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Review Article

Etiology and Treatment of the Nutritional Fatty Liver in Fish: A Review

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ABSTRACT

Nutritional fatty liver disease in cultured fish has seriously restricted the sustainable development of aquaculture due to its adverse effects on fish growth, immune function, and the safety of fish products. This review aims to provide a theoretical basis for the treatment of fish fatty liver disease by summarizing the recent progress in the etiology and treatments of nutritional fatty liver in fish. High-energy diets (high lipid and high carbohydrate) and the nutritional deficiency (carnitine, choline, and vitamins) are the main causes of nutritional fatty liver disease. Dietary solutions to fish fatty liver disease includes carnitine, choline, unsaturated fatty acids, plant extracts (alkaloids, polysaccharides, flavonoids, etc.), short-chain organic acid salts (calcium pyruvate and sodium butyrate), and selenium element (nano selenium and organic selenium).

INTRODUCTION

The aquaculture sector has been growing for a century. Aquatic goods are becoming more and more in demand as a component of human food as the world's population rises. The ecological environment of fish in aquaculture and wild ecology are very different from one another. Yet, fish require a very long period to evolve in an adapted way (Naiel *et al*., 2022). Fish feed manufacturers have the propensity to use more high-energy raw materials, such as carbohydrates and fats (Beamish and Thomas, 1984; Boujard *et al*., 2004; Fang *et al*., 2021; Wang *et al*., 2019), to boost yield and lower production costs due to the scarcity of protein raw resources and the high market demand (NRC, 2011). However, these high-energy meals frequently result in decreased growth performance (Bright *et al*., 2005; Fang *et al*., 2021; Li *et al*., 2016), liver diseases (Jia *et al*., 2020b; Li *et al*., 2021; Zhao *et al*., 2022), and reduced antioxidant and immunological capability (Jia *et al*., 2020a; Zhao *et al*., 2022; Zhou *et al*., 2020). The liver is typically where lipids and glucose metabolism takes place. In aquaculture, the liver health of farmed fish is very important. Many recent pieces of research have found that liver lipid buildup can cause nutritional fatty liver in fish, which can then result in oxidative stress and liver injury in fish (Du *et al*., 2008; Lu *et al*., 2014). Similar to this, lipid buildup in the liver can result from fish feed manufacturing lacking vital nutrients like choline and carnitine. Aquaculture's potential is greatly hampered by the nutritional fatty liver (Gao *et al*., 2014; Khosravi *et al*., 2015; Pan *et al*., 2017). Nutritional fatty liver has received more and more attention in the industry, so this paper mainly discusses the etiology and treatments the nutritional fatty liver in fish.

ETIOLOGY OF THE NUTRITIONAL FATTY LIVER

High-energy diets

High levels of carbohydrates

Raising the percentage of carbohydrates in the meal, though can save feed costs and play a specialized function in protein sparing, it can also have many drawbacks, including a drop in fish development performance that causes liver lipid buildup and even fatty liver (Table I).

The protein, energy, and carbohydrate digestibility of rainbow trout (*Oncorhynchus mykiss*) rapidly reduced as the carbohydrate ratio in the meal rose (Tekİnay and Davies, 2001). It was discovered that adding 19.11% starch to the largemouth bass (*Micropterus salmoides*) diets significantly elevated the levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in blood and that the liver cells were abnormally organized, inflated, and badly

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vacuolated (Zhao *et al.*, 2022). Likewise, snakeheads (*Channa argus*) fed a diet containing 19% carbohydrates acquired high blood lipid levels and their liver's crude fat and glycogen levels rose (Ding *et al.*, 2020). The plasma triglyceride (TG) content and liver vacuolization area of 45% corn starch-supplemented Nile tilapia (*Oreochromis niloticus*) were greater than those of the control group (30% corn starch). Also, a 45% corn starch diet caused liver injury in Nile tilapia; plasma AST and ALT activities were higher than in the control group (Li *et al.*, 2021). Another study on Nile tilapia discovered that the expression of the lipid synthesis genes such as diacyl transferase (DGAT), sterol regulatory element binding protein 1 (SREBP1), and fatty acid synthase (FAS)) was significantly enhanced and that 45% of maize starch levels tended to create fatty livers (Zhu *et al.*, 2020). According to study by Fang *et al.* (2021) early feeding of grass carp (*Ctenopharyngodon Idella*) with 60% maltodextrin improved the fish's growth performance. Nevertheless, sustained feeding of grass carp with 60% maltodextrin led to the development of clear signs of hyperglycemia, an increase in the expression of FAS mRNA, and the deposition of fat. Studies have revealed that eating a high-carbohydrate diet can make blunt snout breams (*Megalobrama amblycephala*) hyperlipemia, suppress the expression of genes involved in lipid oxidation, and increase the expression of genes involved in lipid synthesis (Ge *et al.*, 2022; He *et al.*, 2021).

High levels of lipids

Studies conducted as early as 1978 discovered that raising the quantity of fat in feed might have a specific impact on saving protein (Watanabe *et al.*, 1978). Fish have a limited ability to use lipids in their meal. A range of issues, including lipid metabolic disorder, growth limitation, inappropriate lipid buildup in the liver, and even fatty liver, will result from overly blindly raising the level of lipids in feed (Zhou *et al.*, 2020).

For largemouth bass, it was shown that a diet containing 10% fat had the highest growth results (Table II). Plasma ALT and AST levels rose and liver antioxidant capacity fell when dietary fat levels reached 20% (Zhou *et al.*, 2020). Furthermore, research on largemouth bass found that when dietary fat levels exceed 16%, liver damage already develops (Bright *et al.*, 2005). In the Nile tilapia study, it was discovered that the hepatosomatic index (HSI) and visceral somatic indices (VSI) of fish were greatly enhanced when the fat content in the food was 12%, and the concentration of TG in the liver and plasma was also dramatically elevated (Zhang *et al.*, 2020). Hyperlipidemia in tilapia, increased lipid buildup in the liver, reduced antioxidant capability, and increased apoptosis are all linked to lipid levels of 21% or higher (Jia *et al.*, 2020a, b). Studies on the large yellow

Table I. Physiological effects of high-carbohydrate diets in fish.

Species name	High-carbohydrate diet (%)	Carbohydrate sources	Physiological effects	Feeding cycle (weeks)	Reference
Rainbow trout (*Oncorhynchus mykiss*)	43.5	Wheat meal	↓feed efficiency (FE), ↓specific growth rate (SGR), ↑hepatosomatic index (HSI), after feeding for 24 h, blood glucose remained high.	12	Tekİnay and Davies, 2001
Largemouth bass (*Micropterus salmoides*)	19.11	Cassava starch	**In the plasma:** ↑pyruvic acid (PA), ↑lactic acid (LA), ↑triglyceride (TG), ↑free fatty acid (FFA), ↑aspartate aminotransferase (AST), alanine aminotransferase (ALT). **In the liver:** ↑phosphoenolpyruvate carboxykinase (PECK), ↑ lipase (LPS), ↓total antioxidant capacity (T-AOC), ↓catalase (CAT), ↓glutathione peroxidase (GSH-Px), ↑liver vacuolation.	8	Zhao *et al.*, 2022
Nile tilapia (*Oreochromis niloticus*)	45	Corn starch	↑HSI, ↑visceral somatic index (VSI), ↑TG (plasma, liver, and whole-bady), ↑ALT and AST (liver), ↑ malondialdehyde (MDA) in the liver, ↑liver vacuolation.	8	Li *et al.*, 2021
	45	Corn starch	↑the mRNA expression of lipid synthesis (DGTA, SREBP, and FAS).	8	Zhu *et al.*, 2020
Grass carp(*Ctenopharyngodon idella*)	60	Malty dextrin	**Long-term feeding (8 weeks):** ↓survival, ↑plasma glucose level, short-term feeding (3~7 days): ↑liver glycogen, ↑the mRNA expression of GK and FAS.	9	Fang *et al.*, 2021
Blunt snout bream (*Megalobrama amblycephala*)	43	Corn starch	**In the plasma:** ↑TG, ↑TC, ↑glucose.↑liver lipid drop, **Gene expression:** ↓CPT1,↓IRS,↑FOXO1,↑GLUT2,↑GS, ↑ACCα, ↑FAS. ↑TC (plasma, liver), ↑TG (liver), ↓total bile acid (TBA),	10	He *et al.*, 2021
	45	Corn starch	**Gene expression:** ↑HMGCR, ↓CYP7A1, ↑FXRα	12	Ge *et al.*, 2022
Snakeheads (*Channa argus*)	19	Flour	↑HSI, ↑crude fat of liver, ↑TG (plasma), ↓the activities of alkaline phosphatase (AKP), ↑liver glycogen, ↑hepatocyte size.	8	Ding *et al.*, 2020

DGAT, diacyl transferase; SREBP, sterol regulatory element binding protein; GK, glucokinase; FAS, fatty acid synthase; CPT1, carnitine palmitoyl transferase 1; IRS, insulin receptor substrate; FOXO1, forkhead transcription factor 1; GLUT2, glucose transporter 2; GS, glycogen synthase; ACCα, acetyl-CoA carboxylase α; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; CYP7A1, cholesterol7α-hydroxylase; FXRα, farnesoid X receptor α.

Table II. Physiological effects of high-lipid diets in fish.

Species name	High-lipid diet (%)	Lipid feedstock	Physiological effects	Feeding cycle (weeks)	Reference
Largemouth bass (*Micropterus salmoides*)	20	Fish oil	↑ viscera ratio (VR), ↑ HSI, ↑ intraperitoneal ratio (IPF), ↑ hepatic fat content, ↑ ALT and AST, ↑TG, TC, and FFA (plasma), ↑high-density lipoprotein	8	Zhou *et al*., 2020
	15/20	Soybean oil	cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) in the plasma. **Activities of the proteins in the liver:** ↑CPT1, AMPK, FBPase, and PECK, ↑MDA, ↓SOD and CAT. ↓ FCR, ↑lipid content of whole-bady.		Bright *et al*., 2005
Nile tilapia (*Oreochromis niloticus*)	12	Soybean oil	↑ viscerosomatic index (VSI), ↑ HSI, ↑ TG (liver, plasma, and muscle), **Gene expression:** ↑ PPARα, SREBP, and FAS, ↓CPT1-α, and CPT1-β,	11	Zhang *et al*., 2020
	21		↓ GSH (plasma), ↓SOD (liver and intestine), ↑MDA (liver) ↑ hepatic vacuole, ↑ALT and AST, ↑IL-1β and TNF-α (plasma), ↓SOD, CAT, GSH, T-AOC (liver and plasma), ↑MDA (liver and plasma), **Gene expression:** ↑Caspase 3, ↓ Bcl-2, ↑Bax, ↑P53, ↑TG and TC (plasma and liver), ↑ LDL-C and HDL-C (plasma and liver)	13	Jia *et al*., 2020a, b
Blunt snout bream (*Megalobrama amblycephala*)	11	Fish oil	↑ AST and ALT, ↑ liver vessels dilated and vacuolated, ↓ survival rate, **Gene expression:** ↑IL-1βand TNF-α, ↑Bax, Caspase 3, and Caspase 9. ↓SOD,	8	Dai *et al*., 2019
		Soybean oil	CAT, and GSH (liver), ↑MDA (liver). ↑DNA damage.		
Grass carp (*Ctenopharyngodon idella*)	10.7	Fish oil	↓WG, SGR, and feed intake (FI), ↑ lipid content of whole-bady, ↑TG and Glucose (plasma), **Gene expression:** ↓ ACC and FAS, ↑ PPARα and CPT1.	8	Li *et al*., 2016
	8	Soybean oil	↑TG (liver), **Gene expression:** ↑ACC, FAS, DGAT1a, and DGAT1b	2	Sun *et al*., 2021
Large yellow croker (*Larimichthys crocea*)	17	Fish oil	↑TG (liver, muscle, plasma, and whole fish), ↑TC, LDL-C, FFA, (plasma), ↓HDL-C and Glucose (plasma), ↑liver lipid drop	10	Zhang *et al*., 2023

CPT1, carnitine palmitoyl transferase 1; AMPK, amp-activated protein kinase; FBPase, fructose-1, 6-bisphosphatase; PECK, phosphoenolpyruvate carboxykinase; PPARα, peroxisome proliferators-activated receptor α; IL-1β, interleukin 1β; TNF-α, tumor necrosis factor α; SREBP, sterol regulatory element binding protein; FAS, fatty acid synthase; Caspase3/9, cysteine-aspartic proteases-3/9; Bcl-2, b-cell lymphoma-2; Bax, bcl2-associated x protein; ACC, acetyl-CoA carboxylase; DGAT1a/b, diacyl transferase 1 a/b.

croaker (*Larimichthys crocea*) have revealed that 17% of lipid levels can cause hyperlipidemia and hepatic lipid buildup (Zhang *et al*., 2023). Dai *et al*. (2019) discovered that when the fat content of blunt snout bream feed reached 11%, the antioxidant capacity of the liver reduced compared to the control group (6% lipid). At 11% lipid level, the expression of apoptosis-related genes (cysteine-aspartic proteases 3/9 (Caspase 3/9)) in the liver of blunt snout bream was active. In grass carp, the expression of the lipid synthesis genes [acetyl-CoA carboxylase (*ACC*), *FAS*, and *DGAT*)] increased when the lipid content reached 8% (Sun *et al*., 2021). Nevertheless, other researchers have demonstrated that in grass carp, lipid level reaches 10.7%, lipid synthesis genes (*ACC and FAS*) are down-regulated and lipid deconstruction genes (peroxisome proliferators-activated receptor α (PPARα) and carnitine palmitoyl transferase 1 (CPT1)) are up-regulated (Li *et al*., 2016).

Essential nutrients deficiency

Choline: In addition to being a component of phospholipids, lecithin, and other tanglesome lipids, choline is a nutrient that functions similarly to vitamins by creating unstable methyl in living things (Zeisel, 1981).

It was discovered in research on parrot fish (*Oplegnathus fasciatus*) that a choline deficiency would cause a greater buildup of liver lipids and a reduction in the feed efficiency (FE) of parrot fish (Khosravi *et al*., 2015). By adding the choline synthesis inhibitor 2-amino-2-methyl-1-propanol (AMP) and various levels of choline to the diet of yellowtail kingfish (*Seriola lalandi*), Liu *et al*. (2021a) created a low choline model of yellowtail kingfish. According to the study, high levels of choline can reduce the pathological changes in the liver of yellowtail kingfish, which can lack choline and cause liver inflammation and damage. In the study of yellow catfish (*Pelteobagrus fulvidraco*), it was shown that adding choline to the diet was effective in reducing lipid accumulation in the liver, with the maximum choline addition level of 2273.6 mg/kg decreasing lipid accumulation in the liver (Luo *et al*., 2016). Thus, the lack of choline can cause fish liver lipid accumulation and hepatic damage problems.

Vitamin: Vitamins are vital nutrients for all organisms. Fish cannot produce the majority of vitamins which can only be received from the diet. In a study on grass carp, Pan *et al*. (2017) found that the fish's growth performance, oxidation resistance, and immunology would all suffer from a lack of vitamin E in their diet. Insufficient vitamin E would make grass carp's inflammatory response worse by controlling the expression of nuclear factor kappa-B (NF-κB) and nuclear facter E2-related factor 2 (Nrf2) mRNA.

Nevertheless, the study did not examine how the grass carp's liver would respond to a vitamin deficiency. According to a study on Japanese flounder (*Paralichthys olivaceus*), adding small amounts of vitamins E and C to oxidized fish oil will help the fish maintain its usual development rate. Nevertheless, excessive vitamin E and C intake might result in lipid peroxidation, which was characterized by a rise in thiobarbituric acid reactive substances (TBARs) in liver tissue (Gao *et al*., 2014). Similar results were reported in studies on black sea bream (*Acanthopagrus schlegeli*), which showed that oxidized fish oil can impair growth and significantly raise HSI. Black sea bream's growth performance can be enhanced by adding vitamin E to oxidized fish oil (Peng *et al*., 2009).

Methionine: For fish and terrestrial animals to develop and operate metabolically, methionine is necessary. The ultimate body weight and feed efficiency of rainbow trout are both dramatically decreased by methionine shortage. Moreover, the liver's antioxidant capacity is decreased, and the liver cells' mitophagy is increased (Séité *et al*., 2018). In the research of cobia (*Rachycentron canadum*), it was discovered that the liver lipid of cobia dramatically increased with the rise of dietary methionine supplement level from 0.62% to 1.02%. Nonetheless, the liver lipid was considerably reduced when the methionine supplement amount was raised from 1.02% to 1.42% (Wang *et al*., 2016). Yet with rising dietary methionine levels, tiger puffer fish (*Fugu ocellatus*) were shown to have significantly higher liver and overall fat levels (Xu *et al*., 2019).

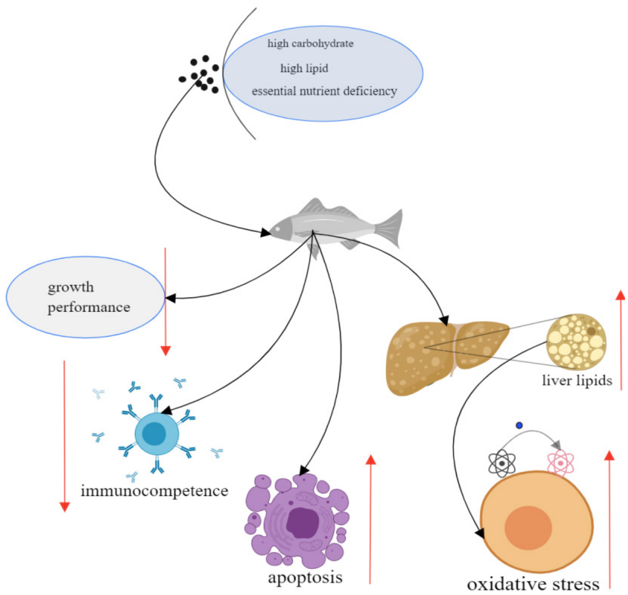

Fig. 1. General overview of the etiology and physiological effects of the nutritional fatty liver.

Table III. Physiological effects of deficiencies of essential nutrients in diets in fish.

Essential nutrient	Species name	Additive amount	Physiological effects	Feeding cycle (weeks)	Reference
Choline	Parrot fish (*Oplegnathus fasciatus*)	0% with AMP	↓ FBW, WG, SGR, and FE, ↑ liver lipid, ↑DHA and EPA (liver).	12	Khosravi *et al*., 2015
	Yellowtail kingfish (*Seriola lalandi*)	(0.59, 1.25, 1.56, 3.11, and 6.22 g/kg) with AMP	**0.59 group:** The lowest SGR and feed intake, ↑ liver lymphocyte abundance,↑fish bile duct epithelial cells necrosis, ↑necrotic hepatocyte.	8	Liu A *et al*., 2021a
	Yellow catfish (*Pelteobagrus fulvidraco*)	239.2, 1156.4, and 2273.6 mg/kg	**239.2 group:** The lowest FBW, WG, SGR, and FI, the highest HSI, the highest lipid content (liver), ↑ lipid accumulation and necrosis of liver cells	8	Luo *et al*., 2016
Vitamin	Grass carp (*Ctenopharyngodon idella*)	0, 45, 90, 135, 180, and 225 mg/kg	**0 mg/kg group:** The lowest FBW, SGR, FI, and FE, **In head kidney, spleen, and skin:** ↓ acid phosphtase (ACP), component 3 (C3), and component 4 (C4), ↑ MDA and protein carbonyl (PC) and reactive oxygen species (ROS), **In head kidney and spleen:** ↓CuZn-SOD, Mn-SOD, CAT, GPx, GST, and GSH,	10	Pan *et al*., 2017
	Japanese flounder (*Paralichthys olivaceus*)	OFO200E/500C OFO200E/1000C (mg/kg)	**OFO200E/1000C group:** ↑feed conversion ratio (FCR), ↓final weight, body weight gain (BWG), and SGR, ↑HSI, ↑TBARS (liver), ↑GPT and GOT (plasma).	8	Gao *et al*., 2014
	Black sea bream (*Acanthopagrus schlegeli*)	Ol/0 E Ol/250 E (mg/kg)	**Ol/250E group:** ↑weight gain and condition factor (CF), ↓HSI, ↓TBARS (liver), ↓crude lipid in whole bady,	9	Peng *et al*., 2009
Methionine	Rainbow trout (*Oncorhynchus mykiss*)	0.93% and 0.41%	**0.41% group:** ↓FBW and FE, ↑HSI, ↓total GSH, GSH, and GSSG (liver), ↑mitochondria autophagy in liver,	7	Séité *et al*., 2018
	Cobia (*Rachycentron canadum*)	0.62, 0.84, 1.02, 1.15, 1.25, and 1.42 (%)	**0.62→1.02:** ↑TG and TC (liver), 1.02→1.42: ↓TG and TC (liver), ↑the mRNA expression of IGF1, **1.02 group:** the highest weight gain (WG) and FE, ↑the mRNA expression of SREBP1, PPARγ, FAS, and SCD1.	10	Wang *et al*., 2016
	Tiger puffer fish (*Fugu ocellatus*)	0.61%, 1.1%, and 1.6%	**0.61→1.6:** ↑lipid in liver, ↑WG, ↑HSI, **0.61 group:** ↑the mRNA expression of FAS, PPARγ, and SCD1, ↓the mRNA expression of ACOX1, HSL, and ApoB100.	9	Xu *et al*., 2019

AMP, 2-amino-2-methyl-1-propanol; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; TBARs, thiobarbituric acid reactive subtances; GPT, glutamic pyruvic transaminase; GOT, glutamic oxaloacetic transaminase; IGF1, insulin-like growth factors 1; SREBP1, sterol regulatory element binding protein 1; PPARγ, peroxisome proliferators-activated receptor γ; FAS: fatty acid synthase; SCD1, delta-9-desaturase 1; ACOX1, acyl-CoA oxidase 1; HSL, hormone-sensitive lipase; ApoB100, apolipoprotein B100.

Table III displays the physiological impacts of essential nutrients on fish. Figure 1 shows an overview of the etiology and physiological effects of nutritional fatty liver disease.

TREATMENT OF THE NUTRITIONAL FATTY LIVER

Carnitine

A key element of lipid metabolism is carnitine. It is a synthetic precursor of the enzymes carnitine acyltransferase (CACT), CPT1, and carnitine palmitoyl transferase 11 (CPT11), and it facilitates the transportation of long-carbon chain fatty acids to the mitochondria for β-oxidation (Li *et al*., 2019b).

The activity of glutathione peroxidase (GPx) and malondialdehyde (MDA) levels in the liver of largemouth bass were considerably raised and lowered, respectively, by 0.02% L-carnitine supplementation (Chen *et al*., 2020). In studies on black sea bream, it was shown that supplementing the high-fat diet with 300 mg/kg of L-carnitine dramatically increased the activity of catalase (CAT) and lysozyme (LZM) in the fish's liver. Also, it can ameliorate the histological abnormalities in the liver brought on by a high-fat diet and promote the expression of genes for β-oxidation in the liver of black sea bream (Jin *et al*., 2019a).

Carnitine has left-handed and right-handed configurations. D-carnitine was discovered to enhance fat buildup in the liver of Nile tilapia and to trigger liver inflammation, oxidative stress, and apoptosis in Nile tilapia. D-carnitine, unlike L-carnitine, does not promote fish development (Li *et al*., 2019a).

Choline

As previously stated, a shortage of choline, an essential nutrient, induces fat buildup in the liver of parrot fish (Khosravi *et al*., 2015), and in yellowtail kingfish, it causes inflammation and liver damage (Liu *et al*., 2021a). Choline shortage is hypothesized to alter lipoprotein translocation in the liver, leading to the buildup of TG and total cholesterol (TC) in the liver and the development of fatty liver (Mai *et al*., 2009).

The liver lipid of cobia is reduced with increasing dietary choline levels, according to a cobia research (Mai *et al*., 2009). Choline supplementation in the diet of yellow catfish lowers fat buildup in the liver (Luo *et al*., 2016). Adding choline to a high-fat diet can minimize the inflammatory response induced by high-fat stress and lower cholesterol levels in the whole fish body and liver. Additional research has revealed that choline can limit the expression of lipogenesis genes, boost the expression of lipolysis genes, and reduce the production of NF-κB and pro-inflammatory cytokines in the liver and gut of black seabream (Jin *et al*., 2019b). Different species and even the same species have different needs for choline at different growth stages. Studying the demand for choline in fish is a means to combat fatty liver.

Unsaturated fatty acid

A high-fat diet suppresses β-oxidation and PPARα expression, resulting in steatosis and liver injury (Kang-Le *et al*., 2014). A study in common carp (*Cyprinus carpio*) discovered that dietary supplementation with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) rich algae boosted the expression of PPARα genes in the liver (Eljasik *et al*., 2020). A study on Atlantic salmon (*Salmo salar*) discovered that EPA can stimulate mitochondrial proliferation, boost lipid metabolism, and decrease intracellular lipid concentration (Kjær *et al*., 2008). Highly unsaturated fatty acid (HUFA) was also discovered to suppress FAS gene activity in the liver, limit fatty acid synthesis, and increase fatty acid catabolism in Atlantic salmon, resulting in hypolipidemia (Morais *et al*., 2011).

Early research has revealed that saturated fatty acids (SFAs) are more readily deposited in tissues than monounsaturated fatty acid (MUFA) and polyunsaturated fatty acid (PUFA) in rats (Clarke *et al*., 1990). According to research on giant yellow croakers, employing fish oil or soybean oil rich in unsaturated fatty acids as a source of fat will significantly lower blood ALT and AST levels (Qiu *et al*., 2017). Studies on silvery black porgy *(Sparidentex hasta*) has revealed that when the n-3 long-chain polyunsaturated fatty acid (n-3 LC-PUFA) content in the diet is too low (0.1%), the range of HSI, plasma TG, and TC of silvery black porgy increases. The rise of n-3 LC-PUFAs will boost the growth performance and immunity of silvery-black porgy, while the plasma TG and TC contents will decrease (Mozanzadeh *et al*., 2015). We can observe that eating unsaturated fatty acids helps to reduce lipid buildup. If the kinds and need for unsaturated fatty acids in various fish are thoroughly examined, it may be utilized as a strategy to combat nutritional fatty liver.

Plant extract

Plant extracts are classified as alkaloids, polysaccharides, flavonoids, organic acids, and so on. A lot of studies have been done on plant extracts as dietary supplements in the battle against fatty liver.

According to a study on black seabream, adding 10g/kg or 20g/kg of betaine to meals with 17% fat content will reduce steatosis and inflammatory reactions in the liver produced by high-fat diets via SIRT1/SREBP1/PPARα (Jin *et al*., 2021). It was shown that blunt-nosed seabream's liver apoptosis and oxidative stress were considerably decreased when berberine at doses of 50 mg/kg or 100 mg/kg was added to diets with 15% fat content (Lu *et al*., 2017). When hybrid grouper (*Epinephelus lanceolatus* ♂ × *Epinephelus fuscoguttatus* ♀) are exposed to the stress of a high-fat diet, it has been discovered that the extract of ginkgo biloba leaves lowers their blood lipid levels, increase their antioxidant capacity, and increases the expression of immune-related genes. In hybrid grouper, fewer apoptosis-related genes were expressed (Tan *et al*., 2018). Forskolin, a type of herbal medicine extract from China, increased the expression of genes for lipolysis and β-oxidation in Nile tilapia diets with 15.31% fat content, which reduced the buildup of lipids in the liver (Zhang *et al*., 2019).

A lot has been written about polysaccharides as well. Fucoidan, for instance, was discovered to suppress non-alcoholic fatty liver disease through the ASGR/$STAT_3$/HNF_4A signaling pathway in research in zebrafish (Wu *et al*., 2020). At a dose of 8000 mg/kg, oxidized konjac glucomannan (OKGM), an oxidized polysaccharide, was shown to dramatically lower plasma levels of Ya-fish (*Schizothorax prenanti*) TG and TC and to boost the activity of hepatic lipase HL and PPARα (Zhang *et al*., 2017). In the tilapia investigation, it was discovered that glycyrrhiza total flavones might reduce liver damage brought on by excessive fat through Nrf2 and toll-like receptor (TLR) signaling pathways and boost the fish's antioxidant abilities (Du *et al*., 2022). The buildup of lipid droplets in the liver caused by excessive fat was also shown to be improved by tea polyphenol in another study on tilapia, and the decrease of lipid droplets was dose-dependent. Also, tilapia's immune system and antioxidant capacities can be boosted by tea polyphenols (Qian *et al*., 2021). Numerous plants contain chlorogenic acid, a kind of polyphenolic acid. Chlorogenic acid can reduce the levels of TG and TC in the plasma of largemouth bass, encourage the expression of genes linked to lipolysis, and enhance the largemouth bass's antioxidant capacities (Yin *et al*., 2021).

Plant extracts will continue to get attention in intensive aquaculture because of their green color and diversity, but more study is still needed on plant extracts' ability to treat fatty livers.

Short-chain organic acid salt

Some studies show that short-chain organic acids salt can improve the nutritional fatty liver in fish. Calcium pyruvate was found to enhance the growth performance and liver antioxidant capacity of juvenile golden pompano (*Trachinotus ovatus*) fed a high-fat diet. Moreover, it was shown that calcium pyruvate might up-regulate the expression of genes involved in lipolysis (PPARα, CPT1, and fatty acid binding protein 1 (FABP1)) and down-regulate the expression of genes involved in lipid synthesis (SREBP1, FAS, and ACC), hence decreasing lipid buildup (Shao *et al*., 2022). Similarly, calcium pyruvate was shown to up-regulate gene expression related to lipolysis and to down-regulate gene expression linked to lipid synthesis in large yellow croaker (Zhang *et al*., 2023).

In the study of largemouth bass, it found that sodium butyrate could up-regulate the expression of genes of lipolysis (CPTI and PPARα) and improve the growing health and intestinal flora composition of largemouth bass under high-fat stress (Chen *et al*., 2023). Related investigations on grass carp discovered that sodium butyrate can lower high-fat diet stress plasma AST and ALT levels, lower liver apoptosis and inflammatory factors, and increase grass carp immunity (Gao *et al*., 2022). Zhou *et al*. (2019) also proved that sodium butyrate has the effect of reducing liver lipid accumulation.

Selenium element

The antioxidant enzyme GPx active center contains selenoprotein. Liver GPx activity may rise with increased dietary selenium (Chen *et al*., 2013). A related study found that feeding grass carp 0.3 or 0.6 mg/kg of selenium together with a high-fat diet significantly reduced the amount of MDA in their blood and boosted the activity of superoxide dismutase (SOD) and GPx (Yu *et al*., 2020; Liu *et al*., 2021b). Comparable improvements were made in the innate immune system, antioxidant capacity, and growth performance in juvenile Atlantic white croakers (*Argyrosomus regius*) by food supplementation with 3.98mg of organic selenium (Mansour *et al*., 2017). Yu *et al*. (2020) have revealed that nano-selenium may boost the mRNA expression of GPx and CAT as well as Nrf2 in grass carp.

Table IV displays the fish nutritional fatty liver therapy measures. Figure 2 shows an overview of treatment options and physiological effects of nutritional fatty liver disease.

Table IV. Therapeutic measures of nutritional fatty liver.

Substance class	Concrete substance	Species name	Levels	Physiological effects	Feeding cycle (weeks)	Reference
Carnitine	l-carnitine	Largemouth bass (*Micropterus salmoides*)	0, 0.01, 0.02, and 0.03 (g/kg)	**0.02 and 0.01 group:** ↑ HDL-C (plasma), **0.01 group:** the highest FBW and WG, **Gene expression: 0 group:** ↓ GSH-Px, ↑ FAS; **0.01, 0.02, and 0.03 group:** ↓ FAS, ↑CPT1, **0.02 group:** ↑GSH-Px.	8	Chen *et al*., 2020
	l-carnitine	Black seabream (*Acanthopagrus schlegelii*)	300 mg/kg	↑ lysozyme (LZM) (liver and plasma), ↑ CAT (plasma), ↓ TG, TC, and HDL-C (plasma), ↓ liver lipid drop, **Gene expression:** ↓ TNFα and IL-1β, ↑ PPARα and CPT1α.	8	Jin *et al*., 2019
Unsaturated fatty acid	DHA+EPA	Common carp (*Cyprinus carpio*)	0.14, 0.60, and 0.89 (%)	**0.60 and 0.89 group:** ↑FBW and SGR, ↓ hepatocyte area and hepatocyte nucleus area, **Gene expression:** ↓ FAS, FADS6, and ACOX1, ↑ PPARα.	14	Eljasik *et al*., 2020
	DHA/ EPA	Atlantic salmon (*Salmo salar*)	DHA (13.5%) EPA (13.5%)	**DHA and EPA group:** ↓ hepatocyte lipid area, ↓triacylglycerols (liver), **DHA group:** ↑the gene expression of PPARα, **EPA group:** ↑ mitochondrial proliferation.	17	Kjær *et al*., 2008
	n-3 PUFA	Atlantic salmon (*Salmo salar*)	25.3 and 13.4 (%)	**Gene expression: 13.4 group:** ↑ FAS and SREBP, ↓GST; **25.3 group:** ↓ FAS and SREBP, ↑ GST.	55	Morais *et al*., 2011
	n-3 LC-PUFA	Silvery-black porgy (*Sparidentex hasta*)	0.1, 0.6, 1.2, 1.9, and 4.2 (%)	**0.1→4.2:** ↑ FBW, SGR, WG and FI, ↓ HSI, **0.6→1.9:** ↓ crude lipid (liver), **0.1→1.2:** ↓TG, TC and ALT (plasma), **0.6→4.2:** ↑ total antioxidant capacity and CAT (plasma).	8	Mozanzadeh *et al*., 2015
Plant extract	Betaine	Black seabream (*Acanthopagrus schlegelii*)	10 and 20 (g/kg)	**20 group:** ↑ SGR, FE, and FI. **10 and 20 group:** ↓ total lipid (liver), ↓ TG and TC (plasma), ↓ hepatocyte lipid drops, **Gene expression: 20 group:** ↓ NF-κB, TNF-α, and IL-1β (liver and intestine), **10 and 20 group:** ↑ SIRT1 and PPARα (liver), ↓ SREBP-1 (liver). **Protein level: 10 and 20 group:** ↑ SIRT1 and PPARα (liver), ↓ SREBP-1 (liver).	8	Jin *et al*., 2021
	Berberine	Blunt snout bream (*Megalobrama amblycephala*)	50 and 100 (mg/kg)	**50 and 100 group:** ↓ hepatic steatosis scores and hepatocyte diameter, ↓ ALT, AST, TG and TC (plasma), ↓ MDA (liver), ↑ SOD and GSH (liver), ↑mitochondrial density, **Gene expression:** ↓ Bax and Caspase 3.	8	Lu *et al*., 2017
	Ginkgo biloba leaf extract	Hybrid grouper (*Epinephelus lanceolatus*♂ × *Epinephelus fuscoguttatus*♀)	0, 0.5, 1, 2, 4, and 10 (g/kg)	**0.5~4 g/kg:** ↑ HDL (plasma), ↓ glucose, LDL, and TG (plasma). **0.5~1 g/kg:** ↓ hepatocyte swelling and cavity, ↑ SOD, CAT, and T-AOC (liver), MDA, **Gene expression:** ↓ Caspase 3 (head kidney), ↑ IL-10 and TGF-β1 (head kidney).	8	Tan *et al*., 2018
	Forskolin (a kind of chinese herbal medicine extract)	Nile tilapia (*Oreochromis niloticus*)	0, 0.5, and 1.5 (mg/kg)	**0.5 and 1.5 group:** ↓ HSI, ↓ mesenteric fat index, ↓ crude lipid of whole fish, ↓ lipid of liver, ↓ glycerol (plasma), ↓ lipid droplet area, **Gene expression: 0.5 and 1.5 group:** ↑ PPARα, ↑ FABP1, ↑ ACO, **1.5 group:** ↑ CPT1.	8	Zhang *et al*., 2019
	Oxidized konjac glucomannan	Ya-fish (*Schizothorax prenanti*)	0.5, 1, 2, 4, and 8 (g/kg)	**0.5~8 g/kg:** ↑ hepatic lipase, lipoprotein lipase, and HDL (plasma), ↓ TG, TC, and LDL (plasma), **Gene expression:** ↑ PPARα(liver), ↑ FABP (back muscle).	8	Zhang *et al*., 2017

Table continued on next page................

Substance class	Concrete substance	Species name	Levels	Physiological effects	Feeding cycle (weeks)	Refer-ence
	Glycyrrhiza total favones	Nile tilapia (*Oreochromis niloticus*)	0.1 and 1 (g/kg)	**0.1 and 1 group:** ↓ GOT, GPT, and TNF-α (plasma), ↑ GSH and SOD (plasma), ↓ LDL-C and TG (plasma), ↑ HDL-C (plasma), **Gene expression:** ↓C3, HSP70, and IgM (liver).), **1 group:** ↓ IL-1β and TC (plasma), **Gene expression:** ↑ GST and NQO1 (liver).	13	Du *et al*., 2022
Plant extract	Tea polyphenol	Nile tilapia (*Oreochromis niloticus*)	50 and 200 (mg/kg)	**50 group:** ↓ **HSI, 50 and 200 group:** ↓ TG and TC (plasma), ↓ fat drops in the liver, **Gene expression:** ↓ HSL, FAS, Caspase 3, and ACCα (liver), ↑ SOD and GST (liver).	8	Qian *et al*., 2021
	Chlorogenic acid	Largemouth bass (*Micropterus salmoides*)	300 and 600 (mg/kg)	**300 and 600 group:** ↑ WG and SGR, ↓ TG and TC (plasma), ↓ FFA (liver), ↑ lipase (liver), ↑ SOD (liver), ↓ MDA (liver), **Gene expression of liver: 600 group:** ↑ HSL, CAT, Bcl-2, Caspase 3, APOA1, APOB, FABP1, and CYP27B1, ↓ CYP8B1, **300 and 600 group:** ↑ T-SOD and GPx, IL-8, IL-15, and TNF-α.	9	Yin *et al*., 2021
Short-chain organic acid salt	Calcium pyru-vate	Golden pompano (*Trachinotus ovatus*)	0, 0.25, 0.50, 0.75, and 1 (%)	**0.25~1:** ↑ FBW, WG, SGR, and HSI, ↓ lipid of liver and whole body, ↓ relative area of lipid drops (liver), ↓ TG, FFA, ALT, and AST (plasma), ↓MDA (liver and plasma), ↑ GSH and SOD (liver and plasma), **0.5~1:** ↑ CAT (liver and plasma), gene expression of liver: ↑ PPARα, CPT1, and HSL, ↓ SREBP1, FAS, and ACC.	8	Shao *et al*., 2022
	Calcium pyru-vate	Large yellow croaker (*Larim-ichthys crocea*)	0, 0.375, 0.75, and 1.5 (%)	**1.5 group:** ↓ HSI, ↓ crude lipid of whole fish and liver, **0.375~1.5:** ↓ TG (plasma, liver, and muscle), ↓ TC, LDL-C, and FFA (plasma), ↓ relative area of lipid drops (liver), **Gene expression of liver: 1.5 group:** ↓ FAS, G6PD, and ACC2, ↑ HSL.	10	Zhang *et al*., 2023
	Sodium bu-tyrate	Largemouth bass (*Micropterus salmoides*)	0.05, 0.1, and 0.2 (%)	**0.05→0.2:** ↑ SGR and WG, ↓ AST, ALT, and DAO (plasma), ↓ TG and TC (liver), ↓ MDA (liver), ↑ T-SOD and GPx (liver), ↓ relative area of lipid drops (liver), **Gene expression of liver:** ↑ CPT1 and PPARα, ↓ SREBP1, TNF-α, and Caspase 3.	8	Chen *et al*., 2023
Short-chain organic acid salt	Sodium bu-tyrate	Grass carp (*Ctenopharyngo-don idella)*	1 g/kg	↑ FBW, SGR, FE, and CF, ↓ TG (plasma), ↓ TC (liver), ↓ ALT and AST (plasma), ↓ MDA (liver), ↑ SOD, GPx, and GSH (liver), **Gene expression of liver:** ↓ IL-8, Caspase 3, Caspase 9, and Keap1, ↑ Nrf2.	8	Gao *et al*., 2022
Slenium element	Nano-selenium	Grass carp (*Ctenopharyngo-don idella*)	0, 0.3, 0.6, 0.9, and 1.2 (mg/kg)	**1.2 group:** ↑ **FBW, 0.6→1.2:** ↓ ALT and AST (plas-ma), **0.3→1.2:** ↑ GPx (plasma), ↓ SOD (plasma), **0.3 and 0.6:** ↓ MDA (plasma), **Gene expression of hepatopancreas: 0.3→1.2:** ↑ Nrf2 and keap1α, **0.3→0.9:** ↑ GP, 0.9 group: ↑ Cu/Zn-SOD.	10	Yu *et al*., 2020
	Organic sele-nium	Atlantic white croaker (*Argyro-somus regius*)	0.77, 1.51, 2.97 and 3.98(mg/kg)	**2.97 and 3.98 group:** ↑ FCR and SR, **1.51→3.98:** ↑ CAT, SOD, and T-AOC (liver), ↓ TBARs (liver), ↑ Albumin, Globulin, and total immunoglobulin (plasma).	9	Mansour *et al*., 2017
	Nano-selenium	grass carp (*Ctenopharyngo-don idella*)	0.3, 0.6, 0.9, and 1.2 (mg/kg)	**0.3→1.2:** ↓ TG and LDL-C (plasma), ↓ HSI, ↓ intraperitoneal lipids, **0.3, 0.9 and 1.2 group:** ↓ lipid content (hepatopancreas), **Expression of hepatopancreas: 0.3→1.2:** ↑ PPARα and LPL, ↓ FAT/CD36, **0.3, 0.9, and 1.2 group:** ↑ CPT1.	10	Liu *et al*., 2021b

FAS, fatty acid synthase; CPT1, carnitine palmitoyl transferase 1; TNF-α, tumor necrosis factor α; IL-1β/8/15, interleukin 1β/8/15; PPARα, peroxisome proliferators-activated receptor α; FADS6, fatty acid desaturase 6; ACOX1, acyl-CoA oxidase 1; SREBP, sterol regulatory element binding protein; GST, glutathione s-transferase; NF-κB, nuclear factor kappa-B; SIRT1, nad-dependent deacetylase sirtuin-1, Bax, bcl2-associated x protein; Caspase3/9, cysteine-aspartic proteases-3/9; Bcl-2, b-cell lymphoma-2; TGF-β1, transforming growth factor β1; FABP1, fatty acid binding protein 1; ACO, acyl-CoA oxidase; NQO1, quinone oxidoreductase 1; HSL, hormone-sensitive lipase; ACC, acetyl-CoA carboxylase; APO A1/B, apolipoprotein A1/B; CYP27B1, cytochrome P450 family 27 subfamily B member 1; CYP8B1, cytochrome P450 8B1; G6PD, 6-phosphoglucose dehydrogenase; Nrf2, nuclear factor E2-related factor 2; TBARs, thiobarbituric acid reactive subtances; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid, PUFA, polyunsaturated fatty acid.

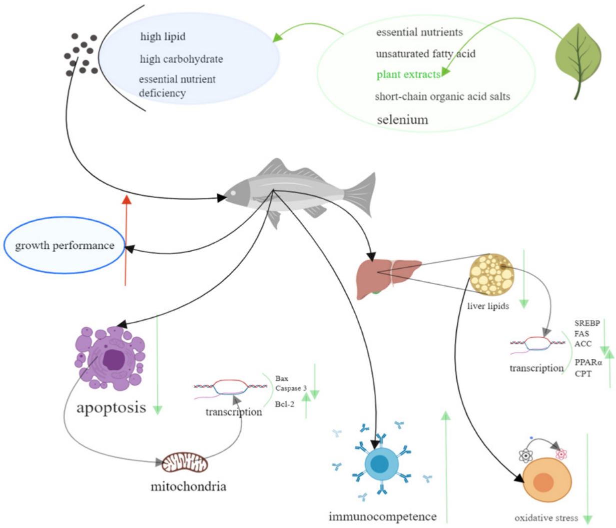

Fig. 2. General overview of treatment options and physiological effects of the nutritional fatty liver.

CONCLUSION

It is difficult for fish to adjust to the rigorous living circumstances of modern intensive aquaculture. We still can't produce fish in simulated natural settings despite the enormous market demand and economic advantages. We should research new environmentally friendly, secure, and effective anti-nutritional fatty liver chemicals for today's heavy fish production. The majority of recent papers only look at one pathway or one crucial gene when examining the causes of nutritional fatty liver in fish. To study feed formula, future studies should concentrate on how to explore the whole metabolic and regulation network of lipid metabolism and nutritional fatty liver, as well as how to develop a pertinent database for each farmed fish. In short, the problem of nutritional fatty liver in cultured fish will not be solved overnight, which requires us to continue to invest in slow research.

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Statement of conflict of interest

The authors have declared no conflict of interest.

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