), transgalactooligosaccharides, polydextrose, wheat dextrin and acacia gum are also known to have certain prebiotic properties (Slavin, 2013). Other algal phytochemicals including fatty acids, pigments and polyphenols, and prebiotic feature of algal polysaccharides and polyphenols makes them malleable towards developing dietary interventional strategies to combat non communicable diseases. A variety of algal prebiotics may be employed to counter IBD; not only based on their antagonistic activity against pathogenic microbes but also their efficacy in stimulating the growth of beneficial organisms and bestowing an anti-inflammatory status to the immune cells.

3.2.1. Green seaweeds

Green seaweeds including *Ulva lactuca* and *U. intestinalis* contain the carbohydrates known as ulvans. These sulphated polysaccharides were shown to stimulate the growth of *Bifidobacterium* and *Lactobacillus* populations as well as promote the production of SCFAs including butyric and acetic acids (Seong et al., 2019). Ulvans represent 8–29% of the dry weight of green seaweeds. However, green seaweeds also contain other carbohydrates including sulphated galactans, xylans and mannans made of rhamnose, xylose, glucose, glucuronic acid, and sulphates that are not fully digested in the human gastrointestinal tract and therefore their potential as prebiotics must be exploited in future experiments. Selenized polysaccharides from *U. pertusa* suppressed the expression of TNF-α, interleukins (IL-1β, IL-6), and cyclooxygenase-2 mRNA mediated by the nuclear factor kappa B (NF-κB) pathway, indicating the potential of ulvans to influence the immune components to reduce intestinal inflammation in IBD patients (Wang et al., 2021). *Enteromorpha clathrata* derived mannose, rhamnose, galactose, glucuronic acid, glucose and xylose increased the abundance of *Akkermansia muciniphila*, *Bifidobacterium* spp., *Lactobacillus* spp. (Shang et al., 2018). *Enteromorpha compressa* (cellobiose, fructose, glucose and maltose) was able to increase the growth of *L. plantarum*, which produces plantaricins that inhibited the activity of gut pathogens such as *Staphylococcus aureus*, *Shigella flexneri*, *E. coli* and *Salmonella typhimurium* (Ajanth Praveen et al., 2019).

3.2.2. Brown seaweeds

Brown seaweeds contain alginate and sulphated fucoidans (structural polysaccharides) and laminarins (storage polysaccharides). The most abundant polysaccharide in brown seaweeds is alginate. Mannuronic acid (M-block) and guluronic acid (G-block) fractions (M1–M5 and G1–G5) of alginate exhibit antibacterial activity and the M oligomer fractions are potent than the G oligomers; mannuronic acid oligomers (molecular weight- 4.2 kDa) had better antibacterial activity against *E. coli*, *Salmonella paratyphi*, *Staphylococcus aureus*, and *B. subtilis* (Hu et al., 2005). Fucoidan is a sulphated polysaccharide and its immunomodulatory property is reported to be the reason behind the gastro-protective effect of fucoidan (Raghavendran et al., 2011). In addition, prebiotics such as fructooligosaccharides (FOS) and GOS were detected in *Laminaria gurjanovae* (Shevchenko et al., 2007). Laminarin, the key storage carbohydrate of brown macroalgae, is a β-glucan, and laminarin extracts from *Ascophyllum nodosum* and *Laminaria hyperborea* inhibited (2,2-diphenyl-1-picrylhydrazyl, DPPH, levels of 93.2% and 87.5%, respectively) the growth of *S. aureus*, *L. monocytogenes* (Gram--positive), *E. coli* and *Salmonella typhimurium* (Gram-negative) (Kadam et al., 2015). The anti-inflammatory property of phlorotannins, one of the polyphenolic compounds found exclusively in brown algae was reported, and polyphenol from *Ulva linza* was effective in countering 2,4, 6-trinitrobenzene sulfonic acid (TNBS)-induced colitis in mice (Kim et al., 2018). Eckol, another phlorotannin facilitated the growth of beneficial bacteria, recruited $CD11c^{+}$ dendritic cells and increased the expression of regenerating islet-derived 3 gamma (Reg3g) and protected the colon of colitis mice model (Zhu et al., 2020). Phlorotannins from *Fucus vesiculosus* was found to positively contribute to the maintenance of a healthy gastrointestinal condition (Catarino et al., 2021). Martelli and colleagues demonstrated that the growth of the probiotic cultures *L. casei, L. paracasei, L. rhamnosus* and *B. subtilis* was enhanced when the strains were grown in a *Himanthalia elongata* flour included at 5% of the growth media (Martelli et al., 2020).

3.2.3. Red seaweeds

Red seaweeds contain sulphated galactans such as agars, carrageenans and porphyrans, in addition to xylans and mannan as main structural polysaccharides. The main storage polysaccharide in these seaweeds is floridean starch. Red seaweeds also contain halocarbons like bromoform with known antimicrobial and carcinogenic properties. FOS from *Chondrus crispus* increased the abundance of *Bifidobacterium breve* but decreased the abundance of *Clostridium septicum* and *Streptococcus pneumonia*, leading to higher SCFA concentrations and elevated the levels of plasma immunoglobulins, IgA and IgG (Liu et al., 2015).

3.2.4. Microalgae

Microalgae contain polysaccharides such as β-glucans that can be utilized by bacteria that colonize the gastrointestinal tract of organisms. As mentioned for macroalgae, microalgae polysaccharides can also aid in the proliferation of *Lactobacillus* and *Bifidobacterium*, and a study has indicated that the outcome can prevent the disruption of epithelial barrier caused by proinflammatory cytokines like TNF-α (Hsieh et al., 2015). The cell counts of SCFA producers, namely bifidobacteria can be increased by fermenting whey and bovine milk with *Chlorella* because the bacteria utilizes their enzymes to modify many carbohydrates (Pokusaeva et al., 2011). Microalgae can be used to alter immune responses also, for example, *Chlorella* powder, (at concentrations >0.5%) decreased pro-inflammatory cytokines produced by human peripheral mononuclear cells (Hyrslova et al., 2021).

As for the ability of microalgae to prevent the growth of inflammation-inducing bacteria, a bloom of *Bilophila* after the intake of saturated milk fat can be thwarted through fructan interventions (Vandeputte et al., 2017). Sulphated polysaccharides derived from the microalga, *Porphyridium* sp. exhibits high antibacterial activity against *E. coli* (Netanel Liberman et al., 2016), and those from *Chlamydomonas reinhardtii* possess antibacterial and antibiofilm activity against *Klebsiella pneumoniae* (Vishwakarma et al., 2021). Extracts from *Euglena viridis* have antibacterial properties against virulent pathogens such as *Pseudomonas aeruginosa*, *P. fluorescens*, *Aeromonas hydrophila*, *Edwardsiella tarda*, *Vibrio alginolyticus*, *V. anguillarum* and *E. coli* (Das et al., 2005). *Chlorella* sp. and *Scenedesmus* sp. also exhibit antibactericidal activity against a number of bacteria, namely *K. pneumoniae*, *Enterococcus faecalis*, *E. coli*, *Staphylococcus aureus* and *B. subtilis* (Shaima et al., 2021). Chlorellin derived from *Chlorella* sp. is effective against both Gram-positive and Gram-negative bacteria (Pratt et al., 1944). Long-chain fatty acids from *Planktochlorella nurekis* has antibacterial activity similar to chlorellin from *Chlorella vulgaris*; the fatty acid mix can reduce the abundance of *E. coli*, *Salmonella enterica* var. Enteritidis, *S. enterica* var. Infantis, *Campylobacter jejuni*, and *Arcobacter butzleri*, but can stimulate the proliferation of *Lactobacillus johnsonii* (Cermak et al., 2015). The antimicrobial activity of total triglycerides and the PUFA docosapentaenoic acid in *Chaetoceros muelleri* can be exploited to keep *S. aureus*, *E. coli* and the yeast *Candida albicans* at bay (Mendiola et al., 2007). Thus, microalgae can perform as prebiotics and stimulate the growth of beneficial bacteria while arresting the proliferation of pathogenic microbes. More details about the bioactives that are thought to be responsible for the prebiotic potential of these strains are indicated in Table 1.

4. 'Biotic' approaches to tackle IBD

It is evident that alternate approaches are needed to tackle IBD, and a dual 'biotic' approach that takes advantage of prebiotics and probiotics to tackle microorganisms that are associated with the disease is proposed in this section. Pathobionts and foodborne infections are known to increase the risk of IBD development. A recent review has compiled the results from clinical trials conducted on IBD patients and indicated the positive effects of several probiotic strains including those of bifidobacteria and lactobacilli (Selvamani et al., 2022). In addition, the review also described FOS and inulin separately and their synergistic effects with these groups of bacteria. The above mentioned bacteria as well as *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* that are associated with pediatric CD (Lopez-Siles et al., 2018) and *Clostridium* cluster with good metabolic capabilities that are lower in both UC and CD patients (Ryan et al., 2020) can also be considered to prevent the proliferation of IBD-related pathobionts and strengthen the epithelial barrier function. Hence, testing the efficacy of selected probiotic strains to suppress the growth of both pathobionts and foodborne infection causers is a prerequisite to devise strategies to combat IBD. Food spoilage or pathogenic bacteria such as *B. cereus, Listeria innocua, E. coli, Pseudomonas* sp. and *Cronobacter sakazakii* can be investigated in *in vitro* studies to understand their interaction with probiotic organisms. In such

Table 1
Prebiotic potential of selected microalgae and suggested bioactivities for observed health benefits.

Bioactive compound with pre-indicated prebiotic potential	Microalga	Health benefits	References
Carbohydrates, proteins, omega-3 fatty acids	*Chlorella* sp., *Arthrospira platensis*[a]	Anti-cancer, reduction of gastric ulcers, control of hypertension, reduction of constipation	(De Jesus Raposo et al., 2015a, 2015b)
Carotenoids	*Arthrospira platensis*[a], *Dunaliella salina*	Anti-viral and antimicrobial activities and antioxidant benefits	(Chan et al., 2019; El-Baz et al., 2017; Lei, 2017)
Polysaccharides including xylose, galactose	*Porphyridium* sp.	Immunomodulatory and hypocholesterolaemic and anti-lipidaemic benefits	(Hayes et al., 2017; Lebrun et al., 2014)
Astaxanthin	*Haematococcus pluvialis*	Anti-inflammatory activity, immunity modulation, improved cardiovascular health, UV protection and anti-coagulant activity	Chan et al. (2019)
Different polysaccharides	*Chlorella* sp. *Phaeodactylum* sp. *Gyrodinium* sp.	Anti-inflammatory activity, immunity modulation	(Chandrarathna et al., 2020; Deremaux & Wils, 2017)
Likely to be chlorophylls, polysaccharides or omega-3 fatty acids[b]	*Arthrospira platensis*[a]	Demonstrated a prebiotic role with probiotic species *Lactococcus lactis* sp., *L. acidophilus*, *L. casei*, *L. bulgaricus, Bifidobacterium bifidum, B. longum, Streptococcus thermophilus*	(Chan et al., 2019; Patel et al., 2021)
Likely to be carbohydrates, omega-3 fatty acids[b]	*Chlorella* sp.	Demonstrated prebiotic role with probiotic bacteria, *Lactobacillus brevis,* and other lactic acid bacteria and *Bifidobacterium longum*	(Chan et al., 2019; Hyrslova et al., 2021; Patel et al., 2021)
Beta-carotene	*Dunaliella tertiolecta*	Promoted growth of the probiotic strain *Bacillus* sp. and improved disease resistance	Marques et al. (2006)
Xylose, Galactose	*Chlorococcum* sp.	Promoted growth of *Lactococcus lactis, L. bulgaricus, Bifidobacterium longum*	Nontando (2016)
Oligosaccharides	*Navicula* sp.	Promoted growth of *Lactobacillus sakei* and improved immunity and antioxidant effects	Reyes-Becerril et al. (2014)

[a] Cyanobacteria.
[b] Bioactivity not determined.

studies phenolic compounds from algae can be employed to find their effectiveness to counter the foodborne microorganisms. After performing studies employing model organisms the emphasis should be on clinical trials on patients with different IBD phenotypes.

Macro and microalgae-derived oligosacharrides that can be considered as prebiotics to counter IBD should have the following characteristics: i) must be resistant to gastric acids and hydrolysis by enzymes found in the upper gastrointestinal tract and must not be absorbed until it reaches the colon where certain bacteria can metabolise carbohydrates employing their enzymes to produce hydrogen, methane, carbon dioxide, SCFAs like acetate, propionate, butyrate and ii) must stimulate the growth or bioactivity of selected, beneficial intestinal bacteria such as bifidobacteria and lactobacilli that affects the host health positively. The general belief is that prebiotics impart a beneficial physiological effect, and this is achieved through the proliferation of beneficial bacteria. For example, in a study on pigs, seaweed extract (fucoidan and laminarin) was able to reduce the abundance of *S. typhimurium*, but GOS derived from lactose extracted from cow's milk that was able to increase the proliferation of *Lactobacillus* did not reduce the growth of pathogenic microorganisms (Bouwhuis et al., 2017). Another study has indicated that GOS (derived from lactose containing tri-, di, tetrasaccharides and pentose) and fucoidan from *Undaria pinnatifida* can increase the abundance of *L. casei* DM8121 and bile salt hydrolase activity of *Adlercreutzia* and *Oscillospira* (Chen et al., 2019). Feed containing FOS from chicory roots along with *Chondrus crispus* powder helped in the proliferation of *Bifidobacterium breve*, decreased the abundance of *Clostridium septicum* and *Streptococcus pneumonia*, increased the levels of acetic, propionic and butyric acids and elevated plasma immunoglobulins in rats (Liu et al., 2015). Furthermore, an *in vitro* human fecal fermentation study has pointed out the slow fermentation of laminarin and the ability of both laminarin and ulvan to selectively increase the abundance of beneficial bacteria such as bifidobacteria and lactobacilli (Seong et al., 2019). Eight-week administration of a mixture of *Enterococcus faecium*, *Lactobacillus plantarum*, *Streptococcus thermophilus*, *Bifidobacterium lactis*, *Lactobacillus acidophilus*, *Bifidobacterium longum* and FOS was able to positively affect the UC endoscopy scores and acute phase reactants of UC patients. Similarly other synbiotic strategies employed in six clinical trials were presented in the review by Selvamani et al. (2022).

Selection of seaweed and microalgae-derived oligosaccharides less than 3 kDa for use as prebiotics should be based on the ability of the oligosaccharides to inhibit pathogenic bacteria and their ability to stimulate growth of lactobacilli and bifidobacteria compared to the well characterised prebiotics GOS, FOS and mixtures of short chain oligosaccharides and inulin (Watson et al., 2013). Fig. 3 illustrates how the polysaccharides or polyphenols can help in the proliferation of specific bacteria in the intestine of humans.

Polysaccharides from seaweeds are known to have anticoagulant, anti-inflammatory, antibacterial, antioxidant and immune activities (Table 2). In addition, seaweeds are rich sources of secondary metabolites including polyphenols, peptides and other small molecules with documented health benefits. As detailed in section 3, seaweed bioactivities can be studied to understand their efficacy in stimulating the growth of beneficial bacteria and reduce the pro-inflammatory cytokines in the inflamed intestine of IBD patients. Several microalgae have demonstrated prebiotic potential (Table 2). Combining algae/their bioactive compounds with probiotic organisms can improve the viability of the probiotic organisms, reduce the growth of pathogenic bacteria, enhance antioxidant activity, improve intestinal adsorption (Patel et al., 2021); all these outcomes can improve host health or can alleviate the symptoms linked to health issues such as IBD. Microalgae can be employed (section 3.2.4) to increase the abundance of lactobacilli and bifidobacteria that can alleviate the issues of IBD. Combining microalgae with milk or other substrates can enhance their bioactivity. Fructans, inulin, β-glucans, sulphated polysaccharides and long-chain fatty acids from different microalgae, and extracts from *Chlorella* sp., *Scenedesmus* sp., *Chlamydomonas reinhardtii*, *Porphyridium* sp., *Euglena viridis*, *Aurantiochytrium limacinum* are effective against IBD-linked microbes and hence can be employed to treat the patients. Microalgae rich in xylan and galactose, astaxanthin, omega-3 fatty acids, and beta glucans should be screened extensively to understand their prebiotic potential.

5. Conclusion and future trends

A highly connected world and the desire to adopt a western lifestyle has brought in new diseases and challenges to developing nations where IBD is less prevalent. The impact on the quality of IBD patients' life and the adverse effects of the current inflammation-alleviation strategies indicate the necessity to find powerful dietary interventions to keep the rapid spread of IBD in check. To ensure a sustainable and healthy life without antibiotic resistance for Millennials, Generation Z and Generation Alpha, researchers should work together to develop diet-based therapeutic and preventative methods. Food habit-related malady such as IBD could be tackled by exploiting the power of probiotic microorganisms or bioactive substances from microalgae and macroalgae. Effective synbiotics that exploit both bioactive compounds from microalgae and macroalgae and ideal probiotic strains can be considered as a holistic route to relieve the IBD patients from their suffering. As our understanding of the importance of maintaining healthy gut microbial environment is evolving rapidly, the need to complement such knowledge with more information on the health benefits of macro- and microalgae and their derivatives as part of human food is far more relevant than ever before.

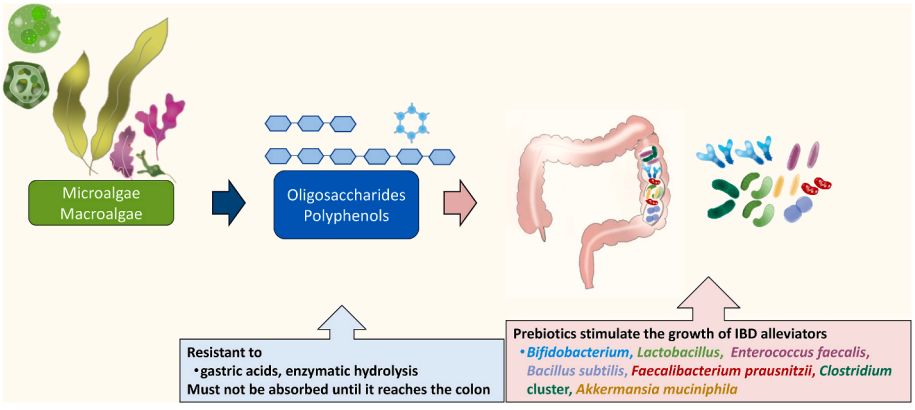

Fig. 3. Utilization of prebiotics to stimulate bacterial proliferation. Oligosaccharides and polyphenols from macroalgae and microalgae that have bactericidal and/or bacteriostatic ability can be employed as an alternative approach to treat IBD patients.

Table 2
Known prebiotics, including those derived from macro and microalgae and their prebiotic and antimicrobial effects.

Prebiotic component	Growth stimulatory effect on probiotic strains	Inhibitory effect on pathogenic strains	References
Agave inulin	*Actinobacteria* sp., *Bifidobacterium* sp.	*Lachnobacterium* sp., *Desulfovibrio* sp., *Ruminococcus* sp.	Holscher et al. (2015)
Alginate	Lactobacilli, Bifidobacteria		Wang et al. (2006)
Fractan	Bifidobacteria	*Bilophila* sp.	Vandeputte et al. (2017)
Fructooligosaccharide	*Lactobacillus* sp., *Bifidobacteria* sp., *Ruminococcus* sp., *Faecalibacterium* sp., *Oscillospira* sp., *Bifidobacterium* sp.	*Salmonella* sp., *Phascolarctobacterium* sp., *Enterobacter* sp., *Coprococcus* sp., *Turicibacter* sp.	Liu et al. (2017); Tandon et al. (2019)
Fucoidan	Lactic acid bacteria	Various pathogenic bacteria of relevance in animal nutrition	Lynch et al. (2010)
Galactooligosaccharides	Bifidobacteria, *Bacteroides* sp., *Atopobium* sp., Actinobacteria	*Bacteroides*	Davis et al. (2011); Vulevic et al. (2015)
Phlorotannin extracts from *Fucus vesiculosus* and *Ascophyllum nodosum*	Enhanced growth of *Enterococcus* sp.	*Escherichia coli* O157, *Salmonella agona*, and *Streptococcus suis*	Ford et al. (2020)
Oligosaccharides and polysaccharides from *Arthrospira* sp.	*Bifidobacterium lactis, Lactobacillus casei, L. acidophilus, Streptococcus thermophillus*	*Proteus vulgaris, Bacillus subtilis, B. pumulis*	Beheshtipour et al. (2013) Bhowmik et al. (2009)
Crude petroleum ether extracts of *Sargassum wightti*	Not examined	*Bacillus cereus*	Venugopal et al. (2014)
Polysaccharide extracts of *Pterocladia capillacea* and *Dictyopteris membranacea*	Not examined	*B. cereus* and *Staphylococcus aureus*	Abou Zeid et al. (2014)
Linear (1 → 3)-β-glucans, proteins and glycosides from *Pavlova lutheri* and *Pavlova gyrans*	Not examined	*Salmonella enterica* sv. Typhimurium	Machado et al. (2020)

Author contributions

VK, MH and DA: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing – original draft and review & editing.

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Ethics statement

This publication reflects only the authors' views. The Agency and the European Commission are not responsible for any use that may be made of the information contained in the review.

Data availability

No data was used for the research described in the article.

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