Developing natural marine products for treating liver diseases

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**Abstract**

In recent years, marine-derived bioactive compounds have gained increasing attention because of their higher biodiversity vs land-derived compounds. A number of marine-derived compounds are proven to improve lipid metabolism, modulate the gut microbiota, and possess anti-inflammatory, antioxidant, antibacterial, antiviral, and antitumor activities. With the increasing understanding of the molecular landscape underlying the pathogenesis of chronic liver diseases, interest has spiked in developing new therapeutic drugs and medicine food homology from marine sources for the prevention and treatment of liver diseases.

**Key Words:** Natural marine products; Liver disease; Treatment; Liver

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**Core Tip:** The prevalence of liver diseases has been rising worldwide, especially non-alcoholic fatty liver disease that is associated with increasingly urbanized lifestyles and dietary changes. Effective and cost-efficient drugs and medicine food homology are needed in concert with improving liver health. Marine sources are rich and play an important role in the generation of unique drugs. A number of marine-derived compounds are proven to improve lipid metabolism, modulate the gut microbiota, prevent reactive oxygen species formation, and possess anti-inflammatory and anticancer activities, which means that they can be an invaluable source for the discovery of new compounds for the prevention and treatment of liver diseases.

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INTRODUCTION

Liver diseases are rapidly emerging as global health priorities. With increasingly urbanized lifestyles and dietary changes involving high caloric contents, the overall prevalence of non-alcoholic fatty liver disease (NAFLD) has increased dramatically. Non-alcoholic steatohepatitis (NASH) has become one of the leading causes of liver transplantation in the United States[1]. NAFLD is associated with metabolic syndrome and the development of cardiovascular and kidney diseases. Alcoholic liver disease (ALD) is caused by heavy alcohol intake. Almost 50% of cirrhosis-related deaths are due to excessive alcohol consumption[2]. Hepatitis B virus (HBV) infection is the most common cause of chronic hepatitis worldwide and remains the primary cause of cirrhosis and hepatocellular carcinoma (HCC) in most Asian nations. Hepatitis C virus (HCV) has infected 71 million people worldwide[3]. HCC is one of the most common malignant tumors worldwide. HBV, HCV, NAFLD, and ALD are significant risk factors for HCC. Drug-induced liver injury (DILI) is an important cause of acute liver failure. All chronic liver diseases can lead to liver cirrhosis and decompensation, thus requiring effective and cost-efficient treatments.

The ocean accounts for 70% of the Earth’s surface area[4]. Marine organisms are known for their ability to produce large amounts of bioactive compounds, whose biological activities could interfere with the pathogenesis of many diseases. Interest in marine organisms as a source of health-promoting agents has increased in recent decades. Marine organisms are classified as marine plants (e.g., seaweeds and mangroves), marine animals (e.g., sponges, corals, shellfish, krill, and ascidians), and marine microorganisms, according to their biological characteristics. They have been found to be rich sources of bioactive compounds with anti-inflammatory, antioxidant, antibacterial, antiviral, anti-tumor, and lipid-lowering activities. This review discusses current applications of bioactive marine compounds in studying liver diseases (briefly summarized in Table 1).

NAFLD

NAFLD is a spectrum of common liver diseases and currently is responsible for a global disease epidemic with an estimated worldwide prevalence of 25%-50%[5]. The highest rates are reported in South America and the Middle East, followed by Asia, the USA, and Europe. NAFLD includes a range of diseases ranging from fatty liver to NASH, liver fibrosis, cirrhosis, and liver cancer. Insulin resistance, lipotoxicity, mitochondrial dysfunction, oxidative stress, intestinal microbiome disorders, and genetic and epigenetic factors are related to NAFLD pathogenesis[6]. Data from several studies have shown improvements in patients with NASH after treatment with vitamin E, liraglutide, statins, glitazones, and pioglitazone[7]. However, no special therapeutic medications have been approved by the Federal Drug Administration (FDA). In the absence of effective pharmacological agents for NAFLD, lifestyle interventions such as increased exercise and energy restriction, lowering hepatic lipid levels, and increasing insulin sensitivity are important measures. Several studies of bioactive marine substances have provided new therapeutic prospects for NAFLD.

Fish oil contains a variety of n-3 long-chain polyunsaturated fatty acids (PUFAs), including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which can activate the peroxisome proliferator receptor (PPAR) and downregulate the expression of sterol regulatory element binding protein 1c (SREBP-1c) and carbohydrate response element-binding protein (ChREBP). N-3 PUFA can not only protect against dyslipidemia, insulin resistance, and obesity, but also has anti-inflammatory and antioxidant properties. Previous findings have shown that n-3 PUFA supplementation can prevent NAFLD[8]. Functional lipids from the starfish Asterias amurensis oil, such as n-3 PUFA and carotennes (which have antioxidant activities and can preserve insulin sensitivity), dose-dependently decreased liver lipid accumulation and improved liver steatosis in C57BL/6N mice fed a high-fat diet (HFD)[9]. Krill represent a rich source of protein with essential amino acids and minerals. In fish oils, EPA and DHA are present in the form of triacylglycerol (TAG), whereas they are present as phospholipids (PLs) in krill, which has stronger anti-inflammatory and insulin hypersensitivity properties. A krill phospholipid-protein complex (PPC) from Euphausia superba can reduce hepatic lipogenesis in rats, which is associated with an increased total antioxidant capacity.

Sea cucumber sulfated polysaccharide (SCSP) inhibits the expression of the main regulatory mediator of liver lipid genesis, SREBP-1c, which leads to inhibited hepatic triglyceride synthesis. SCSP also significantly increases PPARγ expression, thus promoting the β oxidation of fatty acids. SCSP is barely absorbed in the gut, which leads to modulation of the gut microbiota. Therefore, SCSP may have unique effects on NAFLD and other pathological liver diseases[10,11].

Carotenoids are natural pigments with strong antioxidant activities. Their benefits in treating liver diseases and related complications have been widely reported. Astaxanthin (AST) is an important xanthophyll carotenoid, which is mainly derived from marine organisms and algae. Its antioxidant effect is 10 times that of β-carotene and 100 times that of vitamin E. In addition to its strong antioxidant properties, AST can also regulate various signaling pathways, such as reducing the activities of JNK and ERK-1 to lower liver insulin resistance, inhibiting PPAR-γ expression to reduce liver fat synthesis,
| Type of activity                  | Organism          | Species                        | Active compound/extract | Associated mechanism                                                                 | Disease/model                          | Ref. |
|----------------------------------|-------------------|--------------------------------|-------------------------|--------------------------------------------------------------------------------------|----------------------------------------|------|
| Antioxidative and anti-inflammatory | Fish              | Chum salmon                    | MCTs                    | Attenuated serum superoxide dismutase and malondialdehyde levels, thus counteracting increased total cholesterol and TAG levels | ALD/rat model, alcohol-induced          | [33] |
|                                  | Fish              | Cod                            | Oil, n-3 fatty acid     | Fluidization of microsomal membranes                                                  | DILI/mouse model, acetaminophen-induced | [45] |
|                                  | Fish              | Menhaden fish                  | Rich in n-3 PUFAs       | Regulation of TLR4 and NOD signaling pathways                                         | Liver injury/pig model, LPS-induced    | [44] |
|                                  | Krill             | Antarctic krill (Euphausia superba) | PPC, peptides           | Increased total antioxidant capacity in plasma, increased liver gene expression of mitochondrial SOD2, and reduced plasma level of the inflammatory mediator IL-2 | NAFLD/rat model, HFD-induced           | [11] |
|                                  |                   |                                |                         | Upregulated SOD, CAT, and GPx in liver tissues, downregulated TNF-α and IL-6 mRNA expression, increased Nrf2 and HO-1 expression, and suppressed ethanol-induced apoptotic proteins in the liver | ALD/mouse model, ethanol-induced       | [34] |
|                                  | Shellfish         | Meretrix                       | Oligopeptides           | Regulating NF-κB-dependent anti-inflammation signaling pathways to inhibit inflammation; regulating AMPK-α, PPAR-α, and SREBP-1c to improve lipid-metabolism disorders; regulating Bcl-2/Bax anti-apoptosis signaling pathways to prevent liver cell apoptosis | NAFLD/mouse model, HFD-induced         | [25] |
|                                  | Starfish/algae    | Harmatecoccus pluvialis        | Astaxanthin             | Exerted antioxidant and anti-inflammatory activities by increasing SOD, CAT, and GPx activity and GSH, and reducing lipid peroxidation in the liver; inhibited the expression of inflammatory factors such as TNF-α and ROS production; inhibited MAPK and NF-κB pathways | NAFLD/mouse model, HFD-induced; ALD/mouse model, alcohol-induced; DILI/mouse model, APAP, ConA, LPS-induced liver IR, ischemia-induced | [14] |
|                                  | Algae             | Seaweed                        | Fucoxanthin             | Activating the Nrf2-mediated signaling pathway and downregulating the expression of the TLR4-mediated NF-κB signaling pathway | ALD/mouse model, alcohol-induced       | [31] |
|                                  | Algae             | Laminaria japonica             | UAOS                    | Increasing both AMPKα and ACC phosphorylation                                         | NAFLD/mouse model, HFD-induced         | [18] |
|                                  | Algae             | Red alga (Laurencia tristicha)  | Aplysin (a marine bromosesquit-erpene) | Revivified erythrocyte membrane fluidity, attenuated glutathione depletion, restored antioxidant activities, and reduced malondialdehyde overproduction | ALD/rat model, alcohol-induced         | [30] |
|                                  | Algae             | Brown seaweed (Sargassum thunbergii) | Indole-4-carboxaldehyde | Anti-inflammatory activity against MGO-induced inflammation in human hepatocytes by preventing increased expression of pro-inflammatory genes and AGE formation | Inflammation/cell model, methylglyoxal-induced | [17] |
|                                  | Algae             | Fucus vesiculosus              | Fucoidan                | Suppressing hepatic production of inflammatory cytokines such as TGF-β1, COX-2, and NO; enhancing the oxidant-defense | ALD/mouse model, alcohol-induced       | [32] |
| Bioresource | Species/Strain | Compound/Preparation | Activity/Effect | Disease Model/Induction |
|-------------|---------------|----------------------|-----------------|------------------------|
| Algae       | *Hypnea muciformis* | Ethanolic extract | Regulated activities/levels of lipid-peroxidation byproducts, antioxidant enzymes, and biotransforming phase I and II enzymes in the circulation | DILI/rat model/CCl₄-induced |
| Gut microbiota modulation | Sea cucumber | *Stichopus japonicus* Sulfated polysaccharide | Preventing HFD-induced gut disorders, as indicated by enriched levels of the probiotic Akkermansia and reduced endotoxin-bearing Proteobacteria, improved SCFA and endotoxin (LPS) levels, and improved gut tissue index | NAFLD/mouse model, HFD-induced |
| Algae       | *Spirulina platensis* 95% ethanol extracts (SPL95, major fatty acids) | | AMPK-signal pathway; downregulated mRNA and protein levels of SREBP-1c, 3-hydroxy-3-methyl glutaryl coenzyme A reductase, and acetyl-CoA carboxylase pathway members; upregulated levels of adenosine 3,5-monophosphate-activated protein kinase-α in the liver; enrichment of beneficial bacteria including Prevotella, Alloprevotella, Porphyromonadaceae, Bacteriella, and Paraprevotella; decreasing microbes such as Turicibacter, Romboutsia, Phascolarctobacterium, Olsenella, and Clostridium XVII | NAFLD/rat model, HFD-induced |
| Fungus     | *Aspergillus versicolor* LZD-44-03-derived asperlin | Asperlin | Increased energy expenditure and enhanced thermogenic gene expression in adipose tissues, increased diversity and shifted structure of gut microbiota | NAFLD and obesity/mouse model, HFD-induced |
| Lipid metabolism improvement | Fish | Fish oil, omega-3-PUFA | Downregulated sterol regulatory element binding protein 3c (SRBP-3c) and upregulated peroxisome proliferator activated receptor α (PPAR-α) which would favour fatty acid oxidation and reduce steatosis | NAFLD/human study, meta-analysis, RCT |
| Starfish   | *Asterias amurensis* Oil, n-3 PUFA | | Enhanced fatty acid β-oxidation and suppressed TG and cholesterol synthesis | NAFLD/mouse model, HFD-induced |
| Shrimp shell | Chitosan oligosaccharide COS23 (Chitosan oligosaccharide) | | Regulated lipid-related pathways, especially inhibition of the expression of FFA synthesis-related and inflammation-related genes, altered plasma lipid profiles, decreased abundance of Mucispirillum and increased abundance of Coprococcus in gut microbiota, and protected the intestinal barrier by up-regulating the expression of tight junction-related genes | NAFLD and obesity/mouse model, HFD-induced |
| Algae       | Red seaweed | *Palmaria mollis* (bacon-like taste) | Upregulated the expression of genes involved in PPAR pathways, and downregulated the PPAR pathways | NAFLD and obesity/zebrafish and mouse model, HFD-induced |
| Algae       | Green algae | SPX (a carotenoid) | Suppression of LXRα activity, and downregulation of nuclear transcription factor SREBP-1c and a set of related genes | NAFLD/cell model, LXRα agonist-induced |
| Algae       | *Spirulina platensis* 95% ethanol extract (SPL95) | | Downregulating the expression of SREBP-1c, 3-hydroxy-3-methyl | NAFLD/rat model, HFD-induced |
| Category | Organism | Compound | Effect | Model |
|----------|----------|----------|--------|-------|
| Antiviral | Sponge | *Dactyloporeia metachromia* | Metachromin A, merosesquiterpene | Inhibited HBV production via impairment of the viral promoter activity | HBV/cell model |
| | Sponge | Red sea sponge (Amphimedon spp.) | Nakinadine B and 3,4-dihydro-6-hydroxymanzamine A | Anti-HCV NS3 helicase and protease activities | HCV/cell model |
| | Formosan soft coral | *Lobophytum crassum* | Lobohedleolide | Suppressing HCV replication by inhibiting JNK phosphorylation, leading to reduced e-Jun phosphorylation and C/EBP expression, and reduced COX-2 expression | HCV/cell model |
| | Ascidian | *Styela plicata* | Effective components (peptides, alkaloids, saponins, macrolides, terpenoids) | Increased serum IL-2; reduced serum HBV DNA levels | HBV/mouse model, HBV-transgenic |
| | Algae | *Cladosiphon okamuranus* Tokida | Facoidan | Inhibited expression of the HCV replicon | HCV/cell model; chronic HCV infection, and HCV-related cirrhosis and hepatocellular carcinoma/human study |
| | Fungus (a sponge associated fungus) | *Trichoderma harzianum* | Two new sesquiterpene-based analogues, namely, harzianolic acids A (I) and B | Blocking the entry step in the HCV life cycle, potentially targeting the viral E1/E2 proteins and the host cell protein CD81, reducing HCV RNA levels | HCV/cell model |
| Anti-cholestatic | Sponge | *Theonella swinhoei* | Theonellasterol | Selective FXR antagonism, increased MRP4 expression | Cholestasis/HepG2 cells; cholestasis/mouse model, BDL-induced |
| Anti-fibrotic | Algae | *Cladosiphon okamuranus*; *Fucus vesiculosus* | Facoidan | Reduced TGF-β1 expression | Liver fibrosis/mouse model, DEN-induced; Liver fibrosis/mouse model, alcohol-induced |
| | Starfish/algae | *Haematococcus pluvialis* | Astaxanthin | Antioxidant, apoptotic, lipid peroxidation, and autophagy activities; regulation of TGF-1/Smads pathway; downregulating the expression of HDACs | Liver fibrosis/mouse model, CCl4 and BDL-induced; liver fibrosis/rat model, CCl4-induced; liver fibrosis/cell model |
| Category | Source | Product | Effect | Model/Induction |
|----------|--------|---------|--------|----------------|
| Algae    | *Arthrospira platensis* | Spirulina liquid extract | Interfering with the TGF-β pathway, reducing inflammation and oxidative stress, and reversing the hepatotoxic bile acid profile | Liver fibrosis/mouse model, Western diet-induced |
|          | Sea urchin | Sea urchin eggs | Ovothiol A | Negatively regulating redox homoeostasis and the activation of key fibrotic markers TGF-β, α-SMA, and TIMP-1 | Liver fibrosis (CCL4 model) |
|          | Sponge | *Pseudocentrotina spp.* | Heterocyclic alkaloids, ceratamines A and B | Disruption of microtubule dynamics, antimitotic agents | HCC/in vitro, rat liver microsomes |
|          | Sponge | *Crambe crambe* | Crambescidin-816 | Inhibition of cell-cell adhesion; interference with tight junction formation, cell-matrix adhesion, and focal adhesions; altered cytoskeleton dynamics; inhibited cell migration | HCC/cell model |
|          | *Erlyus spp.* sponges | Actinomycetales isolated from *Erlyus genera* | Cytotoxic bioactivity | HCC/cell model |
|          | Soft coral | *Spongodes spp.* | Steroid (MESP) | Inhibition of STAT3 phosphorylation | HCC/cell model |
|          | Soft coral | *Sinularia flexilis* | 11-epi-sinulariolide acetate/sinulariolide/sinularin | Suppressed phosphorylation of members in the ERK, JNK, MAPK, and FAK/PI3K/akt/mTOR pathways; reduced MMP-2, MMP-9, and uPA expression; inhibited HCC migration, invasion, and cell metastasis; increased G2/M cell-cycle arrest; induced apoptosis; activated DNA-damage responses | HCC/cell model |
|          | Shellfish | *Arca subcrenata* | Protein (ASP-3) | Reduced VEGFR2 phosphorylation, and altered the downstream components of the VEGF signaling pathways | HCC/cell model; HCC/transgenic zebrafish model |
|          | Shrimp, crab | Chitin from shells | Chitosan oligosaccharides | Cytotoxicity | HCC/cell model |
|          | Jellyfish | *Nemopilema nomurai* | Venom | Dual inhibition of the Akt and mTOR signaling pathways | HCC/tumor xenograft animal model |
|          | Sea urchin | *Paracentrotus lividus Oocytes* | Ovothiols | Antioxidant capacity, hydrogen peroxide generation | HCC/cell model |
|          | Starfish/algae | *H hematococcus pluvialis* | Astaxanthin | Regulating JAK1/STAT3, NF-kB, Wnt/ beta catenin; inhibiting the binding of AFB1 to liver DNA and plasma albumin; reducing reactive oxygen metabolites/biological antioxidant potential ratio; regulating nucleoside diphosphate kinase (NPK) nm-23 | Hepatoma/rat model, AFB1-induced; HCC/mouse model, DEN-induced; HCC/cell model |
|          | Algae | *Undaria pinnatifida* | Fucoidans | Induced apoptosis via the ROS-mediated mitochondrial pathway | HCC/cell model |
|          | Microorganisms | *Mangrove endophytic fungus* | SZ-685C | Induced apoptosis through the Akt/FOXO pathway | HCC/cell model |
|          | Fungus | *Aspergilus terreus* strain PF-26, associated with marine sponges | (+)Terrein | Induced cell-cycle arrest in G2/M phase; decreased expression of proteins related to cell morphology (fibrinectin, N-cadherin, and vimentin); altered expression of genes related to cell-cycle progression | HCC/cell model |
|          | Bacteria | *Bacillus spp.* T1 (EPS11) | Bacterial polysaccharide | Blocking cell adhesion and attenuating filiform structure formation | HCC/cell model |
downregulating TGF-β1/Smad3 expression to inhibit hepatic stellate cell (HSC) activation and liver fibrosis, and inhibiting the JAK/signal transducer and activator of transcription 3 (STAT3) and Wnt/β-catenin signaling pathways to exert antitumor effects. Therefore, AST plays significant roles in preventing and treating NAFLD, liver fibrosis, HCC, DILI, and ALD[12]. Siphonaxanthin (SPX) is a carotenoid derived from green marine algae that can significantly inhibit liver X receptor α (LXRα) activity and downregulate the expression of SREBP-1c and several related genes to inhibit liver adipogenesis[13].

Data from several studies showed that various bioactive components from brown algae can alleviate liver steatosis to a certain extent, especially fucoidan. Fucoidan is a sulfated polysaccharide extracted from brown marine algae that can regulate the ROS/JNK/Akt signaling pathways, reduce insulin resistance, inhibit sugar transport, regulate lipid metabolism and the gut microbiota, and reduce liver steatosis[14]. Some other bioactive compounds from brown algae, such as indole-4-carboxaldehyde, unsaturated alginate oligosaccharides (UAOS), and diphlorethohydroxycarmalol (DHPC), can inhibit inflammation and lipid metabolism, but further clinical trials are needed to confirm their efficacies against NAFLD. An in vivo animal study showed that the red algae *Palmaria mollis* can upregulate PPAR α expression, thereby activating fatty acid β oxidation and inhibiting lipid synthesis to improve liver steatosis[15].

Spirulina are cyanobacteria capable of photosynthesis, which implies that they are rich in antioxidants. PUFAs in a 95% ethanol extract of the microalgae *Spirulina platensis* (SPL95) can regulate the gut microbiota, and reduce lipid synthesis and liver fat in rats fed an HFD by upregulating AMPK-α and downregulating members of the SREBP-1c-signaling pathway[16].

Asperlin is a natural fungal product isolated from the marine-derived fungus *Aspergillus versicolor* LZD-44-03. Asperlin improved lipid metabolism, ameliorated liver steatosis, and modulated the gut microbiota in mice fed an HFD[17].

Chitosan oligosaccharide (COS), a natural polysaccharide hydrolyzed from shrimp shell chitosan, has attracted extensive attention because of its potential use in various promising biomedical applications, including those related to anti-oxidation, anti-inflammation, immune stimulation, and anti-hypertension. An enzymatically digested product of COS, known as COS23, can reduce hepatotoxic lipid levels, inhibit the expression of FFA synthesis-related genes and inflammatory-related genes, regulate the gut microbiota, and up-regulate the expression of tight junction-related genes to improve intestinal barrier dysfunction, thereby improving diet-induced NAFLD.

Mereflex meretrix oligopeptides (MMOs) are substances with important medicinal value that are extracted from shellfish. In vivo and in vitro data have shown that MMOs can reduce oxidative stress, improve mitochondrial dysfunction, and inhibit the activation of cell death-related pathways, thus exerting protective effects against NAFLD[18].

## ALD

Alcohol abuse is the seventh leading risk factor for death globally, and the liver is the main organ involved in alcohol metabolism. Excessive alcohol intake can damage liver cells and cause ALD[19]. The risk is increased in people who have heavy alcohol use (> 3 drinks per day in men and > 2 drinks in women) for > 5 years. Heavy drinking increases intestinal permeability and the influx of lipopolysaccharide (LPS) to the liver, activates Kupffer cells, and leads to high Toll-like receptor 4 (TLR4) expression, which in turn releases large amounts of ROS and tumor necrosis factor (TNF-α) or other inflammatory factors, leading to liver toxicity. Drinking can also reduce the PL levels in liver cell membranes. Environmental factors and PNPLA3 and TM6SF2 gene mutations can also induce ALD progression[20]. Current treatments for ALD depend on ensuring lasting alcohol abstinence, and the treatment strategies beyond alcohol abstinence are largely those used for complications of cirrhosis, such as controlling ascites, treating and preventing hepatic encephalopathy recurrence and variceal bleeding, and monitoring for hepatocellular cancer[21].
Recent data have shown the effects of natural extracts on preventing and/or lessening alcoholic liver injury. AST may prevent ALD progression through pathways related to chemokine signaling, NOD-like receptor signaling, and TLR signaling[22].

Aplysin was extracted from the red alga Laurencia tristicha and exerts a potent hepatoprotective effect against ALD by enhancing the antioxidant defense system, alleviating oxidative damage, and regulating apoptosis-related gene expression[23].

Fucoxanthin (Fx) is a red-orange carotenoid extracted from marine seaweed that has strong anti-obesity, anti-inflammatory, and anti-cancer activities. In vivo data indicated that Fx attenuated alcohol-induced oxidative lesions and inflammatory responses by activating the nuclear factor erythroid-2-related factor 2 (Nrf2)-mediated signaling pathway and downregulating the expression of members of the TLR4-mediated nuclear factor-kappa B (NF-κB) signaling pathway, respectively.

Fucoidan from Fucus vesiculosus was found to protect against alcohol-induced liver damage in mice. The associated mechanism potentially involved suppressing hepatic production of inflammatory cytokines, such as TGF-β1, COX-2, and NO, and enhancing antioxidant defense systems by activating the HO-1 pathway.

Marine collagen peptides (MCPs) are derived from the skin of chum salmon (Oncorhynchus keta) by enzymatic hydrolysis; MCPs can protect against early alcoholic liver injury in rats, based on their antioxidative activities and improvements in terms of lipid metabolism[24].

Krill (Euphausia superba)-derived peptides are renowned for their antioxidative activities, and peptide fractions from krill protein hydrolysates protect against alcohol-induced oxidative damage in BALB/c mice. This hepatoprotective effect might be attributed to activation of the Nrf2/HO-1 pathway.

**HCV INFECTION**

HCV results in an infectious liver disease, with multiple genotypes. HCV infection can lead to steatosis, liver cirrhosis, and HCC. Approximately 3% of the world’s population are infected with HCV[25]. The most effective HCV treatment regimen depends on the genotype of the predominant viral strain in infected patients. Overall, there are 11 HCV genotypes, with genotypes 1–6 being the most common[26]. Traditional therapy involves treatment with a combination of pegylated interferon alpha and ribavirin. The current FDA-approved direct acting antivirals are commonly used in combinations as pan-genotypic to effectively inhibit HCV replication with minimal side effects. However, the occurrence of resistance (either natural or after failure) and drug-drug interactions can limit treatment effectiveness. Natural HCV inhibitors still need to be investigated.

Harzianic acids A and B, isolated from the sponge-related Trichoderma harzianum fungus, inhibit viral activity by reducing RNA levels[27]. Total extract and derived fractions from red sea Amphimedon spp. sponges exhibited inhibitory potential against HCV NS3 helicase and protease. Among Amphimedon spp.-derived phytochemicals, nakadine B and 3,4-dihydro-6-hydroxymanzamine A were noted as promising anti-HCV drug candidates, warranting future clinical investigation[28]. Fucoidan extracted from the marine alga Cladosiphon okamuranus (C. okamuranus) Tokida dose-dependently inhibited an HCV replicon system, suggesting that fucoidan may be a useful food additive with antiviral activity for treating chronic liver diseases[29].

Lobohedleolide isolated from the formosan soft coral Lobophytum crassum, significantly reduced HCV replication by suppressing cyclooxygenase-2 (COX-2) expression[30].

**DILI**

The main elimination mechanisms of exogenous drugs involve the liver, kidney, and bile. Sixty percent of drugs are metabolized by the liver. DILI is a type of liver disease caused by drugs and their metabolites. Severe cases are life-threatening. The incidence of clinically significant DILI varies from country to country. Despite its rarity (< 1%, as determined with most patient series), it has been found to be the most common cause of acute liver failure in both Europe and the United States[31]. The most important initial step in terms of managing suspected DILI is to discontinue the implicated agent, as ongoing or even worsening injury can occur despite withdrawal of the causative agent. Drugs presently used to treat DILI are mainly those that protect liver cells, scavenge free radicals, inhibit oxidation, stabilize cell membranes, promote detoxification, lower enzymes, and promote immune regulation, including ursodeoxycholic acid, N-acetylcysteine, various steroids, and glutathione, among others. However, there is still a lack of drugs that treat DILI specifically.

Fucoidan displayed a hepatoprotective effect on acetaminophen overdose-induced liver toxicity, based on the suppression of CYP2E1, one of the enzymes that metabolizes acetaminophen. Fucoidan also exerts anti-oxidant, anti-apoptotic, and anti-inflammatory activities by increasing the production and expression of glutathione, superoxide dismutase, glutathione peroxidase, and Bcl-2, but decreasing the expression of Bax, cleaved caspase-3, and inflammatory mediators, including TNF-α, IL-1β, and iNOS[32]. An ethanolic extract of Hyphnea muciformis (red algae) was found to possess antioxidant,
antitumor, and antimicrobial activities and to exhibit hepatoprotective activity against CCl$_4$-induced toxicity in rats[33].

Fish oil can reduce liver damage caused by lipopolysaccharides, cisplatin, and acetaminophen by inhibiting TLR4 and nucleotide-binding oligomerization domain protein signaling pathways, and their antioxidant properties[34,35].

**OTHER LIVER DISEASES**

*Styela plicata* is a marine animal that synthesizes bioactive components with anti-tumor, antibacterial, and antiviral effects. Previous data showed that the bioactive compounds of ascidians can inhibit HBV DNA replication and have potential therapeutic value against chronic HBV infection[36]. Yamashita *et al* [37] also showed that metachromin A, a merosesquiterpene isolated from the marine sponge *Dactylospongia metachromia*, can inhibit HBV production by impairing viral promoter activity.

The farnesoid X receptor (FXR) can mediate bile acid secretion, and theonellasterol (isolated from the marine sponge *Theonella swinhoei*) is a highly selective FXR antagonist that can protect against liver injury in cholestasis[38].

**LIVER FIBROSIS**

Liver fibrosis is a scar-repair process that occurs after liver injury caused by various factors. It is characterized by liver myofibroblast cell (MFC) activation and excessive accumulation of extracellular matrix (ECM) proteins, and is pathologically characterized by the formation of regenerative nodules of hepatocytes, which can lead to cirrhosis and liver failure. Chronic HBV and HCV infections, alcoholic steatohepatitis, and NASH are the main causes of chronic progressive liver disease, leading to the onset of liver cirrhosis and decompensation. During chronic liver injury, silent HSCs are activated to become highly proliferative MFCs at the cellular level, resulting in α-smooth muscle actin (α-SMA) expression and excessive production of type I and type III collagen, as well as other scar tissue components. At the molecular level, pro-fibrotic factors, including transforming growth factor-β (TGF-β1), platelet-derived growth factor, and connective tissue growth factor; multiple signaling pathways such as the TLR4, and damage due to reactive oxygen species (ROS) play key roles in this process[39].

Owing to the unique chemical properties of sulfur atoms, sulfur-containing compounds are powerful antioxidants that exhibit promising activities for treating liver fibrosis. For example, ovothiol A (a sulfur-containing molecule) isolated from sea urchin eggs was found to have an anti-fibrotic effect on mice with carbon tetrachloride (CCL$_4$)-induced liver fibrosis. This anti-fibrotic effect may be related to reduced expression of mediators involved in the progression of liver fibrosis, such as TGF-β, α-SMA, and tissue inhibitor of metalloproteinase (TIMP-1)[40].

In addition, Nakazato *et al*[41] found that fucoidan from *C. okamuranus* Tokida reduced N-nitrosodiethylamine-induced liver fibrosis. It exerted an anti-fibrotic effect by downregulating TGF-β1 and CXCL12 expression and reducing lipid peroxidation.

Spirulina liquid extract (SLE), a patented water extract of *Arthrospira platensis*, protects against hepatic fibrosis by inhibiting inflammation, oxidative stress, and whole-body insulin resistance in a mouse model of Western diet-induced NASH[42]. Astaxanthin (AST) from starfish and algae exerts anti-fibrotic effects through the TGF-β1/Smad3 signaling pathway in hepatic stellate cells[43].

**HCC**

HCC is the most common primary liver cancer, accounting for approximately 75%-85% of such cases[44], and the third leading cause of cancer-related mortality worldwide. HCC has a high fatality rate, with a 5-year survival rate of only 30%-40%[45]. An estimated 70%-90% of HCC cases arise in the setting of cirrhosis[46]. HCC treatment mainly includes liver resection, liver transplantation, radiofrequency or microwave ablation, radiotherapy, and chemotherapy. Sorafenib, a multi-kinase VEGF inhibitor, is the most widely used systemic chemotherapeutic drug approved as a first-line agent for unresectable or advanced HCC. Other small-molecule inhibitors such as sunitinib, brivanib, and erlotinib have been studied for their efficacy in treating advanced HCC[47]. However, these anti-tumor drugs still have disadvantages related to drug resistance, poor efficacy, and large side effects. In recent decades, investigators have become committed to researching natural products as new anti-tumor drugs.

Sponges host diverse microbial communities, such as fungi, bacteria, and microalgae, and are rich in bioactive peptides that are important candidates for drug development. Data from many studies have shown that various sponge metabolites have anti-tumor activities in liver cancer cells *in vitro*. Ceratamine A and B isolates from *Pseudoceratina* spp. sponges can behave as antimitotic agents by disrupting microtubule dynamics[48]. Similarly, (+)-terrein, isolated from the marine sponge *Aspergillus*
terreus strain PF-26, can inhibit human hepatoma Bel7402 proliferation by blocking the expression of genes related to cell cycle progression and changing the cell morphology[49]. Crambescidin-816, purified from the sponge Crambe crambe, exerted an anti-tumor effect by inhibiting cell–cell adhesion, interfering with tight junction formation and cell–matrix adhesion, negatively affecting focal adhesions, and altering cytoskeletal dynamics[50]. Actinomycetals isolated from marine sponges of three Erylus genera collected in Portuguese waters showed anti-cancer activity against HCC cell line[51]. In vitro, the marine-derived steroid methyl spongoate (MESP) molecule from Sanya soft coral Spongodes sp. potently induced apoptosis by activating a proapoptotic caspase cascade and relieving suppression of antiapoptotic STAT3 signaling[52].

Various active components isolated from the soft coral Sinularia flexibilis, such as 11-epi-sinulariolide acetate and sinulariolide, could inhibit HCC cell migration and invasion by reducing matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9), and urokinase-type plasminogen activator (uPA) expression[53]. Sinularin induced DNA damage, G2/M phase arrest, and apoptosis[54].

In recent years, increasing attention has been paid to the anti-tumor activities of cockles. Some data have shown that polypeptides derived from cockles can exert anti-tumor activity by inhibiting the MAPK signaling pathway[55]. Guo et al[56] found that the ASP-3 protein isolated from Arca subcrenata inhibited HepG2 cell proliferation.

Marine microorganisms can produce various metabolites with unique structures and pharmacological activities, such as SZ-685C[57], which is a naturally biological active substance isolated from secondary metabolites of marine mangrove endophytic fungus number 1403 and could induce apoptosis through the Akt/FOXO pathway. EPS11, a bacterial polysaccharide extracted from Bacillus spp. 11, can inhibit the growth and metastasis of HCC-related liver cancer cells (Huh7.5 cells) by blocking their adhesion and destroying the formation of filamentous structures.

Nemopilema nomurai is one of the largest jellyfish species. The venom Nemopilema nomurai (Nv) contains highly selective dual inhibitors of the Akt and mTOR signaling pathways, which induce cytotoxicity and apoptosis in HepG2 cells, but not normal cells[58]. Yet, Nv can inhibit the metastasis and invasion of HepG2 cells by inhibiting the epithelial–mesenchymal transition[59].

Fucoidan extracted from the brown seaweed Undaria pinnatifida induces apoptosis in human HCC SMMC-7721 cells by increasing ROS production and inducing mitochondrial oxidative damage, mitochondrial membrane potential depolarization, and caspase activation. Fucoidan can also reduce lymphangiogenesis and tumor lymphatic (by suppressing HIF-1α/VEGF-C signaling), and then attenuate the PI3K/Akt/mTOR signaling pathways. Phycobiliproteins are components of red algae that include phycocerythin, phycocerycyanin, phycocyanin, and allophycocyanin, which can have anti-oxidative, anti-viral, anti-tumor, immunity-enhancing, and anti-inflammatory effects[60]. Park et al[61] demonstrated that dietary RPE could modulate the gut microbiota of H22 HCC cell-bearing mice. In vitro experiments have revealed that COS showed significant antitumor activity against HepG2 tumor cells.

Ovothiol A, isolated from Paracentrotus lividus oocytes, can inhibit HepG2 cell proliferation by activating an autophagic process.

**CONCLUSION**

Treatments for chronic liver diseases, i.e., etiological treatment, protective treatment for liver injury, antifibrotic treatment, and treatment of decompensated complications of liver cirrhosis, are all effective and of great significance in preventing the progression of liver disease, maintaining liver function, reducing complications of portal hypertension, and preventing liver cancer. In recent years, intense research of marine resources has brought to light new prospects for developing marine-based drugs. Marine-derived bioactive compounds show great potential in health products and medicine. With the discovery of bioactive marine compounds and in-depth discussions of their therapeutic mechanism, their applications will continue to expand, and ultimately benefit more patients and humans. However, most of the information discussed above has only been demonstrated in vitro or in animal studies. The effects of these compounds in humans have yet to be fully characterized. Further research, including clinical trials, must be carried out before such marine compounds can be applied therapeutically.

**FOOTNOTES**

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