An Overview Brown Macroalgae Extract Against Fatty Liver Disease Caused by Metabolic Dysfunction: Animal Models and Evidence in Human Trials

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is estimated to impact between 13% and 32% of the global population. NAFLD has been more clearly described as having 5% or more hepatic steatosis without hepatocellular damage. Hepatic steatosis or the buildup of extra adipose tissue in the liver is a condition inducing NAFLD. The disease development of NAFLD was also known as nonalcoholic steatohepatitis which characterized by inflammatory changes that can lead to progressive liver injury, cirrhosis, and hepatocellular carcinoma. Some species of brown algae were reported and proven to content phytocomplex with polysaccharides, phlorotannins and other polyphenols, and sulfolipids as discussed. The mechanisms of action underlying the preventative effects of brown algae on NAFLD have been the subject of very few investigations. However, the ideal conditions for determining the potential health benefits that these algae may have cannot be established. Moreover, the advantageous benefits of algae reported in rodents must also be proven in humans in future studies and investigations. The aim of this review is to provide scientific information on the therapeutic benefits of brown algae on fatty liver in preclinical and clinical studies, along with the mechanisms of action involved.

Keywords: Nonalcoholic fatty liver disease, brown macroalgae**,** fatty liver disease, nonalcoholic steatohepatitis, NAFLD

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) has become the most common cause of chronic liver disease worldwide, with an increased risk of morbidity and mortality associated with liver disorders and an increased risk of type 2 diabetes (T2D), obesity, and cardiovascular disease (Sanyal et al. 2021; Younossi 2019; Younossi et al. 2019). NAFLD commonly begins with excessive accumulation of lipids or more than 5% in the liver without drug intervention or excessive consumption of alcoholic foods, and develops into a wide spectrum of liver pathophysiology and starts from simple to non-alcoholic steatosis (NASH), hepatic fibrosis, cirrhosis and irreversible heaptocellular carcinoma (Chen 2020). Such improvements are often associated with dramatic lifestyle changes. NAFLD was also reported to affect around 1.7 billion people worldwide with men contributing 30-40% and women 15-20% (Brunt et al. 2015). The term "NAFLD" was replaced by internal medicine specialists as metabolic-associated fatty liver disease (dysfunction) in 2020 to further emphasize the pathogenic relevance of metabolic dysfunction (Eslam et al. 2020; Zheng et al. 2020).

Fatty liver is defined as an abnormal accumulation in the liver which in turn is capable of inducing various cellular changes such as an inflammatory response (Kamiya andIda 2022; Parthasarathy, Revelo, andMalhi 2020). However, when the protective response fails to keep the pathological condition at bay, the liver will begin to change towards a more destructive and fibrotic direction (Parthasarathy et al. 2020). Immune cells such as macrophages and monocytes have an important role in mediating protective changes that are detrimental to liver function (Gao andTsukamoto 2016; Huby andGautier 2022; Robinson, Harmon, andO'Farrelly 2016; Triantafyllou et al. 2018). Till recent update of knowledge, many therapies have been proven through experimental trials by targeting macrophages such as signaling antagonism lipopolysaccharide (LPS), tumor necrosis factor-α (TNF-α) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase which were reported to show effectivity in improving fatty liver and inflammatory responses (Noureddin, Zhang, andLoomba 2016; Xu et al. 2022). Likewise, efforts are being developed to treat NAFLD patients such as by targeting the primary Peroxisome proliferator-activated receptor (PPAR), peptide-1 (glucagon) receptors, and obelcholic acid receptors (Cho, Kwon, andHwang 2022). However, information on the biological mechanisms that take place is still very complicated to find out and therapeutic approaches that are able to improve liver function after NAFLD are still very limited. Likewise, with the increasing frequency and limitations of NAFLD drugs, there is an urgent need to identify new sources of medicinal ingredients that have bioactivity with potential preventive and/or therapeutic effects (González-Arceo et al. 2021).

Natural materials derived from the sea and their derivative products are reported to be able to contribute to the discovery of modern medicine (Atanasov et al. 2021; Bernardini et al. 2018; Malve 2016). Seaweed or macroalgae have supplied various bioactive materials for the discovery and development of new drugs (Cikoš et al. 2018; Lomartire andGonçalves 2022). In this context, increased studies on seaweed have occurred, due to the fact that historically seaweed has been used as a food ingredient and traditional medicine in several countries that have coastal areas which provide extra opportunities considering the scarcity of terrestrial land resources

(Nakhate andvan derMeer 2021). Seaweed consumption has been associated with reduced incidence of chronic diseases such as cancer, hyperlipidemia, and coronary heart disease in epidemiological studies (Peñalver et al. 2020). In addition, seaweed consumption may also be correlated with possible therapeutic effects in weight management and obesity (Wan-Loy andSiew-Moi 2016).

Brown seaweed (Phaeophyceae) is one of the classes of seaweed which has been widely developed as a raw material for medicine and functional food because of its important bioactive content (Permatasari et al. 2022; Rosiana et al. 2022). Brown seaweed is very abundant in marine waters, especially in tropical countries such as Indonesia. Species *Sargassum spp.* has potential industrial applications, for example as a fertilizer, feed and raw material for the production of alginate and other colloids used as thickening agents in the food and drug delivery industries (Permatasari et al. 2022). Hydroethanol extract rich in plorotannin and polysaccharides from brown macroalgae has also been shown to have health functions including antihypercholesterol agent (Patil et al. 2018), antivirus agent (Besednova et al. 2021), antioxidant (Charoensiddhi et al. 2017), and inhibition of the α-glucosidase enzyme (Múzquiz de la Garza et al. 2019). On the other hand, brown seaweed is also rich in alginate, laminarin, fucoidan, sulfated polysaccharides, fiber, and total phenolics (Patil et al. 2018).

To our knowledge, there is no information (*in vivo* and clinical studies) with brown seaweed extract in preventing and treating degenerative diseases such as fatty liver. The aim of this review is to provide scientific information on the therapeutic benefits of brown algae on fatty liver in preclinical and clinical studies, along with the mechanisms of action involved.

2. Methods

The purpose of this narrative review is to provide general information about fatty liver and to assess the effect of brown algae extract in preventing/treating the development of this disease. We searched scientific studies published within the last ten years and presented in English on the PubMed, Google Scholar, SCOPUS, and Crossref websites using search terms such as 'NAFLD', 'metabolic syndrome, cardiovascular disease, 'fatty liver', ' lipogenesis', 'brown algae', 'fucoidan', 'alginate', 'florotanin', 'carbohydrates', 'carotenoids', 'fukosantin' and 'NAFLD related-gene'.

3. Pathophysiological of NAFLD

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease studied so far. It affects about a quarter of the world's adult population and poses a significant threat to human health with far-reaching social and economic consequences. Fatty liver developed for many well-studied reasons which involving many different biochemical mechanisms and leading to different types of liver damage (Yin et al. 2023). Pathophysiology of NAFLD includes fat accumulation (steatosis), inflammation, and variable fibrosis. Steatosis results from accumulation

of triglycerides in the liver. Many studies reported the complex pathophysiological mechanisms and heterogeneity involved in NAFLD disease development. However, there are no specific pharmacological treatments currently approved for NAFLD, although several agents are in advanced stages of development.

3.1 Pathogenesis of NAFLD

NAFLD involves multiple immune cell-mediated inflammatory processes, and inflammation becomes an integral part of disease progression, especially once the NASH stage is reached (Huby andGautier 2022). Metabolic syndrome is the most common cause of chronic liver disease, such as NAFLD. NAFLD is considered a hepatic manifestation of metabolic syndrome and is strongly associated with metabolic complications such as obesity, type 2 diabetes, hyperlipidemia and hypertension (Younossi et al. 2019). Despite some progress that had been achieved by many previous studies worldwide, the evidence-based pharmacological strategy for clinical treatment of NAFLD is still unavailable (Lu et al. 2018). This condition and the increasing rate of NAFLD disease development and patient numbers highlight the importance of identification of new target for the molecular therapy of NAFLD.

Talking about the pharmacological stragegy for NAFLD treatment, previous study reported and proposed an iriod compound, Asperuloside, as a potential molecule for treating NAFLD. Asperuloside itself can be extracted from Rubiaceae, Eucommaceae and herbs such as *Oldenlandia diffusa* and *Morinda officinalis*. Aperuloside has been reported to be able to improve inflammation, oxidative stress and chronic colitis by inhibiting NF-κB signaling pathway and activate nuclear factor (erythroid-derived 2)- like 2/ heme oxygenase-1 (Nrf2/HO-1) signaling pathway (Shen et al. 2023). Previous study had explored the pharmacological activities of Asperuloside as anti-tumor, anti-inflammatory, andtioxidant, and anti-obesity (Chen et al. 2021).

In order to give the exactly correct diagnose for NAFLD, Hepatic steatosis caused by other variables, such as alcohol and drugs, must be "ruled-out". Alcohol is in fact specifically specified as an exclusion criterion for NAFLD diagnose, as the name suggests. According to the recent study, NAFLD may affect outcomes in people with chronic hepatitis C (Leandro et al. 2006). Cardiovascular disease, cirrhosis, and increasing fibrosis are risks for NAFLD patients. By biopsy results (showing characteristics of NASH or increasing fibrosis/cirrhosis), liver fibrosis can be detected as a precursor to cirrhosis and consequent liver-related morbidity and mortality (Clayton-chubb et al. 2023).

3.2 Biomarker related with NAFLD

Several genome-wide association studies have identified sequence variants in the genes encoding patatin-like phospholipase domain protein 3 (PNPLA3) and transmembrane 6

superfamily member 2 (TM6SF2), whose gene located on chromosome 19 in human, as risk factors for advanced hepatocellular carcinoma and NAFLD and hepatocellular carcinoma (Kozlitina et al. 2014; Trépo et al. 2016). Previous study had reported that normal VLDL secretion requires transmembrane 6 superfamily member 2 protein (TM6SF2) activity, whose gene and the impairment of this TM6SF2 function is a causative factor in NAFLD (Kozlitina et al. 2014).

Numerous miRNAs and genes in human cells have been elucidated and reported as key regulators of liver pathophysiology, including NAFLD. In their previous study using hepatocyte-specific *Lilrb4* knockout (LILRB4-HKO) and transgenic (LILRB4-HTG) mice, Lu *et al.* (2014) revealed that LILRB4 significantly suppresses high-fat diet (HFD)-induced insulin resistance, glucose metabolic disorder, hepatic lipid accumulation, and inflammatory responses. In addition, LILRB4 was reported to show the ability to recruit Src-homology protein tyrosine phosphatase-1 protein (SHP1). SHP1 protein was proven to directly interact with TRAF6 in order to block the activation of the downstream nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways, leading to the attenuation of NAFLD development and its metabolic complications (Lu et al. 2018).

Non-alcoholic fatty liver disease (NAFLD) is a chronic inflammatory disease in which the nucleotide-binding domain of the inflammasome, leucine-rich repeat protein 3 (NLRP3), plays an important role. The onset and progression of NAFLD may be associated with several important factors such as lipid deposition, inflammatory factors and oxidative stress. Adenosine monophosphate-activated protein kinase (AMPK) is an energy sensor that regulates glycolipid metabolism in liver and adipose tissue, thereby influencing NAFLD progression (Desjardins andSteinberg 2018; Mccracken et al. 2018). The activate form of AMPK can also inhibit the expression of nuclear factor-κB (NF-κB) by upregulating the concentration of the peroxisome proliferator-activated receptor gamma coactivator-1α, thereby inhibiting NOD-like receptor pyrin-like receptor-pyrin-containing 3 (NLRP3) inflammasome and inhibiting the production and release of interleukin-1β (IL-1β), interleukin-18 (IL-18) and other inflammatory factors, thus alleviating inflammation in NAFLD case (Desjardins andSteinberg 2018; Mccracken et al. 2018) .

RNA adenosine deaminase (ADAR1) was reported to be a potential suppressor factor for NAFLD development by regulating the activation of NLRP3 inflammasome. In addition, previous study also reavealed that the overexpression of ADAR1 could ameliorate high fat diet-induced liver injury, which taken together suggested and predicted that upregulation of ADAR1 could be an effective therapeutic approach for the treatment of obesity- induced liver steatosis (Xiang et al. 2022).

Epidemiological evidence shows a close association between fat mass and obesity associated genes (FTO) and the development of NAFLD. Based on the previously reported *in silico* study, FTO genes, genes encoding the nucleic acid demethylase, have a robust association with obesity and higher BMI (Patnaik et al. 2023). FTO gene polymorphisms are also associated with liver (hepatic) fat content (Zhou, Hambly, andMcLachlan 2017). The FTO gene interacts with telomere length and obesity. FTO includes uncoupling protein 2 (UCP2), AMP-activated protein

kinase (AMPK), retinoblastoma-like 2 protein (RBL2), Iroquois homeobox protein 3 (IRX3), cut-like homeobox 1 (CUX1), and interacts with mammalian targets rapamycin complex 1 (mTORC1). These interactions are important for regulation of feeding behavior and recognition of cellular nutrients. Furthermore, FTO genotype was hypothesized to influence telomere regulation. Taken together, results obtained by previous studies indicated that both miRNAs and genetic informations examined could potentially be used as diagnostic biomarkers for the early stages of liver fibrosis in NAFLD cases.

3.3 NAFLD associated with metabolic disorders

More and more evidences provided by studies and researches in this field are associating metabolic disorders with NAFLD development and progression. Previous studies have shown that abnormal serum levels of sex hormones, thyroid hormones, growth hormones and the composition of gut microbiota can trigger and influence the development of metabolic syndrome (Marcos et al. 2023). In addition, studies had shown that adiponectin levels are influenced by genetics, diet, exercise, and abdominal adipose tissue, all of which are involved in the pathogenesis of NAFLD. Adiponectin was reported to inhibit the production of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-18 (IL-18) (Zarghamravanbakhsh, Frenkel, andPoretsky 2021). Adiponectin also possesses anti-fibrotic activity by inhibiting the synthesis of key proteins and genes involved in fibrotic tissue development. Indeed, adiponectin levels have been shown to be diagnostic clues for NAFLD, and experimental upregulation of adiponectin may represent a future treatment for NAFLD, but more required supporting evidence such claim of research is required (Zarghamravanbakhsh et al. 2021).

The complex interaction among genetic susceptibility variants, environmental factors, insulin resistance, and changes in the gut microbiota leads to altered lipid metabolism and excessive lipid accumulation in hepatocytes, leading to the development of NAFLD. Visceral obesity plays an important role in the pathogenesis of NAFLD. Adipose tissue secretes inflammatory cytokines such as TNF-α and IL-6. Previous studies have shown that the severity of steatohepatitis and fibrosis correlates with higher levels of TNF-α (Giby et al. 2014).

Furthermore, the microbiota contributes to inflammation that can lead to progression to NASH, as it is involved in switching the balance between pro- and anti-inflammatory signals. This may enable improved diagnosis, patient stratification, and the identification of new therapeutic targets (Kolodziejczyk et al. 2019). By using 16S rDNA profiles from mice, previous study found that two bacterial species, *Lachnospiraceae bacterium* and *Barnesiella intestinihominis*, were significantly overrepresented in stool with potency to induce NAFLD (Roy et al. 2013). However, more evidence which hopefully could be provided in future studies are designated as an urgent need to fully understand the pathogenesis of NAFLD, the contribution of the microbiome to his NAFLD, and progression to NASH.

4. Animal Studies

Most of the effects of brown algae have been studied in rodent models. The main effects that have been reported in this review have been summarized in the following descriptions.

4.1 Carotenoids – Fucoxanthin

Carotenoids are bioactive ingredients that are generally produced by plants which have various roles, especially in food products. To date, more than 750 carotenoids are found structurally in terrestrial plants, macroalgae, bacteria (cyanobacteria and photosynthetic bacteria), archae, fungi and mammals. Except in mammals, these species can produce a wide variety of carotenoids through a process known as "carotegenesis" which can be used as a chemotaxonomic indicator. Carotenoids are currently gaining popularity because various research studies have shown that carotenoids could help in reducing the risk of several degenerative diseases such as cancer, cardiovascular disease, diabetes and antihyperlipidemia (Esquivel et al. 2019).

Carotenoids are also important antioxidants found in seaweed. Several types of carotenoids such as β-carotene, α-carotene, zeaxanthin, lutein, violaxanthin, neoxanthin and fucoxanthin have been found in seaweed. Among these carotenoids, fucoxanthin is a unique carotenoid found exclusively in algae which is not found in terrestrial plants. Fucoxanthin is a photonsynthetic pigment found in many brown algae. Interestingly, fucoxanthin also offers health benefits in addition to its important role in photosynthesis and algal photoprotection. Fucoxanthin has health benefits as a stroke treatment (Wang et al. 2022), anticardiovascular (Yunling et al. 2022) , antineurodegenerative (Li et al. 2022), and anticancer (Terasaki et al. 2022).

The effectiveness of fucoxanthin against fatty liver disease has been investigated on an in vivo scale. Previous studies revealed the effect of fucoxanthin on high hyperlipidemia induced by a high-fat diet with choline deficiency. These findings explain that fucoxanthin can reduce liver weight and liver fat accumulation, as well as reduce inflammatory factors and lipid oxidation in the liver. The decreased mRNA expressions of genes associated with inflammation also occurred in the fucoxanthin diet rats. The mechanism of action provided by fucoxanthin is by utilizing its metabolites such as fucoxanthinol and amarouciaxanthin A through inhibition of chemokine production in hyperlipidemic rat hepatocytes (Takatani et al. 2020). The combination of low molecular weight fucoidan and high stability fucoxanthin has been used as an anti-NAFLD agent in rats induced by a high-fat diet. The mechanism of action played by this combination is by reducing liver lipotoxicity and modulating adipogenesis. Interestingly, the combination of fucoxanthin and fucoidan is able to modulate the leptin-adiponectin axis in adipocytes and hepatocytes, which then regulates lipid and glycogen metabolism in treating NAFLD (Shih et al. 2021).

Table 1. The species or family of brown algae which had been studied in animal models and used as treatment with particular effects

Algae Species/Family or other source	Animal model and treatment	Effects	Mechanisms of action	References
Phaeophyceae	Nonalcoholic steatohepatitis (NASH) mice fed a high-fat L-amino acid diet with choline deficiency and NASH + Fx mice models	Weight loss and damage	• Decreased hepatic lipid oxidation • Reduced mRNA expression associated with inflammation and infiltration • Inhibition of chemokine production • Decreased fibrogenic factor	(Takatani et al. 2020)
Sargassum hemiphyllum	A rat model given a high-fat diet and fucoxanthin for 6 weeks	Relative decrease in alanine aminotransferase, aspartate aminotransferase, total cholesterol, triglycerides, fasting blood glucose and liver tissue repair	• Decreased liver lipotoxicity • Modulation of adipogenesis	(Shih et al. 2021)
Phaeophyceae	Stage 1: C57BL/6J male mice aged 7 weeks were given a high fat/high sucrose/cholesterol diet and 0.015% fucoxanthin powder for 12 weeks Stage 2: Male mice were given a diet high in fat/ sucrose/ cholesterol and 0.01% fucoxanthin for 8 weeks.	• Maintain body weight and lipid profile • Reduction in total cholesterol, liver fat accumulation and serum aminotransferase levels	• Increased hepatic fatty acid β-oxidation gene expression • Regulated mitochondrial biogenesis and fatty acid β-oxidase	(Kim et al. 2022)
Sargassum siliquosum	48 male Wistar rats were given a high-fat diet and added *S. siliquosum* extract	Decreased abdominal fat deposition and liver fat vacuole size	Decreased inflammatory cell infiltration but did not change ALT and AST plasma activity	(duPreez et al. 2021)

4.2 Polysaccharides

Polysaccharides in macroalgae are one of the important bioactive components that have been developed as raw materials for functional food to traditional medicines (Widhiantara et al. 2022). In recent years, studies have confirmed that macroalgae polysaccharides have immunomodulatory activity (Lynch et al. 2021), anticancer (Jin et al. 2021), antioxidant (Tziveleka et al. 2021), as well as anticoagulants (Adrien et al. 2019). Previous literature studies have explained the role of macroalgal polysaccharides as anticancer by regulating immune system mechanisms, inducing apoptosis, inhibiting cell cycle rates, regulating transduction and inhibiting the metastatic process of cancer cells (Liu et al. 2022). Until now, there is little current information regarding the development of brown macroalgae polysaccharides as prevention and treatment of non-alcoholic fatty liver disease (NAFLD).

Fucoidan, a sulfated polysaccharide derived from brown algae, has been investigated for its therapeutic effect on non-alcoholic fatty liver disease. In vivo study showed that rats that were induced on a high-fat diet for 12 weeks and given orally fucoidan (100 mg/kg) and metformin (200 mg/kg) orally in the last four weeks were able to attenuate the development of NAFLD (Heeba andMorsy 2015). Decreases was observed and occurred in several parameters such as liver index, liver enzyme activity, total cholesterol, serum triglycerides, fasting glucose, insulin, insulin resistance and body composition index. Molecularly, fucoidan was also reported to significantly reduce hepatic mRNA expression via TNF-α, interleukins-1β, and matrix metalloproteinase-2 (Heeba andMorsy 2015). Dietary supplementation containing 1% and 5% fucoidan for 12 weeks was able to reduce tissue weight (liver and white adipose tissue), total cholesterol, and high-density lipoprotein cholesterol (non-HDL-C) in rats induced by high-fat diet (Yokota et al. 2016). Fucoidan isolated from Laminaria japonica reduced lipid profile, fat accumulation, liver stasis, and adiposity hypertrophy in rats induced by a high-fat diet (Zhang et al. 2022). Likewise, fucoidan isolated from *Lessonia trabeculata* was able to control oxidative stress while improving liver function in rats with diabetes mellitus (Loayza-Gutiérrez et al. 2022).

Fatty liver has also been reported to trigger uncontrolled apoptotic activity, endoplasmic reticulum stress, and oxidative stress in hepatocytes/uncontrolled lipotoxic/inflammatory stimulation in Kupffer cells (Delli Bovi et al. 2021). Previous research has linked a reduction in fatty liver caused by a high-fat diet, one of which is due to a decrease in liver apoptosis or oxidative stress, which in turn has implications for decreasing levels of superoxidase dismutase and catalase (Lin et al. 2017).

Apart from the role of fucoidan, sodium alginate (Na-alginate), a water-soluble dietary fiber, can also be obtained from brown algae. Previous research has proven the role of sodium alginate in repairing liver damage caused by fatty liver as well as by modulating intestinal flora and anti-inflammation. *In vivo* study using 32 male Sprague-Dawley rats given a high-fat diet and each of Na-alginate at a dose of 50 mg/kg/day and 150 mg/kg/day for 16 weeks was able to

reduce body weight, liver steatosis, serum triglycerides, ALT, TNF-α, and increase HDL-C. Interestingly, in these findings, Na-alginate at low doses (50 mg/kg/day) downregulated the protein significantly through levels of toll-like-receptor-4 (TLR-4), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kb), NLRP3, caspase-1, and IL-1β in NAFLD mice confirming that Na-alginate has anti-inflammatory properties (Zhao et al. 2022). The same thing was also expressed in the results of the study Miyazaki *et al.*, (2016) who evaluated the effect of Na-alginate on reducing the expression of IL-1β and TNF-α mRNA in the liver of obese rats.

The anti-oxidative effect played by Na-Alginate contributes to the suppression of the formation of obesity-induced liver carcinogenesis due to hepatic oxidative stress and lipid peroxidation (Rolo, Teodoro, andPalmeira 2012; Starley, Calcagno, andHarrison 2010). Na-Agn also works by inhibiting the proliferation and migration of hepatic stellate cells (HSC) so that it can prevent liver fibrosis by reducing NF-kb signaling (Xia et al. 2020). In contrast to the treatment group, the rat group which was only given a high-fat diet caused dysregulation of secretion and release of adipocytokines which possibly contributed to steatohepatit and inflammation of the liver (Shoelson, Herrero, andNaaz 2007). Transcription factors such as PPAR and SREBP play a role in controlling lipid homeostasis by promoting the expression of genes involved in the production and absorption of cholesterol, fatty acids and triglycerides. SREBP-1c, a pro-adipogenic transcription factor, specifically controls the expression of FAS and AMPK-1, both of which play important roles in regulating lipid and carbohydrate metabolism through lipogenesis and glucose uptake (Tamori et al. 2002).

4.3 Phlorotannins

Phlorotanins are polyphenolic compounds formed by the polymerization of phloroglucinol units. Various florotanins with low, medium to high molecular weight (molecular size up to 650 kDa) have been reported to be sourced from marine algae, especially brown algae (Singh andSidana 2013). The naturally occurring phlorotanins can be classified based on their association with phloroglucinol (PGU) units. Until now it is known that there are three main groups of phlorotannins including (i) fucol, (ii) phloroethol, and (iii) fucophloroethol. By increasing the number of PGUs, the diversity and complexity of the structures will also increase because the related PGUs can be linear or branched or both (Hermund 2018).

In vitro scale studies, animal models and data developed in human trials (clinical studies) have shown that phlorotannins are a type of polyphenol found only in macroalgae, especially those with anti-hyperglycemic and antihyperlipidemic properties (Wardani et al. 2019). However, there is still little information that reveals the ability of florotanin in brown algae as an anti-fatty liver agent due to metabolic syndrome.

Researches showed the potential of high molecular weight florotannins from S. thunbergii (HMPs) in regulating blood lipid levels by reducing total cholesterol, triglyceride, and LDL-C levels. In the liver, these HMPs are able to increase LDL-R levels but are not optimal in

inhibiting HMG-CoA reductase synthesis, which still needs to be investigated for its relevance to cholesterol biosynthesis in the liver (Wei et al. 2011). Polyphenols isolated from Lessonia trabeculate in vitro have antioxidant, α-glucosidase and lipase inhibitory activities. In vivo, induction of polyphenols for 4 weeks was able to improve the architecture and function of the liver which confirmed the inhibition of fatty liver, reduced the content of short-chain fatty acids in rat feces, regulated microbial ecological dysbiosis in diabetic rats (Yuan et al. 2019).

Signaling pathways associated with the development of NAFLD have been extensively studied including with NLRP3-involved pyroptosis. This pyroptosis can be interpreted as cell death with pore formation which can be induced by caspase-1/4/5/11 in the cell membrane after the release of proinflammatory mediators including IL-18 (Bergsbaken, Fink, andCookson 2009). Cell swelling, increased cell permeability, cell lysis, and cytoplasmic release are features of pyroptosis. As an inflammatory response, lipotoxic hepatocytes secrete high mobility group box 1 (HMGB1), a damage-associated molecular pattern (DAMP) in NAFLD formation. (Gan et al. 2014; Guzmán-Ruiz et al. 2014).

Some markers are also mentioned to exacerbate cholesterol accumulation in the liver which is then involved in lipid toxicity such as FASN, SREBP2, PPARγ, and FABP4 (Chen et al. 2018). Lipid accumulation can be inhibited if a natural substance is able to stimulate PPARα, ATGL, and HSL which in turn increases CPT1A expression and promotes β-oxidation and decreases FASN expression (Hu et al. 2020; McGarry andBrown 1997; Tardelli, Bruschi, andTrauner 2020).

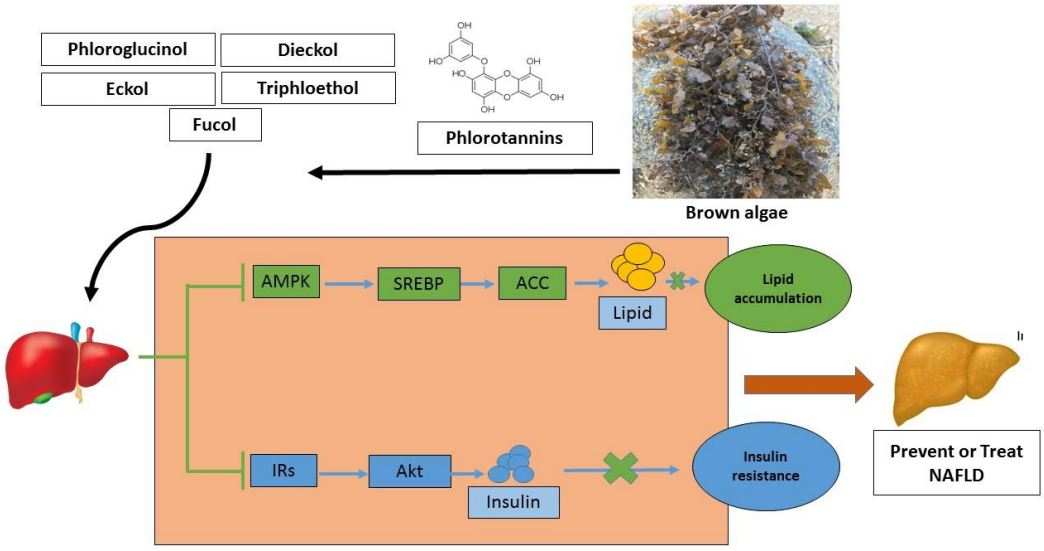

Figure 1. Mechanism of action of florotanin and its derivatives from brown macroalgae on prevention and/or NAFLD.

Several derivatives of florotanin that have been successfully reported, such as phloroglucinol, dieckol, eckol, triphloethol, and fucol from brown macroalgae, especially dieckol, are able to reduce liver steatosis by stimulating levels of β-oxidation of fatty acids in the liver (Liu et al. 2019). Dieckol which was successfully extracted from E. cava was able to reduce the incidence of NAFLD in rats induced with a high-fat diet. Several signaling pathways related to fat metabolism decreased inflammatory factors and expression of pyroptosis NLRP3/ASC/caspase-1 in the dieckol group. There was a decrease in the accumulation of triglycerides and free fatty acids in the liver, improved liver histology, and increased lipogenic gene expression (FASN, SREBP-2, PPARγ, and FABP4), as well as decreased lipotic gene expression (PPARα, CPT11A, ATGL, and HSL) (Oh et al. 2021). The mechanism of action played by florotanin through its derivatives on lipid accumulation and insulin resistance causes NAFLD is illustrated in **Figure 1.**

Table 2. The mechanism of action of brown algae

Algae Species/Family or other source	Animal model studied and treatment	Effects	Mechanisms of action	References
Sargassum thunbergii	Male model rats were given a high-fat diet and intervened with high molecular weight phlorotannins	• Lowering total cholesterol levels • Triglycerides • LDL-C levels	• Increase liver LDL-R levels • But not optimal in inhibiting the synthesis of HMG- CoA reductase	(Wei et al. 2011)
Lessonia trabeculate	Diabetic C57BL/6J rat model given polyphenolic extract for 4 weeks induced by Streptozotocin	• Lowering fasting blood glucose levels • Insulin levels • serum lipid profile	• Maintain liver function by reducing oxidative stress factors and serum lipid profiles	(Yuan et al. 2019)
Ecklonia cava	Mice were induced on a high-fat diet so that they became obese and given polyphenolic extracts orally for 12 weeks	• Weight loss • Mass of adipose tissue • Plasma lipid profile • Liver fat deposition • Insulin resistance • Plasma leptin/adiponectin ratio	• Improve liver protein levels related to lipogenesis, inflammation and oxidative stress as well as AMPK and SIRT-1 activation	(Eo et al. 2015)
Laminaria japonica	Male rats were induced on a high-fat diet causing NAFL and given dieckol-rich extract 50 mg/kg/day for 4 weeks.	• Weight gainIndeks hati • Decreased visceral fat • Plasma lipid profile • Liver fat deposition	• Maintains AMP-activated phosphorylated protein kinase levels • Carnitine palmitoyltransferase-1 • Peroxisome proliferator-α activated receptors • Stimulation of hepatic fatty acid β-oxidation	(Liu et al. 2019)
Ecklonia cava	Male rats were induced on a high-fat diet for five weeks and polyphenol + dieckol extracts were administered	• Maintain body weight • Reduction in total cholesterol,	• Inhibiting lipid accumulation in 3T3-L1 cells	(Yeo et al. 2012)

	orally for four weeks.	triglycerides and serum LDL	• Inhibiting 3-hydroxyl-methyl glutaryl coenzyme A (HMGCoA) reductase activity	
Ecklonia cava	A mixture of polyphenols (Seapolynol) was given to animal models of zebrafish and mice induced by a high-fat diet	Zebra fish • Inhibition of mitotic clone expansion Inhibits the development of the cell cycle Hyperlipidemic rats • Weight loss • Increased plasma lipid • Decreased triglycerides, total cholesterol and LDL levels • Increased liver lipid accumulation	Zebra fish • Cell cycle control (cyclin A, cyclin D and prb) • Increasing p27 and inhibiting cell cycle excessively Hyperlipidemic rats • The activation of AMPKα • Inhibiting the synthesis of lipids in the liver	(Jeon et al. 2015)
Ecklonia cava	Obese and hyperglycemic C57BL/6 male rat model induced by a high-fat diet for 3 weeks and given *E. cava* extract orally for 8 weeks	• Weight loss • Body fat • Hyperglycemia and glucose tolerance	• Increased mRNA expression of adipogenic genes • Decreased mRNA expression of inflammatory cytokines • Decreased macrophage marker genes	(Park et al. 2012)
Ecklonia cava	NAFLD model rats induced by high fat diet and given dieckol *E. cava* extract component were evaluated	• Decreased accumulation of triglycerides and free fatty acids in the liver	• Decreased expression of mobility group box 1/Toll-like receptor 4/nuclear factor –kb	(Oh et al. 2021)

		• Repair of liver histology • Decreased number of pyroptic cells	• Decreased expression of NLRP3/ASC/caspase-1 • Decreased expression of lipogenic genes and increased lipolytic genes	
Ecklonia cava	*E. cava* extracts and dieckol were administered to hyperlipidemic rats and evaluated for body weight, inflammatory factors and lymphangigenesis	• Weight loss • Reducing excess food intake • Decreased steatosis, lobular inflammation and ballooning	• Decreased expression of pro-inflammatory cytokines (IL-6 and TNF-α) • Restoration of lymphangiogenesis signaling pathways, VEGFR-3, PI3K/pAKT and pERK • Recovery of VE-cadherin expression	(Byun et al. 2021)

5. Human studies

Clinical studies developed to determine the effectiveness of consuming brown algae extract have been carried out by several researchers in recent years, especially those intended to treat non-alcoholic fatty liver disease. Studies conducted using Xanthigen (brown algal fucoxanthin + pomegranate seed oil) in obese, non-diabetic female volunteers with non-alcoholic fatty liver disease and normal liver fat content (NFL). This study was conducted over 16 weeks, double-blind, randomized, placebo-controlled. Key records such as food habits, body composition, resting energy expenditure (REE) with 41 volunteers with fatty liver disease and analysis of blood samples were conducted over 16 weeks in 151 non-diabetic and obese pre-menopausal women with liver fat content above 11%. The results showed that Xanthigen at a dose of 300 mg PSO + 300 mg brown algae extract (2.4 mg fucoxanthin) was able to reduce body weight, waist circumference, and liver fat content as well as liver enzymes, serum triglycerides and C-reactive protein compared to placebo (Abidov et al. 2010).

The results of clinical trials conducted by testing Akkermansia muciniphila for three months showed an increase in several parameters related to fatty liver metabolism disorders such as body weight, fat mass, waist circumference, blood markers related to liver dysfunction and inflammatory response (Depommier et al. 2019). Patients suffering from fatty liver because they have excessive energy intake and lack of exercise activities resulting in a positive impact that leads to accumulation of visceral fat, development of hepatic steatosis and is at risk for metabolic disorders (Rozendaal et al. 2019). A clinical study conducted on 36 outpatients with hypertension in the elderly in Japan who were given Undaria pinnatifida extract consumed for 4-8 weeks showed a reduced risk of hypercholesterolemia and related parameters by 8% (Hata et al. 2001). Obese patients suffering from fatty liver generally show increased plasmatic markers of liver function which include AST, ALT, and γ-glutamyltransferase (γ-GT) (Heilbronn, Noakes, andClifton 2001). Changes in these biomarkers are also associated with other metabolic syndrome disorders such as arterial hypertension, central obesity, hepatic insulin sensitivity, and an increased risk of diabetes (Stranges et al. 2005).

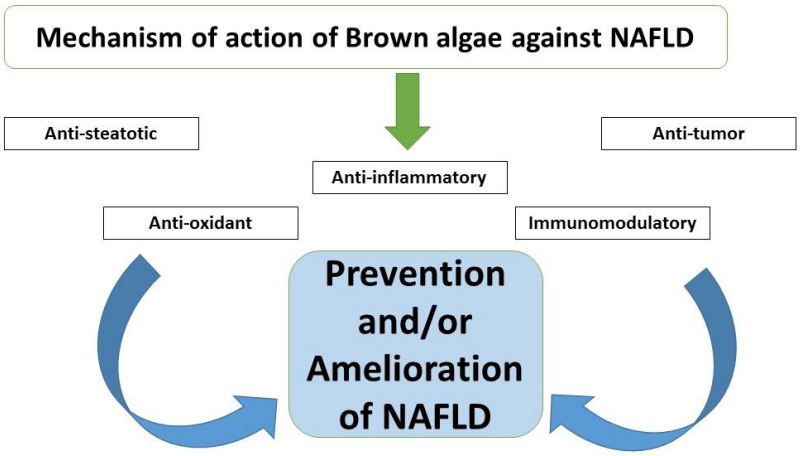

Figure 2. Mechanism of brown macroalgae showing their bioactivity as a promising hepatoprotective against degenerative diseases causing the development of NAFLD

As summarized in **Figure 2**, both *in vivo* and clinical studies of fatty liver, provide evidence for the mechanism of action of brown algae on hepatic steatosis and inflammation. Molecularly, brown algae are able to modulate several genes involved in the homeostasis of fat metabolism in the liver by reducing lipogenic pathways with increased stimulation of lipid catabolism which results in anti-steatotic effects and decreases levels of lipid profiles. On the other hand, the activities of brown algae as antioxidant, anti-inflammatory, and immune system modulation agent against non-alcoholic fatty liver have also been described. Bioactive compounds with a broad spectrum of brown algae are simultaneously able to prevent the negative effects that trigger the pathogenesis of fatty liver while preventing a higher severity of liver disease (Rashed et al. 2022).

6. Conclusions

Non-alcoholic fatty liver disease (NAFLD) is the manifestation liver function disorder associated with metabolic syndrome, such as hypertension, obesity, dyslipidemia, and type 2 diabetes mellitus. In this article, the effectiveness of brown algae against the development of NAFL and metabolic disorders was reviewed and validated. Brown algae itself was proven as a nutraceutical product containing a phytocomplex rich in polysaccharides, phlorotannins and other polyphenols, and sulfolipids as discussed. According to prior preclinical and clinical investigations, the consumption of brown algae could reduce the risk factors for metabolic syndrome. However, detail meachanism on the mode of action of brown algae on inhibiting the development of NAFLD still remains gap which should be explored and unraveled in future studies.

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