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Contents

Thrice Monthly Volume 10 Number 8 March 16, 2022

OPINION REVIEW

- 2363 eHealth, telehealth, and telemedicine in the management of the COVID-19 pandemic and beyond: Lessons learned and future perspectives

Giaccalone A, Marin L, Febbi M, Franchi T, Tovani-Palone MR

MINIREVIEWS

- 2369 Developing natural marine products for treating liver diseases

Wei Q, Guo JS

ORIGINAL ARTICLE

Case Control Study

- 2382 Analysis of bacterial spectrum, activin A, and CD64 in chronic obstructive pulmonary disease patients complicated with pulmonary infections

Fei ZY, Wang J, Liang J, Zhou X, Guo M

Retrospective Cohort Study

- 2393 Computed tomography perfusion imaging evaluation of angiogenesis in patients with pancreatic adenocarcinoma

Liu W, Yin B, Liang ZH, Yu Y, Lu N

Retrospective Study

- 2404 Epidemiological features and dynamic changes in blood biochemical indices for COVID-19 patients in Hebi

Nie XB, Shi BS, Zhang L, Niu WL, Xue T, Li LQ, Wei XY, Wang YD, Chen WD, Hou RF

Clinical Trials Study

- 2420 Identification and predictive analysis for participants at ultra-high risk of psychosis: A comparison of three psychometric diagnostic interviews

Wang P, Yan CD, Dong XJ, Geng L, Xu C, Nie Y, Zhang S

- 2429 Prognostic significance of peritoneal metastasis from colorectal cancer treated with first-line triplet chemotherapy

Bazarbashi S, Alghabban A, Aseafan M, Aljubran AH, Alzahrani A, Elhassan TA

Observational Study

- 2439 Effect of intraoperative cell rescue on bleeding related indexes after cesarean section

Yu YF, Cao YD

Prospective Study

- 2447 Effectiveness of the combination of workshops and flipped classroom model to improve tube fixation training for nursing students
Wang YC, Cheng HL, Deng YM, Li BQ, Zhou XZ

META-ANALYSIS

- 2457 Mortality in patients with COVID-19 requiring extracorporeal membrane oxygenation: A meta-analysis
Zhang Y, Wang L, Fang ZX, Chen J, Zheng JL, Yao M, Chen WY

CASE REPORT

- 2468 Escitalopram-induced hepatitis: A case report
Wabont G, Ferret L, Houdre N, Lepied A, Bene J, Cousein E
- 2474 Fatal community-acquired bloodstream infection caused by *Klebsiella variicola*: A case report
Long DL, Wang YH, Wang JL, Mu SJ, Chen L, Shi XQ, Li JQ
- 2484 Endoscopic extraction of a submucosal esophageal foreign body piercing into the thoracic aorta: A case report
Chen ZC, Chen GQ, Chen XC, Zheng CY, Cao WD, Deng GH
- 2491 Severe tinnitus and migraine headache in a 37-year-old woman treated with trastuzumab for breast cancer: A case report
Liu YZ, Jiang H, Zhao YH, Zhang Q, Hao SC, Bao LP, Wu W, Jia ZB, Jiang HC
- 2497 Metastatic urothelial carcinoma harboring *ERBB2/3* mutations dramatically respond to chemotherapy plus anti-PD-1 antibody: A case report
Yan FF, Jiang Q, Ru B, Fei XJ, Ruan J, Zhang XC
- 2504 Retroperitoneal congenital epidermoid cyst misdiagnosed as a solid pseudopapillary tumor of the pancreas: A case report
Ma J, Zhang YM, Zhou CP, Zhu L
- 2510 Immunoglobulin G4-related kidney disease involving the renal pelvis and perirenal fat: A case report
He JW, Zou QM, Pan J, Wang SS, Xiang ST
- 2516 Fluoroscopic removal of fractured, retained, embedded Z self-expanding metal stent using a guidewire lasso technique: A case report
Bi YH, Ren JZ, Li JD, Han XW
- 2522 Treatment and five-year follow-up of type A insulin resistance syndrome: A case report
Chen YH, Chen QQ, Wang CL
- 2529 Effective response to crizotinib of concurrent *KIF5B-MET* and *MET-CDR2*-rearranged non-small cell lung cancer: A case report
Liu LF, Deng JY, Lizaso A, Lin J, Sun S

- 2537** Idarucizumab reverses dabigatran-induced anticoagulation in treatment of gastric bleeding: A case report
Jia Y, Wang SH, Cui NJ, Liu QX, Wang W, Li X, Gu YM, Zhu Y
- 2543** Immunoglobulin G4-related disease involving multiple systems: A case report
An YQ, Ma N, Liu Y
- 2550** Daptomycin and linezolid for severe methicillin-resistant *Staphylococcus aureus* psoas abscess and bacteremia: A case report and review of the literature
Hong XB, Yu ZL, Fu HB, Cai ZH, Chen J
- 2559** Isolated scaphoid dislocation: A case report and review of literature
Liu SD, Yin BS, Han F, Jiang HJ, Qu W
- 2569** Dual biologic therapy with ocrelizumab for multiple sclerosis and vedolizumab for Crohn's disease: A case report and review of literature
Au M, Mitrev N, Leong RW, Kariyawasam V
- 2577** Cardiac rehabilitation in a heart failure patient after left ventricular assist device insertion and subsequent heart transplantation: A case report
Yang TW, Song S, Lee HW, Lee BJ
- 2584** Large retroperitoneal atypical spindle cell lipomatous tumor, an extremely rare neoplasm: A case report
Bae JM, Jung CY, Yun WS, Choi JH
- 2591** Hepatocellular carcinoma effective stereotactic body radiotherapy using Gold Anchor and the Synchrony system: Two case reports and review of literature
Masuda S, Tsukiyama T, Minagawa Y, Koizumi K, Kako M, Kinbara T, Haruki U
- 2604** Mantle cell lymphoma with endobronchial involvement: A case report
Ding YZ, Tang DQ, Zhao XJ
- 2610** Fatal systemic emphysematous infection caused by *Klebsiella pneumoniae*: A case report
Zhang JQ, He CC, Yuan B, Liu R, Qi YJ, Wang ZX, He XN, Li YM
- 2616** Takotsubo cardiomyopathy misdiagnosed as acute myocardial infarction under the Chest Pain Center model: A case report
Meng LP, Zhang P
- 2622** Cystic teratoma of the parotid gland: A case report
Liu HS, Zhang QY, Duan JF, Li G, Zhang J, Sun PF
- 2629** Silver dressing in the management of an infant's urachal anomaly infected with methicillin-resistant *Staphylococcus aureus*: A case report
Shi ZY, Hou SL, Li XW
- 2637** Drain-site hernia after laparoscopic rectal resection: A case report and review of literature
Su J, Deng C, Yin HM

- 2644** Synchronized early gastric cancer occurred in a patient with serrated polyposis syndrome: A case report

Ning YZ, Liu GY, Rao XL, Ma YC, Rong L

- 2650** Large cystic-solid pulmonary hamartoma: A case report

Guo XW, Jia XD, Ji AD, Zhang DQ, Jia DZ, Zhang Q, Shao Q, Liu Y

LETTER TO THE EDITOR

- 2657** COVID-19 pandemic and nurse teaching: Our experience

Molina Ruiz JC, Guerrero Orriach JL, Bravo Arcas ML, Montilla Sans A, Escano Gonzalez R

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Developing natural marine products for treating liver diseases

Qian Wei, Jin-Sheng Guo

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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%[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 carotenoids (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 PPAR α 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,

Table 1 Bioactive marine compounds and extracts used for treating liver diseases

Type of activity	Organism	Species	Active compound/extract	Associated mechanism	Disease/model	Ref.
Antioxidative and anti-inflammatory						
	Fish	Chum salmon	MCPs	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 (<i>Euphausia superba</i>)	PPC, peptides	Increased total antioxidant capacity in plasma, increased liver gene expression of mitochondrial <i>SOD2</i> , 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 <i>TNF-α</i> and <i>IL-6</i> mRNA expression, increased Nrf2 and HO-1 expression, and suppressed ethanol-induced apoptotic proteins in the liver	ALD/mouse model, ethanol-induced	[34]
	Shellfish	<i>Meretrix</i>	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	<i>Haematococcus pluvialis</i>	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- and ROS production; inhibited MAPK and NF-B 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	<i>Laminaria japonica</i>	UAOS	Increasing both AMPKα and ACC phosphorylation	NAFLD/mouse model, HFD-induced	[18]
	Algae	Red alga (<i>Laurencia tristicha</i>)	Aplysin (a marine bromosquiterpene)	Revivified erythrocyte membrane fluidity, attenuated glutathione depletion, restored antioxidant activities, and reduced malondialdehyde overproduction	ALD/rat model, alcohol-induced	[30]
	Algae	Brown seaweed (<i>Sargassum thunbergia</i>)	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	<i>Fucus vesiculosus</i>	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]

			systems by upregulating the hepatoprotective enzyme hemeoxygenase-1		
Algae	<i>Hypnea muciformis</i>	Ethanol extract	Regulated activities/levels of lipid-peroxidation byproducts, antioxidant enzymes, and biotransforming phase I and II enzymes in the circulation	DILI/rat model/CCl ₄ -induced	[43]
Gut microbiota modulation					
Sea cucumber	<i>Stichopus japonicus</i>	Sulfated polysaccharide	Preventing HFD-induced gut disorders, as indicated by enriched levels of the probiotic <i>Akkermansia</i> and reduced endotoxin-bearing Proteobacteria, improved SCFA and endotoxin (LPS) levels, and improved gut tissue index	NAFLD/mouse model, HFD-induced	[12]
Algae	<i>Spirulina platensis</i>	95% ethanol extracts (SPL95, major fatty acids)	AMPK-signal pathway; downregulated mRNA and protein levels of SERBP-1c, 3-hydroxy-3-methylglutaryl 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 <i>Prevotella</i> , <i>Alloprevotella</i> , <i>Porphyromonadaceae</i> , <i>Barnesiella</i> , and <i>Paraprevotella</i> ; decreasing microbes such as <i>Turicibacter</i> , <i>Romboutsia</i> , <i>Phascolarctobacterium</i> , <i>Olsenella</i> , and <i>Clostridium</i> XVIII	NAFLD/rat model, HFD-induced	[21]
Fungus	<i>Aspergillus versicolor</i> 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	[22]
Lipid metabolism improvement					
Fish	Fish	Fish oil, omega-3-PUFA	Downregulated sterol regulatory element binding protein 1c (SREBP-1c) and upregulated peroxisome proliferator activated receptor α (PPAR- α) which would favour fatty acid oxidation and reduce steatosis	NAFLD/human study, meta-analysis, RCT	[9]
Starfish	<i>Asterias amurensis</i>	Oil, n-3 PUFA	Enhanced fatty acid β -oxidation and suppressed TG and cholesterol synthesis	NAFLD/mouse model, HFD-induced	[10]
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 <i>Mucispirillum</i> and increased abundance of <i>Coprococcus</i> 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	[23]
Algae	Red seaweed	<i>Palmaria mollis</i> (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	[20]
Algae	Green algae	SPX (a carotenoid)	Suppression of LXR α activity, and downregulation of nuclear transcription factor SERBP-1c and a set of related genes	NAFLD/cell model, LXR α agonist-induced	[15]
Algae	<i>Spirulina platensis</i>	95% ethanol extract (SPL95)	Downregulating the expression of SERBP-1c, 3-hydroxy-3-methyl	NAFLD/rat model, HFD-induced	[21]

				glutaryl coenzyme A reductase, and members of the acetyl CoA carboxylase pathway; upregulating adenosine 3,5-monophosphate-activated protein kinase- α in the liver; enrichment of beneficial bacteria		
	Algae	Brown alga (<i>Ishige okamurae</i>)	DPHC	Stimulated AMPK and ACC phosphorylation in both liver and epididymal adipose tissue, reduced the expression of critical enzymes for lipogenesis, including PPAR α , C/EBP, SERBP-1c, FABP4, and FAS	NAFLD and obesity/mouse model, HFD-induced	[19]
	Algae	<i>Fucus vesiculosus</i>	Fucoidan	Improved MetS <i>via</i> ROS-mediated regulation of JNK, pAkt, and AMPK signaling pathways	NAFLD/mouse model, HFD-induced; NAFLD/cell model, sodium palmitate-induced	[16]
	Fungus	<i>Aspergillus versicolor</i> LZD-44-03-derived asperlin	Asperlin	Increased energy expenditure and enhanced thermogenic gene expression in adipose tissue, and increased diversity and shifted structure of the gut microbiota	NAFLD and obesity/mouse model, HFD-induced	[22]
Antiviral						
	Sponge	<i>Dactylosporgia metachromia</i>	Metachromin A, merosquit-erpene	Inhibited HBV production <i>via</i> impairment of the viral promoter activity	HBV/cell model	[47]
	Sponge	Red sea sponge (<i>Amphimedon</i> spp.)	Nakinadine B and 3,4-dihydro-6-hydroxymanzamine A	Anti-HCV NS3 helicase and protease activities	HCV/cell model	[38]
	Formosan soft coral	<i>Lobophytum crassum</i>	Lobohedleolide	Suppressing HCV replication by inhibiting JNK phosphorylation, leading to reduced c-Jun phosphorylation and C/EBP expression, and reduced COX-2 expression	HCV/cell model	[40]
	Ascidian	<i>Styela plicata</i>	Effective components (peptides, alkaloids, saponins, macrolides, terpenoids)	Increased serum IL-2; reduced serum HBV DNA levels	HBV/mouse model, HBV-transgenic	[46]
	Algae	<i>Cladosiphon okamuranus</i> Tokida	Fucoidan	Inhibited expression of the HCV replicon	HCV/cell model; chronic HCV infection, and HCV-related cirrhosis and hepatocellular carcinoma/human study	[39]
	Fungus (a sponge associated fungus)	<i>Trichoderma harzianum</i>	Two new sesquiterpene-based analogues, namely, harzianoic acids A (1) 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	[37]
Anti-cholestatic						
	Sponge	<i>Theonella swinhoei</i>	Theonellasterol	Selective FXR antagonism, increased MRP4 expression	Cholestasis/HepG2 cells; cholestasis/mouse model, BDL-induced	[48]
Anti-fibrotic						
	Algae	<i>Cladosiphon okamuranus</i> ; <i>Fucus vesiculosus</i>	Fucoidan	Reduced TGF- β 1 expression	Liver fibrosis/mouse model, DEN-induced; Liver fibrosis/mouse model, alcohol-induced	[32, 51]
	Starfish/algae	<i>haematococcus pluvialis</i>	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	[14]

Algae	<i>Arthrospira platensis</i>	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	[52]
Sea urchin	Sea urchin eggs	Ovothiol A	Negatively regulating redox homeostasis and the activation of key fibrotic markers TGF- β , α -SMA, and TIMP-1	Liver fibrosis (CCl ₄ model)	[50]
Anti-tumor					
Sponge	<i>Pseudoceratina</i> spp.	Heterocyclic alkaloids, ceratamines A and B	Disruption of microtubule dynamics, antimetabolic agents	HCC/ <i>in vitro</i> , rat liver microsomes	[58]
Sponge	<i>Crambe crambe</i>	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	[60]
<i>Erylus</i> spp. sponges	Actinomycetales isolated from <i>Erylus</i> genera		Cytotoxic bioactivity	HCC/cell model	[61]
Soft coral	<i>Spongodes</i> spp.	Steroid (MESP)	Inhibition of STAT3 phosphorylation	HCC/cell model	-
Soft coral	<i>Sinularia flexibilis</i>	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	<i>Arca subcrenata</i> Lischke	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	<i>Nemopilema nomurai</i>	Venom	Dual inhibition of the Akt and mTOR signaling pathways	HCC/tumor xenograft animal model	-
Sea urchin	<i>Paracentrotus lividus</i> Oocytes	Ovothiols	Antioxidant capacity, hydrogen peroxide generation	HCC/cell model	-
Starfish/algae	<i>haematococcus pluvialis</i>	Astaxanthin	Regulating JAK1/STAT3, NF- κ B, Wnt/ β 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	[14]
Algae	<i>Undaria pinnatifida</i>	Fucoidans	Induced apoptosis <i>via</i> the ROS-mediated mitochondrial pathway	HCC/cell model	-
Microorganisms	Mangrove endophytic fungus	SZ-685C	Induced apoptosis through the Akt/FOXO pathway	HCC/cell model; HCC/xenografted tumor model	-
Fungus	<i>Aspergillus terreus</i> strain PF-26, associated with marine sponges	(+)Terrein	Induced cell-cycle arrest in G2/M phase; decreased expression of proteins related to cell morphology (fibronectin, N-cadherin, and vimentin); altered expression of genes related to cell-cycle progression	HCC/cell model	[59]
Bacteria	<i>Bacillus</i> spp. 11 (EPS11)	Bacterial polysaccharide	Blocking cell adhesion and attenuating filiform structure formation	HCC/cell model	-

ACC: Acetyl-CoA carboxylase; AFB1: Aflatoxin B1; ALD: Alcohol-induced liver damage; AMPK: Adenosine monophosphate-activated protein kinase; AMPK α : AMP-activated protein kinase α ; C/EBP: CCAAT/enhancer binding protein alpha; CAT: Catalase; DEN: Diethylnitrosamine; DPHC: Diphlorethohydroxycarmalol; HDAC: Histone deacetylase; GPX: Glutathione peroxidase; HFD: High-fat diet; IL-2: Interleukin-2; IL-6: Interleukin-6 mRNA; JNK: c-Jun N-terminal kinase; LPS: Lipopolysaccharide; LXR α : Liver X receptor α ; MCP: Marine collagen peptide; mTOR: Mammalian target of rapamycin; NAFLD: Non-alcoholic fatty liver disease; NF- κ B: Nuclear factor-kappa B; NOD: Nucleotide-binding oligomerization domain protein; Nrf2: Nuclear factor erythroid-2-related factor 2; pAkt: Protein kinase B; PPAR: Proliferator-activated receptor alpha; PPAR γ : Peroxisome proliferator-activated receptor gamma; PPC: Phospholipid-protein complex; PUFA: Polyunsaturated fatty acid; ROS: Reactive oxygen species; SCFA: Short-chain fatty acid; SERBP-1c: Sterol regulatory element-binding protein-1c; SOD: Superoxide dismutase; STAT3: Signal transducer and activator of transcription 3; TGF- β 1: Transforming growth factor beta 1; TLR4: Toll-like receptor 4; TNF: Tumor necrosis factor; RCT: Randomized controlled trial; UAOS: Unsaturated alginate oligosaccharides; VEGFR: Vascular endothelial growth factor receptor.

downregulating TGF- β 1/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 (LXR α) 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 (DPHC), 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 microalga *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.

Meretrix 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 erythrocyte-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 oxidant 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 antioxidant 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 pangenotypic 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.

Harzianoic 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, nakinadine 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 *Hypnea muciformis* (red algae) was found to possess antioxidant,

antitumor, and antimicrobial activities and to exhibit hepatoprotective activity against CCl₄-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 1 (TGF- β 1), 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 (CCl₄)-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- β 1 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- β 1/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]. Actinomycetales 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 natural biologically 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 HCV-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* (NnV) 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, NnV 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-1 α /VEGF-C signaling), and then attenuate the PI3K/Akt/mTOR signaling pathways. Phycobiliproteins are components of red algae that include phycoerythrin, phycoerycyanin, 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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