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Brown-Algae Polysaccharides as Active Constituents against Nonalcoholic Fatty Liver Disease

Authors
Zeinab El Rashed[1,2], Elena Grasselli[1], Hala Khalifeh[2], Laura Canesi[1], Ilaria Demori[1]

Affiliations
1 Department of Earth, Environmental and Life Sciences (DISTAV), University of Genoa, Genoa, Italy
2 Rammal Rammal Laboratory (ATAC group), Faculty of Sciences I, Lebanese University, Beirut, Lebanon

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Correspondence
Dr. Ilaria Demori, PhD
Department of Earth, Environmental and Life Sciences (DISTAV), University of Genoa
Corso Europa 26, 16132 Genoa, Italy
Phone: + 39 01 03 53 82 46, Fax: + 39 01 03 53 82 67
idemori@unige.it

ABSTRACT

Nonalcoholic fatty liver disease is a metabolic disorder characterized by lipid overloading in hepatocytes that can progress pathogenically and even end in hepatocellular carcinoma. Nonalcoholic fatty liver disease pharmacological treatment is still limited by unwanted side effects, whereas the use of food components with therapeutic potential is advisable. The culinary use of marine algae is traditional for some populations and reviving worldwide, with promising health outcomes due to the large number of bioactive compounds found in seaweeds. The present review focuses on brown-algae polysaccharides, particularly fucoidan, alginate, and laminarin, and summarizes the experimental evidence of their potential effects against nonalcoholic fatty liver disease onset and progression. *In vitro* and *in vivo* studies demonstrate that brown-algae polysaccharides exert beneficial actions on satiety feeling, caloric intake, fat absorption, and modulation of the gut microbiota, which could account for indirect effects on energy and lipid homeostasis, thus diminishing the fat overload in the liver. Specific effects against nonalcoholic fatty liver disease pathogenesis and worsening are also described and sustained by the antioxidant, anti-inflammatory, and antisteatotic properties of brown-algae polysaccharides. Further studies are required to clarify the mechanism of action of brown-algae polysaccharides on liver cells, to determine the composition and bioavailability of brown-algae polysaccharides present in different algal sources and to probe the clinical availability of these compounds in the form of algal foods, food supplements, and regulated therapeutics.

Introduction

Besides their traditional use in oriental cuisine and their unique nutritional properties, algae have recently gained interest due to their potential role as functional foods or nutraceuticals [1, 2]. The high presence of several bioactive compounds displaying antioxidant and anti-inflammatory properties points to candidate algae as a source of phytochemicals with beneficial effects against modern-age noncommunicable diseases, including cardiovascular disorders, cancer, autoimmunity, and neurodegenerative diseases, as well as metabolic impairments such as nonalcoholic fatty liver disease (NAFLD). Moreover, seaweeds contain peculiar polysaccharides that can act as beneficial alimentary fibers and regulate energy intake, nutrient absorption, and metabolic homeostasis [3].

In this work, we focus on brown-algae polysaccharides (BAPs), particularly fucoidan (FU), alginate (ALG), and laminarin (LAM), and review the experimental evidence of their potential effects against NAFLD onset and progression. A PubMed and BASE (Bielefeld Academic Search Engine) search was conducted by combining the terms “algae”, “seaweeds”, “polysaccharides”, “fucoidan”, “alginate”, and “NAFLD” to identify articles that have been published until the year 2019. Results from *in vitro* and *in vivo* studies are summarized and discussed in the next paragraphs, after a brief overview of NAFLD pathogenesis and current therapeutic strategies.

NAFLD: Mechanisms and Treatments

Unhealthy diet and lifestyle can lead to diverse metabolic disorders, including NAFLD, in which more than 5% of hepatocytes accumulate lipids in the form of cytosolic lipid droplets that contain mainly triglycerides (TGs). Despite being a benign and reversible condition at its first stages, NAFLD can progress to more severe pathologies such as nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and eventually hepatocellular carcinoma [4]. NAFLD pathogenesis and worsening are complex and sustained by the synergistic action of a variety of nutritional, environmental, metabolic, and hormonal factors that act as "multiple hits" on genetically predisposed subjects [5]. Starting from the initial "2 hits" hypothesis, which suggests that lipid accumulation sensitizes the liver to subsequent hits leading to inflammation and fibrogenesis, it has now become clear that different processes act concurrently and/or sequentially to determine different severities of the disease. Major hits include dietary and lifestyle factors, insulin resistance (IR), intestinal dysbiosis, lipotoxicity, oxidative stress, and inflammation.

First of all, fat accumulation may be due to a combination of i) increased *de novo* lipogenesis from a nonlipid source like carbohydrates, ii) increased free fatty acids (FFAs) due to excessive lipolysis or increased dietary fat intake, iii) reduced FFA oxidation, and iv) decreased secretion of TGs as very low-density lipoproteins [6].

At the cellular level, mitochondria, endoplasmic reticulum (ER), and peroxisomes all contribute to the development of oxidative stress and inflammation in a steatotic liver. FFA overload increases mitochondrial β-oxidation, which may impair the electron transport chain and raise electron leakage, thus lowering ATP synthase capacity and over-producing reactive oxygen species (ROS). Furthermore, lipid peroxidation leads to the formation of highly reactive aldehydes, such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal. Such byproducts have longer half-lives than ROS and can diffuse into the extracellular space to affect distant cells, thus amplifying the effects of oxidative stress. In the same way, FFA overload induces ER stress, characterized by unfolded and misfolded protein accumulation in the ER lumen, activating a specific signaling response known as the "unfolded protein response", which, in turn, induces the expression of pro-inflammatory genes and suppresses that of antioxidant enzymes. Moreover, peroxisomes, which are implicated in long-chain FFA oxidation, produce hydrogen peroxide as an end-product, thus providing an additional source of radicals [7, 8].

Lipids and lipid metabolites, as well as molecules associated with oxidative stress and hepatocellular damage, activate Kupffer cells, the liver-resident macrophages, to release pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, leading to inflammation and NAFLD worsening [9]. Moreover, activation of Kupffer cells leads to systemic IR, which is strictly associated with NAFLD and NASH, independently of body mass index and fat distribution [10, 11].

A new concept in NAFLD pathogenesis is the involvement of the gut-liver axis, which refers to the complex interactions between nutrition, gut microbiota, the intestinal barrier, and the liver [12]. According to this point of view, an unbalanced diet, especially if rich in fats and fructose, may impair the gut microbiota and the intestinal barrier functions, thus favoring metabolic endotoxemia, Kupffer cell activation, and systemic low-grade inflammation [13]. Microbiota-derived metabolites, namely short-chain fatty acids (SCFAs), are known to be both a source of energy, particularly for colonocytes, and signaling molecules able to interfere with the host metabolism at different levels, including the regulation of carbohydrates and lipid metabolism [14]. Moreover, different strains of gut bacteria are also able to produce neurotransmitters and neuropeptides that can interfere with the mechanism regulating energy homeostasis and food intake [15]. Interestingly, germ-free (GF) animals (raised in sterile conditions to avoid microbial colonization) appear to be resistant to diet-induced obesity, liver steatosis, and IR [13], suggesting that the gut microbiota affects energy harvest from food and energy storage in the host. Accordingly, microbial colonization of GF mice results in increased hepatic TG content. Moreover, when the donor for microbiota transplantation suffers from NAFLD, this phenotype is replicated in GF recipients. Particular microbial strains are associated with the NAFLD phenotype in mice, for example *Lachnospiraceae bacterium 609* and a relative of *Barnesiella intestinihominis* [16, 17].

To date, there is no specific pharmacological treatment approved for NAFLD, so the use of any drugs should be considered off-label, and the prescription of medicines should start from NASH patients after a careful analysis of the risk/benefit ratio [18]. In the past, anti-obesity drugs such as orlistat, sibutramine, and rimonabant have been used against NAFLD, but gastrointestinal and psychiatric adverse events led to therapy discontinuation or even market withdrawal [19].

Insulin sensitizers such as metformin have been used in NAFLD/NASH, revealing scarce efficacy on liver histology and lipid accumulation [20]. Agonists for the nuclear transcription factors peroxisome proliferator-activated receptors (PPARs), including fibrates, thiazolidinediones, and glitazars, are promising compounds due to their multiple actions on glucose and lipid metabolism, inflammation, and vascular control [21]. Pioglitazone proved to be beneficial in NASH, but observed side effects such as weight gain, bone fractures in women, bladder cancer, and congestive heart failure raise important concerns [18]. Pioglitazone has also been used in combination with vitamin E [22], which has also been proven beneficial for its high antioxidant capacity, but the safety of high doses (> 800 IU/day) and long-term treatment is still a matter of debate [23].

Administration of statins is common to control dyslipidemia and cardiovascular risk in NAFLD/NASH patients, even if the use of statins in subjects with liver diseases still raises some concerns regarding hepatotoxicity; therefore, statins should not be used in case of advanced cirrhosis and liver failure [18]. PUFA (polyunsaturated fatty acids) ω-3 could be a safer choice for the same purpose, but there is still a lack of data to support their use specifically in NAFLD/NASH [18, 24]. Innovative pharmacological therapies for NAFLD/NASH aim to target the different pathways and mechanisms underlying the pathogenesis of the disease. Drugs such as novel ligands for PPARs, farnesoid X receptor axis modulators, caspase inhibitors, antibiotics, and antifibrotic agents are currently been evaluated in international clinical trials [25]. The re-establishment of intestinal eubiosis for the better functionality

of the gut-liver axis through the use of probiotics also represents a promising therapeutic approach, especially for the unlikelihood of side effects [26].

Despite still being discordant about the use of drugs, all clinical practice guidelines recommend lifestyle modifications and weight loss as a mainstay of the strategies to prevent and reverse NAFLD/NASH [18, 24, 27]. Along with moderate physical activity and a reduction in caloric intake, several natural products and phytochemicals present in food display multiple bioactivities (such as anti-obesity, antisteatotic, antioxidant, anti-inflammatory, and prebiotic) able to counteract the multiple hits involved in NAFLD pathogenesis and worsening [28–30].

Beneficial Activities of BAPs against NAFLD

Brown algae include about 250 genera for a total of over 1500 species that exhibit a great variety of shapes and sizes [31]. They can be abundantly harvested, and some species (such as *Hijikia fusiforme, Laminaria japonica*, etc.) are cultivated on a large scale to be used as food or food additives [2]. As for plant cells, algal cells are surrounded by a polysaccharide-rich cell wall. However, BAPs exhibit some unique structural features, such as the presence of sulfate, fucose, and uronic acid, that differentiate them from the polysaccharides of terrestrial plants [32]. This seems to be related to marine algae adaptation to a high salt environment: as an example, sulfated polysaccharides facilitate water retention in extracellular matrices, thus preventing desiccation in low tide conditions [33]. The most represented sulfated polysaccharide in brown algae is FU, but major BAPs also include ALG and LAM. Structural BAP diversity can be appreciated among different algal species or even within the same species, notably depending on the environment, seasonal variations, and reproductive status of the organism [34].

Evidence indicates that BAPs can exert antisteatotic effects and prevent NAFLD onset and progression through different mechanisms, acting on the multiple "hits" that sustain the development of the disease [5]. Indirect effects can be mainly ascribed to the role of BAPs as dietary fibers, able to modulate energy intake and counteract obesity and related dysmetabolism [35]. Moreover, BAPs can be beneficial for the gut microbiota, thus ameliorating the gut-liver axis functionality [36]. More direct antisteatotic actions addressed to the regulation of hepatic lipid metabolism and liver functions might be related to the antioxidant and anti-inflammatory activities demonstrated for different BAPs in NAFLD experimental models [2, 37, 38]. The next paragraphs and ▶ **Table 1** describe the results obtained for FU, ALG, and LAM.

Fucoidan

FU is a fucose-rich sulfated polysaccharide very abundant in the cell wall of Phaeophyta but also found in marine invertebrates, such as in the jelly coat from sea urchin eggs and in the sea cucumber body wall [39]. More recently, FU has been isolated also in terrestrial plants such as *Eucalyptus globulus* [40]. FU is characterized by a backbone of α-(1–3)-linked fucose units or α-(1–3)- and α-(1,4)-alternating linked fucose residues (▶ **Fig. 1 a**); yet, the structures of FU from different sources have not been completely defined. FU is found in many edible brown seaweeds, such as *Cladosiphon okamuranus, L. japonica*, and *Undaria pinnatifida* [41] The main commercially available form is extracted from *Fucus vesiculosus* and is composed of 44% fucose and 26% sulfate [42].

The literature about the potential clinical applications of FU is extremely rich, due to its wide spectrum of biological activities ranging from anticoagulant/antithrombotic, antiviral, immune-potentiating, angiogenic, anticancer, antidiabetic, antioxidant, and anti-inflammatory [43].

Orally administered FU can be significantly absorbed and detected also in liver cells, as demonstrated in 2014 by Nagamine et al. [44]. FU purified from *C. okamuranus* was transported across Caco-2 cells in a dose-dependent manner. The intestinal absorption was confirmed *in vivo* in rats fed 2% FUs for 1 or 2 wk: immunohistochemistry assays revealed the presence of FU in jejunal epithelial cells, mononuclear cells in the jejunal lamina propria, and sinusoidal nonparenchymal cells in the liver.

FU is the most extensively studied BAP in experimental models of NAFLD. High-fat diet (HFD)-fed rats represent a widely used model to mimic human NAFLD [45]. In these animals, intrahepatic lipid accumulation, increases in liver transaminase activities, dyslipidemia, and signs of oxidative stress and inflammation are induced [46]. In rats fed an HFD for 12 wk, FU administered orally (100 mg/kg) for the last 4 wk was able to reduce body weight index, liver index, hepatic fat accumulation, ALT and AST activities, serum total cholesterol (TC) and TGs, and fasting glucose levels as compared to NAFLD group (HFD only) [47]. Moreover, FU treatment decreased MDA and nitric oxide (NO) hepatic levels, whereas those of glutathione (GSH) were increased. This was accompanied also by an anti-inflammatory effect of FU that downregulated the expression of hepatic inflammatory cytokines (IL-1β, TNF-α), and matrix metalloproteinase 2 (MMP-2). Thus, FU could alleviate NAFLD by ameliorating inflammation, oxidative stress, and lipid metabolism [47].

Another *in vivo* study employed apolipoprotein E-deficient mice that were fed an HFD supplemented with either 1% or 5% FU for 12 wk [48]. The antisteatotic action of FU was confirmed, since FU treatment inhibited body weight gain and reduced liver and white adipose tissue weight, blood lipid, TC, TGs, nonhigh-density lipoprotein cholesterol (nonHDL-C), and glucose levels, as compared to HFD-mice. On the other hand, plasma lipoprotein lipase (LPL) activity and HDL-C were increased. Moreover, this study investigated the effects of FU on the expression of genes regulating lipid metabolism. At the hepatic level, FU treatment suppressed the expression of genes involved in lipogenesis, such as sterol regulatory element binding protein 1 (SREBP-1), cytochrome P450, family 7, subfamily a-1 (Cyp7a1), and cytochrome P450, family 8, subfamily b-1 (Cyp8b1). On the other hand, the expression of genes implicated in FA transport and oxidation, like PPARα and fatty acid-binding protein 1 (FABP-1) was upregulated. These results indicated that in NAFLD models, FU administration activated the pathways involved in FA oxidation rather than in their accumulation [48].

This indication appeared to be confirmed by Park et al. [49], who used the model of poloxamer-407 (P407)-induced hyperlipidemic mice (injected intraperitoneally with a single 250 mg/kg dose of P407). FU from *F. vesiculosus* (10, 30, and 50 mg/kg) was administered intraperitoneally to mice 2 h after P407, and de-

▶ **Table 1** Reported activities of BAPs in experimental models of NAFLD/NASH.

BAP, source	Model system	Concentration	Reported activities	Conclusions	Ref. No.
FU, *Laminaria japonica, Ascophyllum nodosum*	16-wk HFD-fed rats	200 mg/kg	↓: body weight gain, liver weight and lipid content, serum TC, TGs, TNF-α, IL-1β, MCP-1. ↑: growth of *A. muciniphila* and SCFA-producer strains in the gut microbiota.	FU is a functional food beneficial for metabolic diseases. The therapeutic effects could be exerted through modulation of the gut microbiota.	[36]
FU, *Fucus vesiculosus*	12-wk HFD-fed rats	100 mg/kg for the last 4 wks	↓: body weight index, liver index, hepatic fat content, ALT, AST, TC, TGs, fasting glucose, MDA and NO hepatic levels, hepatic expression of IL-1β, TNF-α and MMP-2. ↑: GSH.	FU ameliorates the development of HFD-induced NAFLD due to its hypolipidemic, insulin sensitizing, antioxidant, and anti-inflammatory effects.	[47]
FU, *Cladosiphon okamuranus*	12-wk HFD-fed apolipoprotein E-deficient mice	1–5% of diet	↓: body weight index, liver and white adipose tissue weight, TC, TGs, non-HDL-C, expression of SREBP-1, Cyp7a1, CYP450 and Cyp8b1. ↑: HDL-C, expression of PPARα and FABP-1.	Antidyslipidemic and anti-atherosclerotic effects by inducing LPL activity and inhibiting the effects of inflammation and oxidative stress.	[48]
FU, *Fucus vesiculosus*	P407-induced hyperlipidemic mice	10 mg/kg	↓: TC, TGs, expression of HMG-CoA reductase, FAS, ACC, and SREBP-2.	FU improves serum lipid levels by regulating the expression of key enzymes of cholesterol and triglyceride syntheses in the liver.	[49]
	HepG2 cells	100 µg/mL			
FU, *Laminaria japonica*	*db/db* mice	40 and 80 mg/kg	↓: superoxide production and lipid peroxidation; PGC1α. ↑: CAT and SOD activities, SIRT1 and AMPK.	FU prevents lipotoxicity-related oxidative stress and inflammation, thus providing a potential supplementary treatment for obesity/diabetes-induced NAFLD.	[53]
	PA-treated HepG2 cells	30 µg/mL			
FU, *Sargassum pallidum*	IR-HepG2 cells	5–50 mg/L	↓: intracellular TG, IR. ↑: Akt/GSK-3β and AMPK.	IR attenuation by targeting Akt/GSK-3β and AMPK pathways.	[54]
ALG, different sources	Human and animal studies	–	Satiating effects, inhibition of fat digestion and absorption.	ALG is anti-obesity agents, beneficial for obesity-related metabolic disorders including NAFLD.	[35], [57], and refs. therein
SA, commercial (Acatris, Bunschoten)	Pigs	5% of diet	↑: SCFA-producer strains in the gut microbiota.	Beneficial effects on the gut-liver axis.	[59]
SA, commercial (Kaigen Pharma)	MCD-fed mice	5% of diet	↓: villus shortening and damage, endotoxemia, hepatic lipid overload and inflammation. ↑: intestinal mucus production.	SA prevents hepatic inflammation and fatty degeneration by maintaining the intestinal barrier function.	[60]
SA, commercial (Kaigen Pharma)	MSG-treated mice	5% of diet	↓: body weight gain and liver weight, hepatic ballooning, steatosis, and inflammation; FAS and SREBP1c expression, TNF-α, IL-1β, F4/80, and CCL2; DEN-induced tumorigenesis. ↑: PPARα, CAT, GPx expression.	SA may have ability to suppress steatosis-related carcinogenesis in the liver of obese and diabetic subjects	[61]
LAM, commercial (Sigma-Aldrich)	4-wk HFD-fed mice	1% LAM-supplemented water	↓: Firmicutes. ↑: Bacteroides, carbohydrate active enzymes.	LAM reduces the adverse effects of HFD by shifting the gut microbiota towards a higher energy metabolism.	[64]

cont.

▶ **Table 1** *Continued*

BAP, source	Model system	Concentration	Reported activities	Conclusions	Ref. No.
LAM, commercial (Sigma-Aldrich)	4-wk HFD-fed mice	1 g/kg of LAM every 2 days	↓: body weight gain, fat deposition, blood glucose level. ↑: glucose tolerance, GLP-1 intestinal secretion.	LAM inhibits food intake, improves glucose homeostasis, and chronically exhibits anti-obesity functions associated with GLP-1 secretion.	[65]
LAM, commercial (Goëmar)	Rats	5–10% of diet	↓: LPS-induced ALT, AST, LDH, nitrite, TNF-α, liver monocytes/neutrophils. ↑: Kupffer cells.	LAM is a potential therapeutic agent in the oral treatment of hepatic inflammation.	[66]
LAM, *Laminaria japonica*	Hepa 1–6 tumor-bearing mice	400–1200 mg/kg	↓: tumor growth.	LAM is a promising therapeutic agent against NAFLD/NASH worsening toward hepatocellular carcinoma.	[67]
	Bel-7404 and HepG2 cells	5–45 mg/mL			

creased serum TC and TG levels in a dose-dependent manner. In the liver of P407-mice, FU downregulated the expression of key enzymes of cholesterol and TG syntheses [HMG-CoA reductase, fatty acid synthase (FAS), and acetyl-CoA carboxylase (ACC)] [49].

As aforementioned, a more recently recognized mechanism to achieve benefits against NAFLD is the modulation of gut microbiota [12, 13]. The main determinant of the gut microbiota composition is diet, and it is known that obesity is associated with differences in microbial populations at the phylum level, with less overall diversity [50]. In this regard, Shang et al. [36] showed that in mice, HFD feeding decreased bacterial richness and lead to dysbiosis. FUs purified from *L. japonica* or *Ascophyllum nodosum* were administered (200 mg/kg) to these mice. Besides the confirmation of the hepatoprotective, anti-inflammatory, and hypolipidemic actions, the authors were able to demonstrate that FU ameliorated gut dysbiosis by promoting the growth of benign microbes, including *Akkermansia muciniphila*, whose abundance has been inversely associated with obesity and diabetes [51, 52], and SCFA-producer strains, such as Alloprevotella, Blautia, and Bacteroides [36].

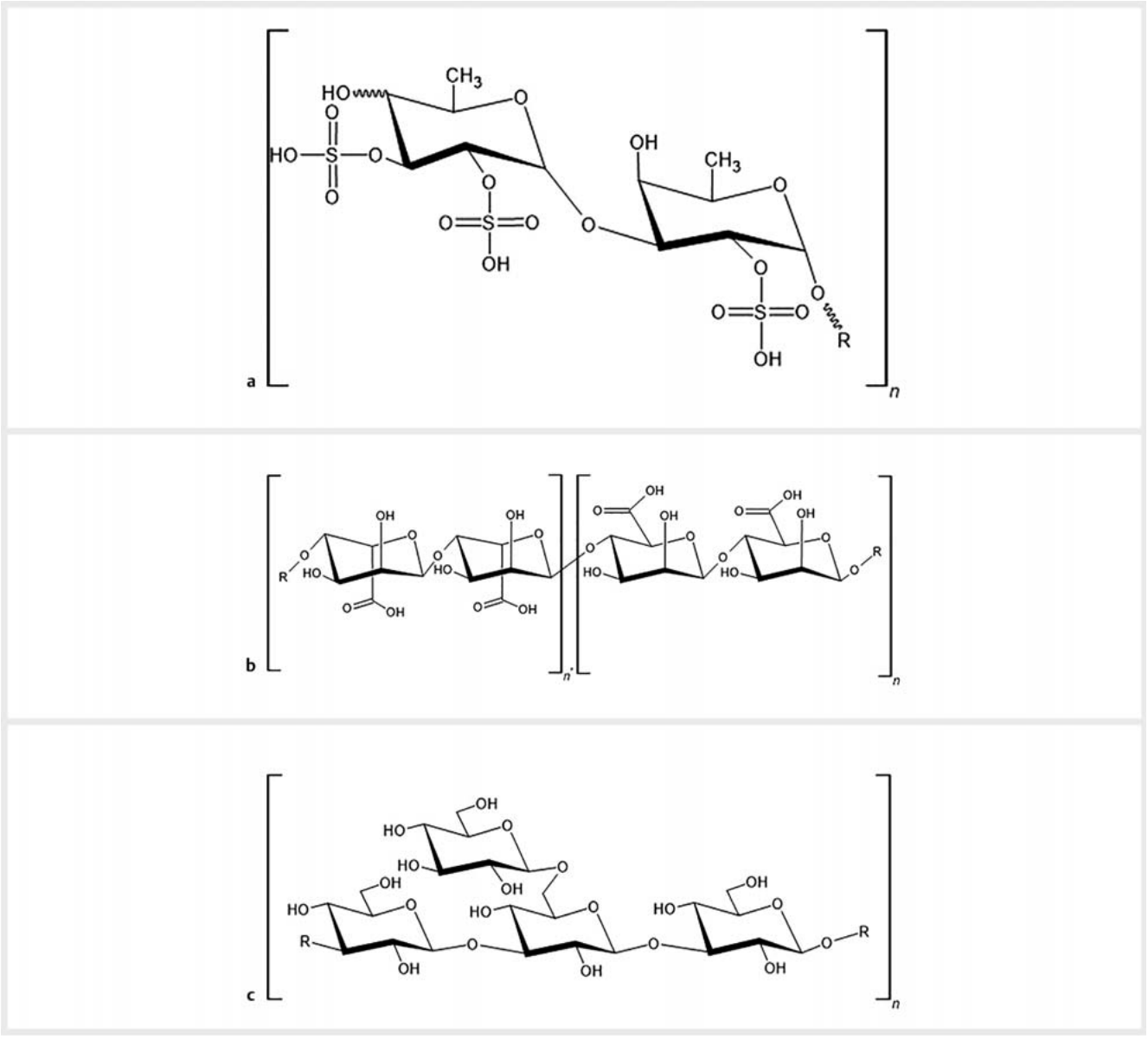
Besides the use of dietary patterns, genetic models are frequently employed to study NAFLD. In 2018, Zheng et al. [53] investigated the therapeutic potential of FU purified from *L. japonica* for NAFLD associated with obesity and type 2 diabetes. For this approach, *db/db* mice were treated with FU at different concentrations (40 and 80 mg/kg) daily for 7 wk. Also in this model, FU exhibited antisteatotic, hypolipidemic, and anti-inflammatory effects. Oxidative stress was prevented by suppressing superoxide production and lipid peroxidation, and the activities of antioxidant enzymes such as catalase (CAT) and superoxide dismutase (SOD) were increased. The authors also demonstrated the modulation of SIRT1/AMPK/PGC1α signaling: sirtuin 1 (SIRT1) and AMP-activated protein kinase (AMPK) were downregulated in *db/db* mice with NAFLD, while PPARγ coactivator 1α (PGC1α) was upregulated; however, these effects were reversed by FU treatment. The latter results were confirmed by using an *in vitro* model of NAFLD, consisting in HepG2 cells treated with palmitic acid (PA), which were exposed to 30 µg/mL FU for 24 h [53].

HepG2 cells were also used by Park et al. [49]. In their model, the cells were incubated for 24 h with human lipoprotein deficient serum to increase the mevalonate pathway, and with FU concentrations up to 100 µg/mL. Confirming their *in vivo* results, they found that FU downregulated the expression of key enzymes of cholesterol and TG syntheses [49]. More recently, He et al. [54] employed HepG2 cells to test the effects of FU isolated from *Sargassum pallidum* and combined with deep sea water (DSW). Results indicated that in HepG2 cells treated for 24 h with high glucose, FU (concentration range: 5–500 mg/mL) and DSW, the intracellular TG content was decreased, and IR was attenuated due to phosphorylative signaling in Akt/GSK-3β and AMPK pathways [54].

Alginate

ALG is another type of negatively charged polysaccharide isolated from brown algal cell wall, as well as from some bacterial strains. ALG is a linear biopolymer that consists of 1,4-linked β-D-mannuronic acid (M) and 1,4 α-L-guluronic acid (G) residues arranged in homogenous (GG/MM) or heterogeneous (MG) block-like patterns (▶ **Fig. 1 b**). The well-known physical properties of ALG, such as viscosity and gel-forming, and its biological potentials are determined by molecular weight, M/G ratio and distribution, temperature, environmental pH, and extraction method [55]. The nontoxic and biodegradable ALG has gained great importance due to its several applications in food industry, as gelling and thickening agent, in dermatological and cosmetic preparations, and in textile industry. Furthermore, ALG is pharmaceutically used due to its antibacterial, antidiabetic, antitumor, and anti-oxidant potentials [56].

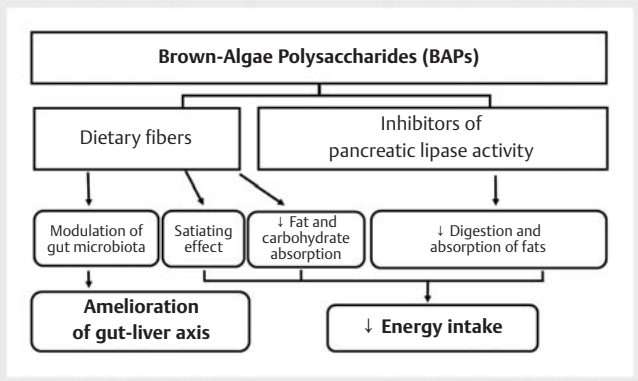
ALG is less explored than FU for the possible effects against NAFLD. However, just because of its gelling and thickening properties, ALG can increase satiation through gastric stretching action, while lowering down the absorption of fats, sugars, and excess calories, which is a must in NAFLD therapy and prevention



▶ **Fig. 1** Basic chemical structures of FU (**a**), ALG (**b**), and LAM (**c**).

strategies. Another indirect effect of ALG against NAFLD is related to its inhibitory activity on pancreatic lipase, which is one of the main targets for anti-obesity drugs. The role of ALG as a satiation molecule and anti-obesity agent has been extensively reviewed elsewhere [35, 57]. Nevertheless, satiation is not just volumetric (i.e., due to the mechanical action of food on gastric and intestinal distension), and satiety feelings are also highly dependent on the gut microbiota and SCFAs production, since these metabolites are of great importance for the development and functions of enteroendocrine cells producing intestinal satiation peptides such as cholecystokinin and glucagon-like peptide 1 (GLP-1) [58]. In this context, it is of interest the demonstration that ALG can directly increase the abundance of some genera known as SCFA producers (i.e., *Roseburia, Ruminococcus, Lachnospira*) in the gut microbiota of growing pigs [59].

The ability of ALG to modulate the gut microbiota is beneficial against NAFLD because it can help maintain a functional gut-liver axis, which leads to liver protection from lipid accumulation and inflammation. This topic has been addressed in a recent study by Kawauchi et al. [60], who considered the involvement of an impaired intestinal barrier in the pathogenesis of NAFLD/NASH. In this study, the methionine- and choline-deficient (MCD) diet, which is the most widely used model of NAFLD/NASH in mice, increased lipid accumulation and inflammation in the liver, enhanced the hepatic mRNA expression of TNF-α and collagen 1α1, and induced macrophage infiltration. In the small intestine of the MCD-mice, villus shortening, disruption of tight junctions, depletion of mucus production, and macrophage infiltration were observed. Sodium alginate (SA), mixed with the standard diet at a concentration of 5%, improved villus damage and increased mu-



▶ **Fig. 2** Indirect anti-steatotic actions of BAPs. BAPs can act as dietary fibers that increase satiety and decrease fat and carbohydrate absorption, leading to lower total energy intake. BAPs can be metabolized by the gut microbiota, thus improving intestinal health, intestinal barrier integrity, and a physiological function for the gut-liver axis, which plays a crucial role in NAFLD onset and development. Moreover, BAPs can act as inhibitors of pancreatic lipase activity, resulting in lowered energy intake and fat delivering to the liver.

cus production, which in turn limited the concentration of bacterial toxins in the portal vein, thus preventing hepatic lipid overload and inflammation [60].

Five percent SA mixed with basal diet was also administered for 16 wk to monosodium glutamate (MSG)-treated mice showing obesity, diabetes, and NASH-like histopathological changes (steatosis, inflammation, and hepatocyte ballooning). SA inhibited body weight gain, reduced liver weight, and improved liver histology. Moreover, SA suppressed the expression of lipogenic genes such as FAS and SREBP1c, as well as inflammatory markers like TNF-α, IL-1β, F4/80, and CCL2. PPARα, a transcription factor implicated in FA oxidation, was overexpressed under SA treatment, as well as the antioxidant enzymes CAT and glutathione peroxidase (GPx) [61]. In the same mice, SA significantly reduced the incidence of hepatic premalignant and neoplastic lesions induced by intraperitoneal injection of diethylnitrosamine (DEN100 mg/kg).

Laminarin

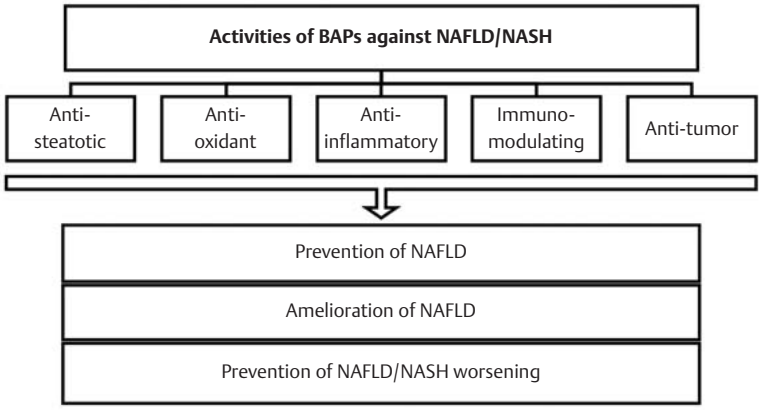
LAM is a low molecular weight polysaccharide (approximately 5 kDa), composed of (1,3)-b-D-glucan (▶ **Fig. 1 c**) and showing a variety of biofunctional properties [62, 63]. However, compared to FU and ALG, there are fewer studies that link LAM actions to NAFLD. Nguyen et al. [64] administered 1% LAM-supplemented water to mice on an HFD for 4 wk and reported significant changes in the gut microbiota (less Firmicutes, more Bacteroides and carbohydrate active enzymes) that could enhance energy metabolism, counteract obesity, and reduce obesity-related dysmetabolism. The anti-obesity effect of LAM in HFD-fed mice was confirmed by Yang et al. [65], who demonstrated that intragastric administration of 1 g/kg of LAM every 2 days for 4 wk decreased HFD-induced body weight gain and fat deposition. Moreover, glucose homeostasis was improved by the induction of GLP-1 intestinal secretion, which in turn stimulated insulin secretion and suppressed food intake [65]. In these 2 studies, no data are presented on the state of the liver in HFD and LAM-treated mice. However, hepatoprotective effects of LAM have been described in other models. For example, Neyrinck et al., [66] showed that in rats, a standard diet supplemented with LAM for 25 days (5% for the first 4 days followed by 10% for the next 21 days) prevented the effects of an intraperitoneal injection of *Escherichia coli* LPS (10 mg/kg). Serum levels of ALT, AST, lactate dehydrogenase (LDH), nitrite, and TNF-α were lower in LAM-treated compared to untreated rats. Within the liver, monocytes/neutrophils were decreased, whereas macrophages (Kupffer cells) were increased, so the authors proposed that the hepatoprotective effect of LAM was mediated through immune response modulation [66]. Recently, Tian et al. [67] demonstrated that LAM from *L. japonica* inhibited hepatocellular carcinoma both *in vitro* (Bel-7404 and HepG2 cells treated with 5 to 45 mg/mL LAM) and *in vivo* (Hepa 1–6 tumor-bearing mice injected with 400, 800, and 1200 mg/kg LAM).

Discussion

NAFLD is a global burden recognized as the leading cause of more severe liver diseases. There is an urgent need to find new, effective, safe, and easy-to-follow preventive and therapeutic strategies [68]. We searched the literature to explore whether polysaccharides contained in the cell wall of brown seaweeds could be considered as active constituents against NAFLD. Even if still limited in number, we found studies presenting concordant results obtained in different NAFLD/NASH models, both *in vitro* and *in vivo* (▶ **Table 1**). Most of the data regard FU and ALG. LAM is less explored in specific relation to NAFLD, nevertheless, the anti-obesity and hepatoprotective properties that have been demonstrated are in accordance with the results obtained with FU and ALG.

As summarized in ▶ **Fig. 2**, BAPs, particularly ALG, modulate satiety, fat absorption, and energy intake, thus proving beneficial for decreasing the total amount of calories and lipids being delivered to the liver. Moreover, BAPs are dietary fibers that are metabolized by the intestinal microbiota, which is now recognized as an important player in NAFLD onset and progression, through the involvement of the gut-liver axis [12, 13]. Therefore, *in vivo* results obtained by using dietary or genetic models of NAFLD could be due to the absorbed portion of the polysaccharides as well as to the actions of microbiota metabolites, such as SCFAs, released upon BAP metabolism by intestinal bacteria. The contribution of the gut microbiota to the biological activities of BAPs must be taken into account to better understand their mechanism of action and the possibility to use them as therapeutics, together with other dietary factors and integration with prebiotics and probiotics that can help maintain the integrity of the intestinal barrier. Studies must keep on going in this emerging field, which requires new experimental approaches.

As summarized in ▶ **Fig. 3**, experimental models of NAFLD/NASH provided evidence for a specific action of BAPs on hepatic steatosis and inflammation (see also ▶ **Table 1**). BAPs regulate the expression of several genes involved in hepatic lipid homeostasis: lipogenic pathways are decreased, while lipid catabolism is stimulated, thus resulting in antisteatotic and lipid-lowering ef-



▶ **Fig. 3** Activities of BAPs against NAFLD/NASH. *In vitro* and *in vivo* studies demonstrated several bioactivities for BAPs that can lead to hepatoprotective effects beneficial against NAFLD onset and progression. See also ▶ **Table 1**.

fects. Moreover, antioxidant, anti-inflammatory, immune-modulating, and antitumor actions have been described. The wide spectrum of BAP bioactivities suggests that such compounds can simultaneously counteract the multiple hits that trigger NAFLD pathogenesis and worsening towards higher severity grades of liver diseases.

Most of the specific antisteatotic actions of BAPs are ascribed to FU, which proved to be effective also in *in vitro* models of steatotic liver cells, thus suggesting a possible role of this polysaccharide directly on hepatocyte functions. Interestingly, FU can be extracted also from sea cucumbers and, as recently reported, from the leaves of *E. globulus*. However, algal sources are more advantageous in terms of costs and sustainability. Algae are a renewable resource that can be harvested or easily cultivated in high volumes [2], whereas wild sea cucumbers are heavily overexploited and expensive. Moreover, the extraction yield of FU from *U. pinnatifida* can increase up to 16% w/w as the plant matures [69]. Conversely, the yield of FU from different species of sea cucumbers ranges approximately from 2.5 to 3.8% w/w [70], and from *E. globulus* leaves is even less (2.1% w/w) [40].

Algae are already part of the diet of coastal populations in most parts of the world, and the global curiosity in oriental cuisine is increasing their consumption worldwide. Medical doctors and health care providers could take advantage of these arguments in the attempt to engage their patients in following a healthy and varied diet, which is a cornerstone in NAFLD prevention and therapy.

Even if the results obtained in experimental settings look promising, several points arise when considering the possibility of using BAPs as regulated therapeutics. In this case, the sources and the compounds should be well defined, and the extraction methods should be standardized and reproducible. However, the chemical composition of the algal cell wall, and thus the relative abundance of different types of polysaccharides, can greatly vary not only among the different species but also within the same species with respect to growth environment, harvest season, and reproductive status of the organism. When considering the possibility to extract and purify the different BAPs to be used as food supplements or medicaments, it is obvious that the extraction method can have a great impact on the yield and purity of the final product. On the other hand, when consuming edible algae, food preparation methods can also dramatically influence the potential effects of algal bioactive compounds and polysaccharides [71]. Moreover, the bioavailability of the different BAP fractions should be quantified in the different experimental and clinical settings, knowing that their absorption is quite low when administered orally. Conversely, unabsorbed BAPs might be differently metabolized by diverse arrays of gut microbiota enzymes, which varies a lot among the different human populations, basically concerning the diversity in food habits [72].

Concluding Remarks

The use of algal food in the context of a healthy and varied diet is advisable for NAFLD patients to help counteract obesity and increase the intake of antioxidant and anti-inflammatory constituents without risks. In our opinion, the potentiality of BAPs against NAFLD/NASH, which was demonstrated in experimental settings, deserves attention and further studies up to randomized clinical trials, which are still missing at this stage. Data from different studies and referring to *in vitro* and *in vivo* models are consistent and indicate an action on the regulation of genes involved in hepatic lipid homeostasis. From a pharmacological point of view, the most effective BAPs, their doses, timings, and route of administration, and the mechanism of action need to be identified, without forgetting to pay attention to possible side effects.

Contributors' Statement

ZER, LC and ID conceived the study; ZER performed literature search; ZER, EG and HK wrote the initial draft; LC and ID revised the draft and prepared the final version of the manuscript.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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