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Natural Bioactive Compounds as Metabolic Modulators in Cultured Fish: A Critical Review of Lipid Homeostasis, Oxidative Stress, and Cellular Responses

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Abstract

High-fat diets (HFDs) are increasingly used in aquaculture to increase dietary energy density and spare protein for growth, but excessive lipid supply can promote hepatic lipid accumulation, oxidative stress, inflammation, intestinal dysfunction, and impaired metabolic homeostasis. Natural bioactive compounds have therefore attracted attention as functional feed additives capable of improving metabolic resilience. This critical review evaluates evidence from fish studies on curcumin, resveratrol, chlorogenic acid, berberine, quercetin, tea polyphenols, hydroxytyrosol, glycyrrhetinic acid, and related plant-derived compounds used under high-fat or high-lipid feeding conditions. Particular attention is given to mechanisms involving PPAR-mediated fatty-acid oxidation, SREBP/FAS-regulated lipogenesis, AMPK-associated energy sensing and mitochondrial quality control, Nrf2-linked antioxidant defense, and NF-κB-associated inflammatory signaling. Across the available evidence, several natural bioactives reduce hepatic or circulating lipid accumulation and improve antioxidant, inflammatory, histological, or metabolic indicators, although growth responses are less consistent. Responses depend strongly on fish species, dietary lipid level and source, bioactive dose, feeding duration, compound purity, and the physiological endpoint examined. Current evidence therefore supports selected natural bioactives primarily as metabolic modulators rather than universal growth promoters. Future research should emphasize standardized HFD models, dose-response designs, chemical characterization of extracts, correct identification of the experimental unit, mechanistic validation, and testing under commercial farming conditions.

Keywords:

Aquaculture, high-fat diet, phytochemicals, lipid metabolism, hepatic steatosis, oxidative stress, fish physiology.

1. INTRODUCTION

Dietary lipids are concentrated energy sources and, when supplied at appropriate levels, can spare dietary protein from catabolism. This principle is attractive in aquaculture because protein is generally the most expensive macronutrient in formulated feeds. However, the capacity to utilize dietary lipid differs among fish species, life stages, temperatures, and lipid sources. When lipid supply exceeds metabolic demand, lipid deposition can increase in the liver, viscera, muscle, and adipose tissues, with consequences for health and product quality. A broad review of HFD studies in farmed fish has documented adverse effects on growth efficiency, liver function, antioxidant status, immunity, intestinal integrity, and lipid homeostasis when dietary fat becomes excessive (Naiel et al., 2023).

At the cellular level, excessive dietary lipid can disturb the balance between fatty-acid uptake and synthesis on one side and lipid oxidation and export on the other. Hepatic steatosis may be accompanied by oxidative stress, endoplasmic-reticulum stress, mitochondrial dysfunction, inflammatory signaling, and impaired autophagy. These disturbances are not independent; lipid overload can increase reactive oxygen species, oxidative injury can amplify inflammatory responses, and mitochondrial dysfunction can further limit fatty-acid oxidation (Naiel et al., 2023; Dong et al., 2020).

Natural bioactive compounds are increasingly investigated as nutritional interventions because many can act on several of these processes simultaneously. Studies in fish exposed to high-fat or high-lipid diets have examined curcumin, resveratrol, chlorogenic acid, berberine, quercetin, tea polyphenols, hydroxytyrosol, and glycyrrhetinic acid, among others (Ji et al., 2018; Desouky et al., 2020; Dong et al., 2020; Ji et al., 2021; Dong et al., 2021; Wu et al., 2022; Ma et al., 2023; Jia et al., 2024). The expanding evidence provides an opportunity to interpret these compounds not simply as growth promoters but as regulators of metabolic resilience.

This review critically synthesizes current evidence on natural bioactive compounds used to mitigate HFD-associated metabolic dysfunction in cultured fish. The discussion focuses on hepatic lipid deposition, circulating lipid metabolism, oxidative stress, inflammation, intestinal health, and the molecular pathways that connect these responses. Particular attention is given to the limitations that currently restrict translation from controlled feeding trials to practical aquafeed formulation.

2. REVIEW APPROACH

A focused critical literature review was undertaken using PubMed, Google Scholar, publisher databases, and backward citation tracking. Search concepts combined fish or aquaculture terms with high-fat/high-lipid feeding and specific natural bioactive compounds. Priority was given to peer-reviewed in vivo finfish feeding studies in which a plant-derived or naturally occurring bioactive was incorporated into a high-fat or high-lipid diet and metabolic, biochemical, histological, molecular, or performance outcomes were reported. This article is a critical narrative review rather than a formal systematic review or meta-analysis; consequently, its objective is mechanistic synthesis and identification of evidence gaps rather than exhaustive study enumeration or pooled effect-size estimation.

3. HIGH-FAT DIETS AND METABOLIC DYSFUNCTION IN FISH

3.1. From dietary energy to lipid overload

Moderate increases in dietary lipid can improve energy utilization, but excessive lipid supply may exceed the capacity of fish to oxidize and export fatty acids. The resulting imbalance favors triacylglycerol storage and can increase hepatic and whole-body lipid. The threshold at which a diet becomes metabolically excessive is species-specific, making the term 'high-fat diet' inherently contextual rather than a single universal lipid percentage (Naiel et al., 2023).

3.2. Hepatic steatosis, mitochondria, and endoplasmic reticulum

The liver is a central organ for lipid processing in fish and is therefore particularly vulnerable to dietary lipid overload. In blunt snout bream, HFD-induced hepatic fat accumulation was associated with mitochondrial ultrastructural damage; hydroxytyrosol supplementation reduced hepatic fat accumulation and supported mitochondrial biogenesis and autophagy through an AMPK-associated mechanism (Dong et al., 2020). In spotted seabass, HFD also impaired mitochondrial biogenesis and mitophagy and promoted endoplasmic-reticulum stress, while quercetin attenuated excessive fat deposition and reversed several of these disturbances (Dong et al., 2021).

3.3. Oxidative stress and metabolic inflammation

High lipid flux can increase reactive oxygen species production and lipid peroxidation. If endogenous antioxidant defenses are insufficient, oxidative damage can interact with inflammatory signaling and aggravate metabolic dysfunction. In common carp, resveratrol supplementation during high-fat feeding increased antioxidant enzyme activities, reduced malondialdehyde, and attenuated inflammatory and lipid-metabolic disturbances (Wu et al., 2022). In tilapia, berberine similarly affected antioxidant and immune signaling while improving indices of hepatic lipid metabolism (Jia et al., 2024).

3.4. Intestinal involvement and the gut-liver axis

HFD-associated dysfunction is not restricted to the liver. Intestinal morphology, inflammatory signaling, microbial communities, and metabolites can also be altered. In red tilapia, resveratrol supplementation improved intestinal lipid metabolism and affected PPAR-associated pathways under high-fat feeding, alongside changes in inflammatory markers and gut-associated variables (Zheng et al., 2024). Chlorogenic acid supplementation in spotted sea bass also influenced intestinal and hepatic histology and gut microbiota under HFD conditions (Ma et al., 2023).

4. MAJOR NATURAL BIOACTIVES AND THEIR PHYSIOLOGICAL TARGETS

4.1. Curcumin

Curcumin is a polyphenolic constituent of Curcuma longa with antioxidant and lipid-regulatory properties. In large yellow croaker receiving an 18% crude-lipid diet, graded dietary curcumin affected antioxidant capacity, fatty-acid composition, lipid deposition, and expression of lipid-metabolism-related genes. The study reported lower body and hepatic lipid-related indices at effective supplementation levels and changes consistent with increased fatty-acid oxidation and reduced lipogenesis, including regulation of pparα, cpt1, aco, srebp1, and fas (Ji et al., 2021). More recent work in spotted sea bass has also reported that curcumin supplementation to a high-fat diet alleviates oxidative damage and lipid-metabolic disturbance, reinforcing the relevance of this compound across marine finfish models (Wang et al., 2026).

4.2. Resveratrol

Resveratrol is a stilbene polyphenol with strong evidence for metabolic regulation in HFD-fed fish. In common carp, resveratrol improved antioxidant status and attenuated inflammatory and lipid-metabolic responses to a high-fat diet (Wu et al., 2022). In red tilapia, resveratrol altered hepatic lipid metabolism and was associated with SIRT1- and PPAR-related regulation, including changes in fatty-acid oxidation and lipogenic genes (Zheng et al., 2022). Follow-up work using multi-omics approaches linked resveratrol with MAPK-PPAR signaling and reduced fatty-acid synthesis (Li et al., 2023), while an intestinal study showed improved lipid metabolism through PPAR-associated pathways under high-fat feeding (Zheng et al., 2024). Together, these studies make resveratrol one of the best mechanistically characterized natural bioactives in fish HFD models.

4.3. Chlorogenic acid

Chlorogenic acid is a phenolic acid found in coffee and many plant materials. In spotted sea bass fed a high-fat diet, supplementation at 100-400 mg/kg was evaluated for growth, lipid metabolism, intestinal and hepatic histology, and gut microbiota. Effective supplementation reduced several HFD-associated lipid and liver-injury indicators and improved antioxidant and tissue responses, while also modifying the intestinal microbial community (Ma et al., 2023). These findings are particularly relevant because they demonstrate that a single dietary bioactive may influence hepatic metabolism and the intestinal environment simultaneously.

4.4. Berberine

Berberine is an isoquinoline alkaloid present in several medicinal plants. In Nile tilapia under high-fat feeding, berberine supplementation improved hepatic lipid-metabolism indicators, antioxidant status, and immune responses. Mechanistic observations included regulation of PPARα/CPT1-associated lipid oxidation, Nrf2-related antioxidant signaling, and TLR2/MyD88/NF-κB-associated inflammatory pathways (Jia et al., 2024). A separate zebrafish feeding study also reported effects of berberine on antioxidant capacity, lipid metabolism, and intestinal health under HFD conditions, although growth responses were not necessarily improved (Hu et al., 2024).

4.5. Quercetin

Quercetin is a flavonoid that has been directly tested in a well-defined spotted seabass HFD model. Fish received a normal-fat diet, an HFD, or the HFD supplemented with 0.5 or 1.0 g/kg quercetin. HFD impaired growth and feed utilization and increased serum and hepatic fat, whereas quercetin reduced excessive fat deposition. Ultrastructural and gene-expression evidence indicated improved mitochondrial biogenesis and mitophagy and suppression of endoplasmic-reticulum stress (Dong et al., 2021). This study illustrates why mitochondrial quality control is an important target beyond conventional measurements of serum triglycerides or hepatic lipid.

4.6. Tea polyphenols

Tea polyphenols represent a mixture of plant-derived phenolic compounds rather than a single purified molecule. In large yellow croaker, dietary tea polyphenols reduced body and hepatic lipid-related measures and altered antioxidant responses and expression of lipid-metabolism genes. CPT1, ACO, and PPARα were upregulated at effective supplementation levels, supporting increased lipid oxidation as a plausible mechanism (Ji et al., 2018). Although this experiment is best described as a high-lipid feeding context rather than a disease model, it provides relevant evidence for phytochemical modulation of lipid handling in cultured marine fish.

4.7. Hydroxytyrosol and glycyrrhetinic acid

Hydroxytyrosol provides a particularly clear mechanistic example. In blunt snout bream, a 15% fat HFD induced hepatic fat accumulation and mitochondrial abnormalities, while 100 mg/kg hydroxytyrosol reduced fat deposition. Complementary hepatocyte experiments supported activation of AMPK, mitochondrial biogenesis, and autophagy-related processes (Dong et al., 2020). Glycyrrhetinic acid, a triterpenoid derived from licorice, has also been evaluated in channel catfish fed a high-fat diet, with effects on growth, feed utilization, and lipid-metabolism-related gene expression (Desouky et al., 2020). These studies broaden the evidence beyond polyphenols and show that structurally distinct natural compounds may converge on lipid homeostasis through different molecular targets.

5. INTEGRATED MECHANISMS OF METABOLIC PROTECTION

5.1. PPAR-driven fatty-acid oxidation versus SREBP/FAS lipogenesis

A recurring pattern across compounds is a shift from lipid synthesis and storage toward lipid utilization. PPARα and downstream targets such as CPT1 and ACO/ACOX support mitochondrial and peroxisomal fatty-acid oxidation, whereas SREBP1 and FAS promote de novo lipogenesis. Curcumin, resveratrol, berberine, tea polyphenols, and quercetin have each been associated with regulation of one or more of these targets in fish lipid-overload models (Ji et al., 2018; Ji et al., 2021; Dong et al., 2021; Wu et al., 2022; Zheng et al., 2022; Jia et al., 2024).

5.2. AMPK, mitochondrial quality control, and autophagy

Energy sensing and mitochondrial quality control provide a second mechanistic axis. Hydroxytyrosol reduced HFD-associated hepatic fat accumulation in blunt snout bream while promoting AMPK activation, mitochondrial biogenesis, and autophagy-related signaling (Dong et al., 2020). Quercetin similarly improved mitochondrial biogenesis and mitophagy in spotted seabass and reduced endoplasmic-reticulum stress (Dong et al., 2021). These findings suggest that restoring the capacity of hepatocytes to oxidize fatty acids and maintain functional mitochondria may be as important as suppressing lipogenesis.

5.3. Antioxidant and inflammatory signaling

Nrf2-related antioxidant defense and NF-κB-associated inflammatory signaling are repeatedly implicated in HFD pathology. Berberine in tilapia influenced both antioxidant and inflammatory pathways, while resveratrol in common carp improved enzymatic antioxidant defenses and attenuated pro-inflammatory responses (Wu et al., 2022; Jia et al., 2024). The overlap among lipid, redox, and immune pathways supports an integrated interpretation: natural bioactives may protect fish not through a single biochemical endpoint but by reducing the positive feedback between lipid overload, oxidative injury, and inflammation.

6. REPRESENTATIVE VERIFIED EVIDENCE

Table 1. Representative studies used in the mechanistic synthesis. All references in this table were bibliographically verified before inclusion.

Bioactive	Species	Dietary context	Main reported responses	Mechanistic emphasis	Reference
Curcumin	Large yellow croaker	18% crude lipid + graded curcumin	Improved antioxidant and lipid-related indices; altered hepatic lipid deposition	PPARα/CPT1/ACO; SREBP1/FAS	Ji et al., 2021

Curcumin	Spotted sea bass	HFD + graded curcumin	Lower oxidative damage and lipid-metabolic disturbance at effective doses	Nrf2; PPARα/CPT1	Wang et al., 2026
Resveratrol	Common carp	HFD + resveratrol	Improved antioxidant status; attenuated inflammation and lipid disturbance	Nrf2-related defense; inflammatory and lipid genes	Wu et al., 2022
Resveratrol	Red tilapia	HFD + resveratrol	Improved hepatic and intestinal lipid metabolism	SIRT1/PPAR; MAPK-PPAR; β-oxidation	Zheng et al., 2022; Li et al., 2023; Zheng et al., 2024
Chlorogenic acid	Spotted sea bass	HFD + 100-400 mg/kg	Improved lipid, histological and antioxidant indicators; altered microbiota	Hepatic-intestinal metabolic regulation	Ma et al., 2023
Berberine	Nile tilapia	HFD + 50 or 100 mg/kg	Improved hepatic lipid, antioxidant and immune indices	PPARα/CPT1; Nrf2; TLR2/MyD88/NF-κB	Jia et al., 2024
Quercetin	Spotted seabass	HFD + 0.5 or 1.0 g/kg	Reduced excessive fat deposition; improved growth/feed utilization	Mitochondrial biogenesis, mitophagy, ER stress	Dong et al., 2021
Tea polyphenols	Large yellow croaker	High-lipid feeding + graded TP	Lower body/hepatic lipid-related indices; improved antioxidant status	CPT1/ACO/PPARα	Ji et al., 2018

Hydroxytyrosol	Blunt snout bream	15% HFD + 100 mg/kg	Reduced hepatic fat accumulation and mitochondrial injury	AMPK; mitochondrial biogenesis; autophagy	Dong et al., 2020
Glycyrrhetinic acid	Channel catfish	HFD + GA	Affected growth, feed utilization and lipid-metabolism genes	Lipid-metabolism regulation	Desouky et al., 2020

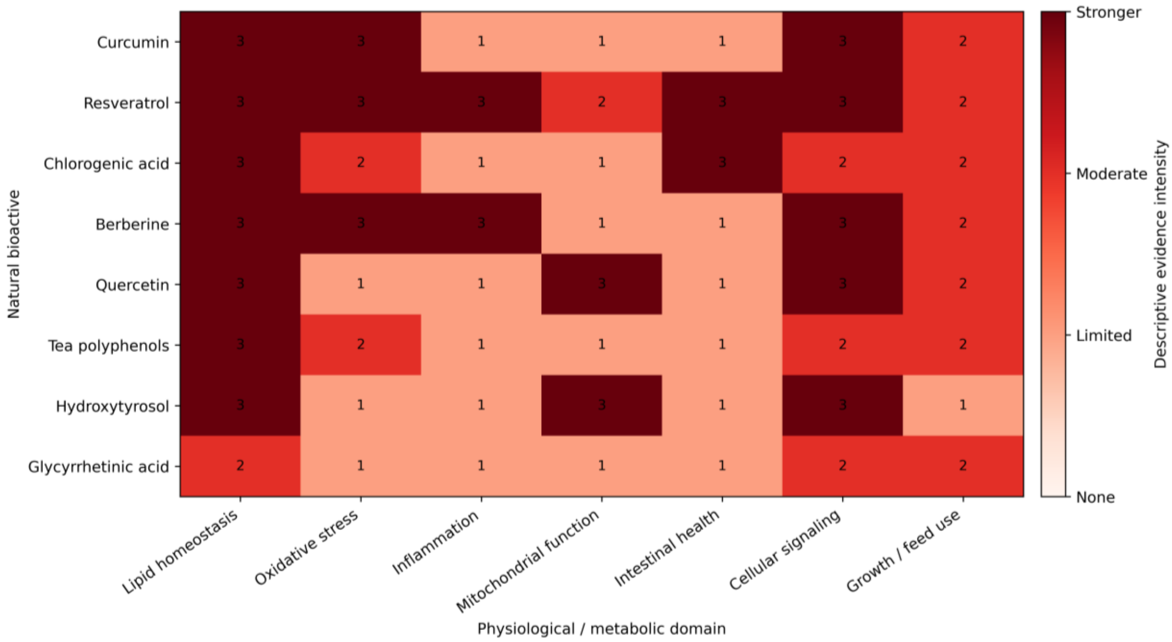

Figure 1. Comparative evidence map of natural bioactives and the physiological/metabolic domains reported in the representative studies summarized in Table 1. Filled circles indicate reported evidence within a domain; dashes indicate that the domain was not a principal outcome in the cited representative study set. The map is descriptive and does not represent pooled effect size or meta-analysis.

7. LIMITATIONS OF THE CURRENT EVIDENCE

The present evidence base is promising but heterogeneous. First, HFD definitions differ among species and studies, so the absolute lipid percentage cannot be interpreted independently of species requirements, protein level, energy density, and lipid source. Second, experimental durations and doses vary widely, and beneficial effects at one dose do not establish a linear dose-response relationship. Third, growth outcomes are less consistent than biochemical or molecular outcomes; metabolic protection should therefore not automatically be described as growth promotion.

Fourth, the experimental unit requires careful attention. Feeding treatments are generally applied to tanks, yet some studies report biochemical or molecular measurements from individual fish without clearly describing whether tank-level replication was retained in the statistical model. Future studies should explicitly distinguish biological sampling from the true experimental replicate. Fifth, crude botanical extracts require better chemical characterization because variation in source material, extraction procedure, active-compound concentration, feed processing, and storage can limit reproducibility.

8. RESEARCH GAPS AND FUTURE DIRECTIONS

Future work should use designs that include a normal-fat control, an unsupplemented HFD control, and multiple bioactive doses. Such designs allow investigators to distinguish prevention of HFD injury from general nutritional effects and to identify dose-response relationships. The severity of the lipid challenge should be reported relative to established species requirements rather than described only by the label 'high-fat'.

Mechanistic studies should integrate classical physiology with molecular approaches. Transcriptomics, proteomics, metabolomics, lipidomics, and microbiome analyses are most informative when anchored to hepatic lipid content, histology, blood biochemistry, antioxidant status, feed utilization, and growth. Particular priorities include the gut-liver axis, bile-acid metabolism, mitochondrial quality control, autophagy, and the interaction between metabolic and inflammatory signaling.

Finally, commercial validation is essential. Most evidence derives from controlled tank trials. Future studies should test whether benefits persist across longer production cycles, variable temperatures, high stocking densities, disease exposure, and practical feed formulations. Economic analysis is also needed because purified natural bioactives may be effective biologically but impractical if the inclusion cost exceeds gains in feed efficiency, survival, health, or product quality.

9. CONCLUSION

Natural bioactive compounds can attenuate several components of HFD-induced metabolic dysfunction in cultured fish. The strongest current evidence supports effects on hepatic and circulating lipid regulation, antioxidant defense, inflammatory signaling, mitochondrial function, and tissue integrity. Curcumin, resveratrol, chlorogenic acid, berberine, quercetin, tea polyphenols, hydroxytyrosol, and glycyrrhetinic acid illustrate the diversity of natural compounds capable of influencing lipid homeostasis.

Despite differences among compounds, several mechanistic themes recur: promotion of PPAR-associated fatty-acid oxidation, suppression of lipogenic signaling, restoration of mitochondrial quality control and autophagy, enhancement of antioxidant defense, and attenuation of metabolic inflammation. However, efficacy remains species-, dose-, and diet-dependent. Natural bioactives should therefore be viewed as targeted metabolic modulators rather than universally effective growth promoters. Standardized HFD models, rigorous dose-response studies, chemical characterization, correct experimental replication, and farm-scale validation are required before these compounds can be translated reliably into functional aquafeeds.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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DATA AVAILABILITY

No new datasets were generated or analyzed in this critical review.

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