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Therapeutic potential of *Phyllanthus* spp. in sustainable aquaculture: a phytopharmacological perspective

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The increasing demand for sustainable and antibiotic-free aquaculture has intensified the search for natural alternatives supporting animal health, enhancing environmental quality, and improving production efficiency. To this end, medicinal plants such as *Phyllanthus* spp. provide potential values. *Phyllanthus* spp., widely known for their ethnopharmacological applications, possess a rich profile of bioactive compounds, including flavonoids, tannins, terpenoids, steroids, lignans, and polyphenols, that exhibit multifunctional biological effects beneficial for aquaculture. Nevertheless, no comprehensive review has been conducted on the therapeutic potential of *Phyllanthus* spp. in sustainable aquaculture. Hence, this review focuses on *Phyllanthus* spp. applications in aquaculture, highlighting their roles in promoting growth performance, stimulating immune responses, providing protection against bacterial and viral infections, and offering antioxidant and hepatoprotective benefits. Moreover, we present emerging data on their contributions to water quality improvement and environmental remediation, including modulation of microbial communities and pollutant adsorption. Last but not least, the current challenges of phytochemical variability, regulatory constraints, and limited field-scale validation; as well as the suggested future research to address these gaps are also discussed. Ultimately, *Phyllanthus* spp. represent a compelling resource for next-generation aquafeeds and integrated aquaculture management.

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1. Introduction

Global aquaculture has become a cornerstone of food security, supplying nearly half of the world's seafood and serving as a vital source of high-quality protein. With the global population projected to surpass 9 billion by 2050,[1] the demand for sustainable aquatic food systems is accelerating. However, the intensification of aquaculture has precipitated critical challenges, including heightened disease outbreaks, environmental degradation, and the alarming spread of antimicrobial resistance stemming from excessive antibiotic and chemical use.[2] Conventional approaches to disease prevention and growth enhancement, including prophylactic antibiotic use, chemical disinfectants, and synthetic feed additives, are becoming increasingly unsustainable.[2–4] Not only do these practices disrupt aquatic microbial communities and degrade water quality, but they also contribute to the emergence of multidrug-resistant pathogens that pose risks to both aquatic organisms and human health.[2–4] Furthermore, chemical residues in aquaculture effluents can accumulate in surrounding ecosystems, triggering eutrophication, altering biodiversity, and threatening food safety. As regulatory restrictions tighten and consumer demand for "antibiotic-free" and "environmentally friendly" aquaculture products grows, the sector faces mounting pressure to transition toward sustainable solutions based on natural bioactives with minimal ecological footprint.

To this end, plant-derived compounds have gained considerable attention as a promising alternative to synthetic therapeutics and feed additives in aquaculture.[5] These natural bioactives offer a diverse array of biological activities, such as immunomodulation, antimicrobial action, antioxidation, hepatoprotection, and water detoxification, often acting synergistically and without harmful side effects.[6] Amongst numerous plants, the *Phyllanthus* spp. demonstrate interesting multifunctionality for sustainable aquaculture.

The genus *Phyllanthus*, encompassing over 750 species in the family Phyllanthaceae, has been extensively employed in traditional medicines across Asia, Africa, and South America for its hepatoprotective, antiviral, antibacterial, and antioxidant effects.[7–10] Notably, species such as *P. niruri*, *P. amarus*, and *P. urinaria* are rich in bioactive metabolites (flavonoids, lignans, tannins, and alkaloids) that demonstrate inhibitory effects

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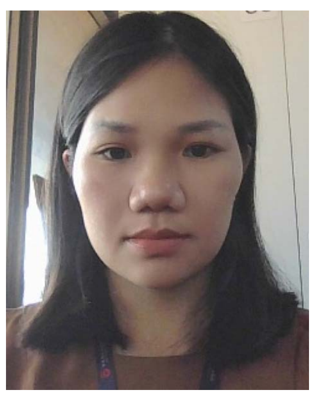

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against major aquaculture pathogens including *Vibrio* spp., *Aeromonas hydrophila*, and *Edwardsiella tarda*.[11–13] The multifunctionality of *Phyllanthus* spp. offers unique advantages in aquaculture systems. For instance, their immunostimulatory properties can enhance the non-specific immune defenses of fish and shellfish, improving resistance against opportunistic pathogens.[11,14] Their potent antimicrobial metabolites provide natural alternatives to antibiotics by disrupting bacterial cell walls, inhibiting quorum sensing, or interfering with virulence factor production.[9,15] Moreover, the strong antioxidant capacity of *Phyllanthus*-derived polyphenols helps mitigate oxidative stress induced by intensive farming practices, thereby improving growth performance and survival rates.[16,17] Hepatoprotective effects further support metabolic efficiency and detoxification processes, which are essential under high-nutrient feeding regimes.[18,19] Additionally, the presence of bioadsorptive polyphenols and metal-chelating compounds contributes to water purification and environmental remediation by neutralizing pollutants and improving effluent quality.

Despite the well-documented pharmacological relevance of *Phyllanthus* spp. in human and veterinary medicine, its translational application in aquaculture remains underexplored. Thus, bridging this gap offers a unique opportunity to develop plant-derived, multifunctional additives that support both animal health and environmental sustainability.

Hence, this review aims to critically examine the potential of *Phyllanthus* spp. species in aquaculture, drawing upon ethnopharmacological knowledge, phytochemical data, and experimental evidence in aquatic species. The review highlights *Phyllanthus* spp. roles in promoting aquaculture growth performance, stimulating immune responses, providing protection against bacterial and viral infections, and offering antioxidant and hepatoprotective benefits. Additionally, data on *Phyllanthus* spp. contributions to water quality improvement and environmental remediation are also focused. Lastly, the challenges of phytochemical variability, regulatory constraints, and limited field-scale validation; and the suggested future research to address these gaps are discussed. Ultimately, through this comprehensive review, we try to propose an integrative framework to guide the development and deployment of *Phyllanthus*-based interventions for next-generation sustainable aquaculture.

2. Overview of the *Phyllanthus* genus

2.1. Taxonomy and global distribution

The *Phyllanthus* genus is a taxonomically diverse and globally distributed group within the family Phyllanthaceae, comprising an estimated 750 to 1200 species.[10,20] This genus includes a broad spectrum of growth forms, ranging from annual and perennial herbs to shrubs, trees, and climbers, many of which exhibit high adaptability to tropical and subtropical ecosystems. It is considered one of the largest genera among angiosperms with wide-ranging ecological and pharmacological significance.[21] Morphologically, *Phyllanthus* spp. species are characterized by alternate or distichous leaves that are simple and entire, often arranged in a manner resembling pinnate compound leaves. The flowers are generally small, unisexual or bisexual, and typically borne in axillary clusters. Fruit morphology varies but is commonly capsular or drupaceous, with small, triangular seeds adapted for efficient dispersal.[22] These structural features not only aid in taxonomic classification but also contribute to their resilience and utility in traditional medicine.

Phyllanthus spp. are widely distributed across Asia, Africa, Central and South America, and the Pacific Islands.[20] Several species such as *P. niruri*, *P. amarus*, *P. urinaria*, and *P. emblica* are currently cultivated or semi-domesticated in regions outside their native range due to growing demand in herbal medicine, nutraceuticals, and, more recently, aquaculture applications. In Vietnam alone, more than 40 native *Phyllanthus* species have been documented, with *P. urinaria* and *P. emblica* being the most widely utilized in folk medicine and research.

2.2. Phytochemical compositions and bioactive constituents

The *Phyllanthus* genus has high phytochemical diversity, encompassing a wide range of secondary metabolites with numerous biological activities. As of 2025, more than 250 compounds have been identified in this genus, mostly belonged to the *P. emblica*, *P. urinaria*, *P. niruri*, *P. acidus*, and *P. muellerianus* species. To avoid redundancy, a summary of these compounds, together with their main therapeutic activities, is presented in Table S1. Among the most prominent phytochemical groups in *Phyllanthus* are alkaloids, which include nirurine and phyllochristine.[16,23–25] These alkaloids have demonstrated neuromodulatory, antispasmodic, and anti-inflammatory effects, potentially through interactions with neurotransmitter pathways and smooth muscle regulation. Such properties may be particularly beneficial in aquaculture, where stress-induced disorders and parasitic infections are common.

Flavonoids represent another major class of bioactives within this genus. Compounds such as quercetin, kaempferol, rutin, and astragalin exhibit potent antioxidant and immunomodulatory activities.[10] These effects are mediated through the enhancement of endogenous antioxidant defenses such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px), and the suppression of pro-inflammatory cytokines like IL-6 and TNF-α.[17,26,27] In aquaculture settings, these mechanisms help mitigate oxidative stress and support immune homeostasis in aquatic animals.

Phyllanthus spp. lignans such as phyllanthin and hypophyllanthin are highly bioactive constituents, particularly noted for their antiviral activity against hepatitis B virus (HBV) and other pathogens.[15] These lignans exert their effects by inhibiting viral replication enzymes, blocking viral entry into host cells, and modulating immune responses. Their potential applicability in preventing or managing viral infections in aquaculture species, such as white spot syndrome virus (WSSV), is a promising area of exploration.[18,28]

Tannins and other polyphenols, including geraniin, corilagin, and ellagic acid, contribute to the antimicrobial profile of *Phyllanthus* through multiple pathways.[29,30] These include

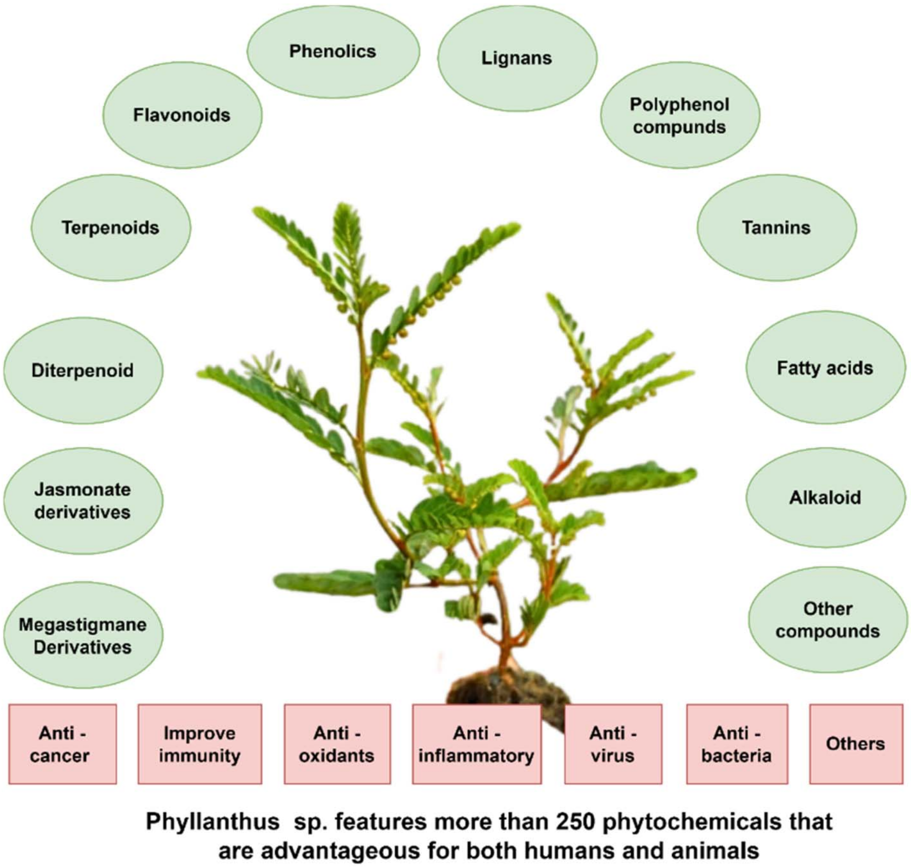

Fig. 1 Phytochemicals from *Phyllanthus* spp. And their biological effects on humans and animals.

disruption of bacterial cell membranes, inhibition of quorum sensing and biofilm formation, and suppression of virulence factor expression. Such actions are relevant for combating common aquaculture pathogens like *Vibrio* spp., *Aeromonas hydrophila*, and *Streptococcus agalactiae*.[31]

Terpenoids, steroids, and phytosterols such as lupeol, β-sitosterol, and stigmasterol, respectively, are also abundantly found in *Phyllanthus* species. These compounds demonstrate anti-inflammatory, hepatoprotective, and analgesic properties by modulating prostaglandin synthesis and stabilizing cellular membranes. Their presence supports the use of *Phyllanthus* extracts in enhancing resilience and liver function in cultured aquatic animals.[32,33]

Lastly, phenolic acids such as gallic acid, methyl gallate, and ethyl gallate contribute significantly to the hepatoprotective and antioxidant capacities of the plant.[9,16,34] These compounds, along with minor constituents like saponins and glycosides, enrich the therapeutic potential of *Phyllanthus* and provide a broad foundation for its use as a natural additive in aquafeeds.

The rich phytochemical repertoire of the *Phyllanthus* genus underpins its broad-spectrum pharmacological potential. The synergistic effects of these compounds offer compelling advantages in aquaculture, where natural, multi-target solutions are needed to enhance growth performance, immune status, and disease resistance while reducing reliance on synthetic chemicals (Fig. 1).

2.3. Traditional applications and ethnomedicinal significance

The *Phyllanthus* genus has a long-standing presence in traditional medicine systems across Asia, Africa, and South America. Species such as *P. niruri*, *P. amarus*, and *P. urinaria* have been widely employed in ethnomedicine for their therapeutic efficacy in treating hepatic disorders, urinary tract infections, skin ailments, and metabolic diseases.[21] These species, often known by vernacular names such as “Chanca Piedra” (Stone Breaker) in Latin America and “Diệp hạ châu” in Vietnam, are among the most culturally significant and pharmacologically studied taxa within the genus.

In traditional Chinese medicine, *Phyllanthus* species are categorized as herbs that “clear heat,” “eliminate toxins,” and “invigorate the liver,” and are used in formulations targeting jaundice, hepatitis, and inflammatory conditions.[21,35] Similarly, Ayurvedic medicine utilizes *P. amarus* and *P. niruri* for the management of “Yakrit roga” (liver disorders), “Ashmari” (renal calculi), and as a diuretic and digestive tonic.[8,36] In Vietnamese and Southeast Asian folk medicine, decoctions made from whole plants are traditionally used to treat liver dysfunction, edema, skin eruptions, and postpartum abdominal pain.

In most traditional practices, the entire whole plant, including leaves, stems, and roots, is typically harvested, dried, and used in aqueous extracts or crude powder. In some practices, fresh plant material is pounded and applied externally for abscesses and wounds, or taken orally for infections and detoxification. Despite differences in cultural practices, a common theme in traditional use is the plant's perceived ability to "cleanse" the liver and kidneys, reduce heat and inflammation, and promote general vitality.

3. Phytopharmaceutical preparation techniques of *Phyllanthus* for aquaculture

The pharmacological potential of *Phyllanthus* species in aquaculture depends not only on their phytochemical profile but also on the method of extraction and formulation. Various processing techniques have been developed to enhance the bioavailability, stability, and efficacy of *Phyllanthus* spp. compounds when administered to aquatic species. This section outlines the principal methods of preparation utilized in experimental and applied aquaculture research (Table 1).

Crude powder remains the simplest and most widely used form of *Phyllanthus* processing.[37,38] Fresh aerial parts or the whole plant are harvested, washed thoroughly to remove debris and contaminants, and dried under controlled conditions (typically below 50 °C) to preserve bioactive constituents. The dried material is then ground into fine powder using mechanical mills and sieved to ensure homogeneity. This form can be directly incorporated into aquafeeds or used as a base material for further extraction. While cost-effective and scalable, crude powder preparations may exhibit lower bioavailability due to limited solubility of certain phytochemicals.

Fermentation of *Phyllanthus* biomass using beneficial microorganisms such as *Lactobacillus* spp. or *Aspergillus* spp. is an advanced technique that enhances the digestibility and biological potency of plant materials.[39,40] The fermentation process leads to the breakdown of complex plant matrices, liberation of bound phenolics, and production of bioactive peptides and enzymes. Post-fermentation, the material is dried, milled, and stored under sterile, moisture-controlled conditions. Fermented *Phyllanthus* powders, when added to aquafeeds, have been shown to improve gut health, immune function, and disease resistance in various fish and shrimp species.

Concentrated extracts, aqueous, ethanolic, methanolic, or hydroalcoholic, are widely used to isolate and concentrate bioactive compounds such as flavonoids, lignans, and polyphenols.[41–44] The extraction process typically involves maceration or Soxhlet extraction under specific temperature and solvent conditions. Extracts are then filtered, concentrated under reduced pressure, and in some cases lyophilized to obtain dry residue. These extracts can be standardized based on marker compounds (*e.g.*, phyllanthin, quercetin) and formulated into feed additives or water treatments. Solvent choice and extraction parameters critically influence both yield and bioactivity.

Advanced fractionation techniques such as liquid–liquid partitioning, column chromatography, and solid-phase extraction allow for the isolation of specific bioactive molecules or enriched fractions from *Phyllanthus* spp.[45–47] Compounds such as phyllanthin, gallic acid, or kaempferol can be further characterized using HPLC or LC-MS and tested *in vitro* or *in vivo*. These purified principles are invaluable in mechanistic studies and dose-optimization trials in aquaculture, although they are often costlier and less accessible for large-scale use.

Recent innovations have focused on developing next-generation delivery systems for *Phyllanthus* compounds using nanotechnology, microencapsulation, and biodegradable polymers.[48,49] Techniques such as nanoemulsion formulation, liposomal encapsulation, and polymeric bead embedding (*e.g.*, using gelatin and agar) have been used to improve solubility, protect compounds from degradation, and ensure targeted release within the gastrointestinal tract of aquatic animals.[49] Furthermore, integration of *Phyllanthus*-based extracts into

Table 1 Preparation techniques of *Phyllanthus* and their applications in aquaculture

Technique	Advantages	Limitations	Applications in aquaculture	Ref.
Crude powder	Simple, low-cost, easy to scale; retains full spectrum of plant compounds	Lower bioavailability; variability in compound release	Mixed into fish/shrimp feed to improve general health	52 and 53
Fermented biomass	Enhances digestibility and bioactivity; introduces probiotic benefits	Requires controlled microbial processes; higher processing time	Feed additive for immune modulation and gut health	39 and 53
Extracts & concentrates	Concentrated bioactives; standardized dosing; versatile formulation	Solvent dependency; equipment-intensive; possible residual solvents	Used in disease control, water additives, or functional feeds	31, 41, and 53
Purified fractions	Allows mechanistic studies; high specificity and potency	High cost; complex isolation; not practical for mass application	Used in research trials to identify active compounds and optimal doses	14 and 54
Novel delivery systems	Improved stability and bioavailability; targeted delivery; reduced degradation	Advanced technology needed; regulatory and cost barriers	Used for encapsulated feed additives or water treatment innovations	48

biochar, biosorbents, or smart packaging materials is under exploration for applications in water remediation and post-harvest preservation.[50,51]

4. Biological effects of *Phyllanthus* spp. In aquaculture systems

The biological effects of *Phyllanthus* spp. relating to aquaculture are summarized in Fig. 2. The flowchart illustrates the conversion of *Phyllanthus* spp. into functional preparations for diverse aquaculture applications, including feed supplementation, immune modulation, water treatment, and disease control in fish and shrimp production systems. Table 2 presents the main bioactive compounds from *Phyllanthus* spp. with functional activities in aquatic species. For the full list of compounds, please refer to Table S1 (SI).

4.1. Enhancement of aquatic species growth performance

The application of bioactive compounds extracted from *Phyllanthus* species has demonstrated substantial growth-promoting effects in aquaculture species, attributable to their metabolic modulation, antioxidant properties, and impact on nutrient assimilation. Specifically, *Phyllanthus* phytochemicals promote gut health and digestive function by stimulating digestive enzyme secretion (amylase, protease, lipase), improving nutrient breakdown, as well as modulating gut microbiota composition by suppressing pathogenic bacteria (*Vibrio*, *Aeromonas*) and promoting beneficial genera (*Lactobacillus*, *Bacillus*).[11,53,98] Moreover, these chemicals enhance gut mucosal integrity and villus morphology, increasing surface area for absorption. Some secondary metabolites from *Phyllanthus* can also influence growth-related metabolic pathways, including (1) activation of growth hormone and insulin-like growth factor-1 signaling, which promotes protein synthesis and muscle development, (2) improving lipid metabolism and glycogen storage, optimizing energy availability for growth, and (3) enhancing mitochondrial activity and ATP production, supporting anabolic processes.[13,99,100]

For instance, kaempferol, isolated from *P. urinaria* and *P. emblica*, has been shown to significantly enhance growth performance in *Ctenopharyngodon idellus* when incorporated into the diet at 0.8 g kg^{-1}. This dosage improved weight gain by 5.6% and reduced feed conversion ratio by 0.08, accompanied by increased levels of free amino acids, SOD, CAT, and GSH-Px in fish tissues.[101] Additionally, naringenin from *P. emblica* promoted growth and digestive enzyme activity in *Procambarus clarkii* and mitigated cadmium-induced oxidative damage in

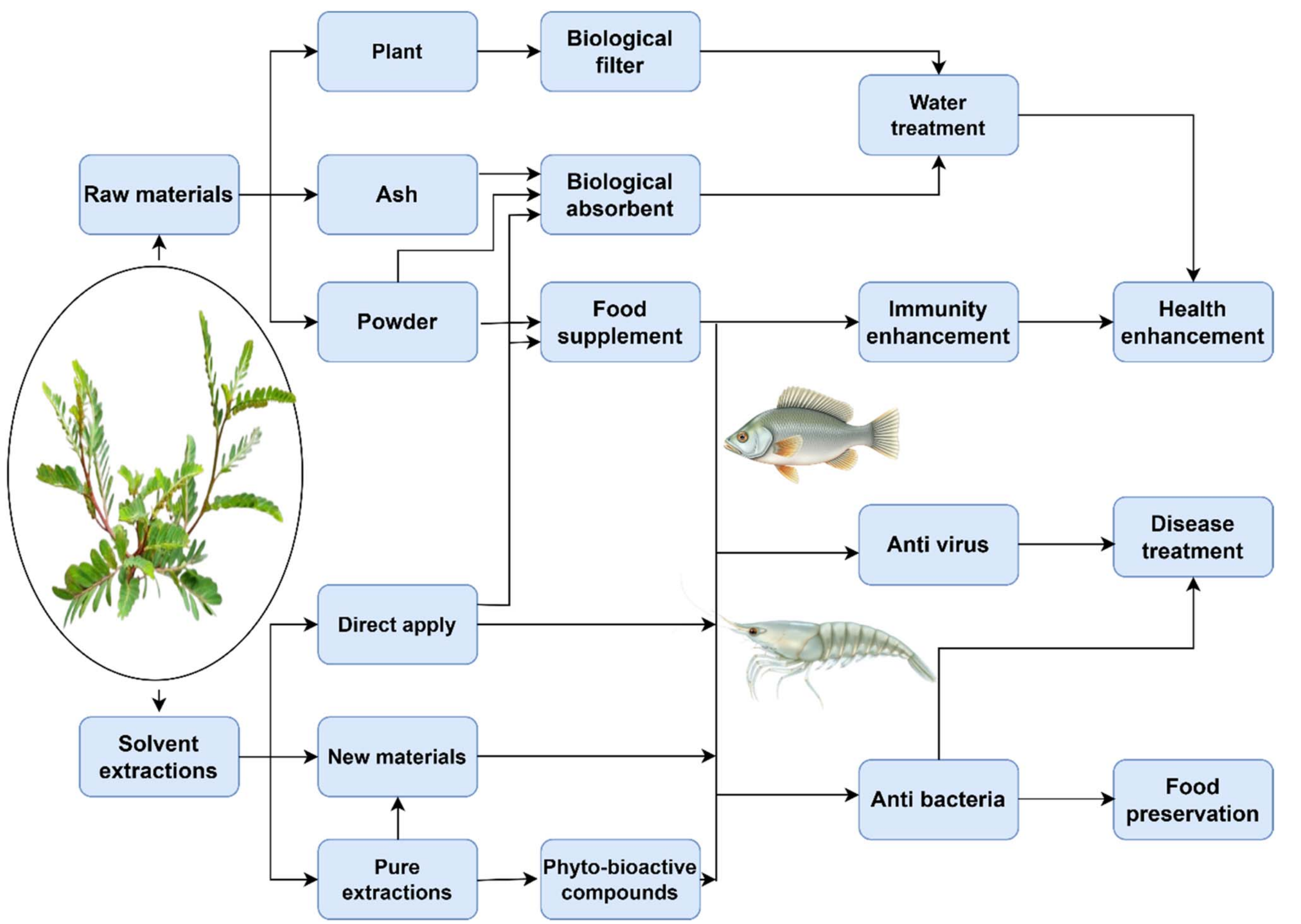

Fig. 2 Application flowchart of *Phyllanthus* spp. in aquaculture applications.

Table 2 Main bioactive compounds from *Phyllanthus* spp. with functional activities in aquatic species. For the full list of compounds, please refer to Table S1 (SI). MIC: minimum inhibitory concentration; MBC: minimum bactericidal concentration; ZOI: zone of inhibition; LC_{50}: lethal concentration of 50%; TC: test concentration

No.	Compound/extract	Concentration/numerical results	Biological activity
(A) Flavonoids			
1	Kaempferol ($C_{15}H_{10}O_6$) from *P. urinaria*, *P. emblica*[55,56]	TC = 50 mg L^{-1}	Inhibits *M. aeruginosa*, 69.2% (96 h)[48,57]
		TC = 30 ppm and 200 ppm	Antioxidant activity in *Scomberomorus commersoni*[58]
		TC = 50 mg kg^{-1}	Anti-WSSV activity (92.85%)[59]
2	Naringenin ($C_{15}H_{12}O_5$) from *P. emblica*[55]	TC = 200–400 μM	Inhibits *Edwardsiella tarda*, the causative agent of Edwardsiellosis in aquaculture species[12]
3	Quercetin ($C_{15}H_{10}O_7$) from *P. urinaria*, *P. emblica*, *P. acidus*[55,60–62]	MIC = 0.8 μM MBC > 1.6 μM	Inhibits *V. parahaemolyticus* (15.9–23.6%)[63]
		MIC = 125 μg mL^{-1}	Inhibits *V. parahaemolyticus*[64]
		TC = 0.09–0.36 mM	Inhibits the expression of *flaA* and *flgL* genes encoding flagellin, a structural component of bacterial flagella[65]
		ZOI = 14.00 ± 0.82 mm	Inhibits *V. parahaemolyticus*
		TC = 200 ppm	Exhibits antioxidant activity in *Scomberomorus commersoni*[58]
4	Myricetin ($C_{15}H_{10}O_8$) from *P. acidus*, *P. emblica*[25,55,62]	MIC = 250 μg mL^{-1}	Inhibits *V. parahaemolyticus*[64]
		TC = 200 ppm	Exhibits antioxidant activity in processed *Scomberomorus commersoni*[58]
5	Rutin/Rutoside/Quercetin 3-rutinoside ($C_{27}H_{30}O_{16}$) from *P. emblica*, *P. amarus*, *P. acidus*, *P. muellerianus*, *P. urinaria*[16,19,29,34,55,60,66–69]	ZOI = 26.75 ± 2.22 mm	Inhibits *V. parahaemolyticus*
		MIC = 35 μg mL^{-1}	Exhibits antifungal activity against *Aspergillus ochraceus*[70]
(B) Lignans			
6	Hypophyllanthin ($C_{24}H_{30}O_7$) from *P. urinaria*, *P. amarus*, *P. niruri*[46,68,71–74]	TC = 7.5 μM	Exhibits immunomodulatory activity in *Pangasianodon hypophthalmus*[14]
7	Phyllanthin ($C_{24}H_{34}O_6$) from *P. urinaria*, *P. amarus*, *P. acidus*[46,68,71–74]	—	Protects *Cyprinus carpio* liver from CCl_4-induced damage *via* enhanced antioxidant activity, free radical scavenging, and inhibition of lipid peroxidation[75]
(C) Phenolics			
8	*p*-Coumaric acid ($C_9H_8O_3$) from *P. amarus*[76]	Dose = 1.0–1.5 g kg^{-1} food	Enhances intestinal IL-8 and TNF-α in *Cyprinus carpio*[77]
9	Chlorogenic acid ($C_{16}H_{18}O_9$) from *P. amarus, P. muellerianus*[19,29,76]	TC = 50 mg kg^{-1}	WSSV inhibition: 94.7–95.03%[78]
10	Ferulic acid ($C_{10}H_{10}O_4$) from *P. urinaria*, *P. acidus*, *P. amarus*[60,62,76,79]	Dose = 163.99–183.33 mg kg^{-1} food	Improves growth, innate immunity, and *V. cholerae* resistance in *M. nipponense*
		TC = 1–3% w/v	Inhibits melanosis in chilled *Litopenaeus vannamei*[80]
		TC = 1–2%	Inhibits polyphenol oxidase and reduces melanosis in *L. vannamei*[81]
11	Methyl gallate ($C_8H_8O_5$) from *P. urinaria*, *P. emblica*, *P. muellerianus*[29,55,68,69,82]	MBC = 30 ± 1 to 50 ± 1 μg mL^{-1}	Antibacterial compound disrupting membrane function of *V. cholerae*[83]
		MIC = 31.25 μg mL^{-1}	Inhibits the growth of *Edwardsiella tarda*[84]
12	Protocatechuic acid/3,4-dihydroxybenzoic acid ($C_7H_6O_4$) from *P. urinaria*, *P. emblica*[63,85]	MIC = 28.43 μM MBC > 35.03 μM	Inhibits *V. parahaemolyticus* (91.04–93.12%)[63]

Table 2 (*Contd.*)

No.	Compound/extract	Concentration/numerical results	Biological activity
(D) Polyphenol compounds			
13	Ellagic acid ($C_{14}H_6O_8$) from *P. urinaria*, *P. emblica*, *P. niruri*, *P. acidus*[54,62,68,73,82,86–88]	TC = 10^3 pmol/100 g	Inhibits heavy metal-induced lipid oxidation in cooked *Scomberomorus commersoni*[89]
		TC = 30 ppm and 200 ppm	Exhibits antioxidant activity in steamed and cooked *Scomberomorus commersoni*[58]
14	(Epi)catechin ($C_{15}H_{14}O_6$) from *P. urinaria*, *P. emblica*, *P. niruri*, *P. acidus*[62,68]	TC = 0.05%, 0.1%, and 0.2% (w/v)	Reduces melanosis in *Litopenaeus vannamei* during freeze–thaw cycles[80]
15	Gallic acid/3,4,5-trihydroxybenzoic acid ($C_7H_6O_5$) from *P. emblica*, *P. urinaria*, *P. niruri*, *P. acidus*, *P. muellerianus*[11,15,25,34,53,60,90]	TC = 1%	Exhibits preservative effect in *Lateolabrax japonicus*[91]
		ZOI = 15.00 ± 0.82 mm	Inhibits *V. parahaemolyticus*[92]
16	Pyrogallol ($C_6H_6O_3$) from *P. urinaria*[16]	TC = 64 μg mL^{-1}	Inhibits both AHPND and non-AHPND strains of *Vibrio parahaemolyticus*[93]
17	Pentagalloylglucose ($C_{41}H_{32}O_{26}$) from *P. urinaria*[68]	LC_{50} = 55 ppm	Molluscicidal activity against snails[94]
(E) Terpenoids			
18	Oleanolic acid ($C_{30}H_{48}O_3$) from *P. urinaria*, *P. emblica*[55,79,95]	TC = 30 μM	Exhibits immunomodulatory activity in fish[14]
		TC = 10.95 μM	Antiviral effect against nervous necrosis virus[96]
19	Betulin ($C_{30}H_{50}O_2$) from *P. urinaria*[95]	TC = 20.0 mg mL^{-1}	Antimicrobial effects against *E. coli*, *V. cholerae*, and *P. aeruginosa*[97]

Oreochromis niloticus, with notable improvements in metallothionein expression and hepatosomatic index.[102,103]

Caffeic acid, present in *P. urinaria*, *P. emblica*, and *P. amarus*, further demonstrated dose-dependent growth stimulation in species such as *Huso huso* and *Cyprinus carpio*, with optimal dietary inclusion levels ranging from 5–10 g kg^{-1}. It enhanced trypsin, lipase, and pepsin activity, modulated growth hormone and insulin-like growth factor expression, and supported improved digestive and immune responses.[13,99,100]

Ferulic acid supplementation (92–120 mg kg^{-1}) in *C. idellus* yielded improved specific growth rate, protein utilization efficiency, and intestinal morphology.[104] Furthermore, in *Macrobrachium nipponense*, dietary supplement of ferulic acid at a dose of ~180 mg kg^{-1} significantly enhanced growth and resistance to *Vibrio cholerae* infection.[98]

Chlorogenic acid, a phenolic compound abundant in *P. amarus* and *P. muellerianus*, enhanced muscle fiber density, collagen content, and reduced oxidative stress markers in *Protonibea diacanthus* and *Micropterus salmoides*. The optimal dietary level to improve flesh texture and quality was determined to be 1173 mg kg^{-1}.[105,106]

Conclusively, the metabolic and physiological evidences confirm that *Phyllanthus* spp. compounds act as effective growth enhancers for aquatic species through antioxidant defense activation, improved enzymatic digestion, and modulation of anabolic signaling.

4.2. Immunostimulatory activity

Beside growth enhancement, several phytochemicals extracted from *Phyllanthus* species have demonstrated potent immunostimulatory properties, enabling aquatic organisms to mount effective defense responses against a wide array of pathogens and environmental stressors (Table 3). In short, the immunomodulatory mechanisms of *Phyllanthus* spp. bioactive compounds, including flavonoids, lignans, and polyphenols, are mainly macrophage-mediated immune responses. Upon exposure to these phytochemicals, macrophages are activated, leading to enhanced production of cytokines such as IL-1β, TNF-α, and IFN-γ, as well as stimulation of respiratory burst and phagocytic activity. The secreted cytokines, in turn, upregulate the expression of downstream immune effectors like lysozyme, thereby strengthening host defense mechanisms (Fig. 3).

Kaempferol, found in *P. urinaria* and *P. emblica*, upregulates host antiviral mechanisms and significantly reduces mortality associated with Ictalurid herpesvirus 1 infection in catfish. Mechanistically, it inhibits viral replication by downregulating transcription and protein synthesis of viral genes, in a dose–dependent manner, thereby limiting cytopathic effects.[107] Additionally, kaempferol activates host antioxidant pathways, modulating the activity of key defense enzymes such as superoxide dismutase and catalase, which are critical in managing infection-induced oxidative stress.[101]

Naringenin, isolated from *P. emblica*, is particularly effective against WSSV, achieving a 92.85% inhibition rate at 50 mg kg^{-1} in *Procambarus clarkii*. The immunoprotection involves STAT pathway suppression, along with modulation of key stress- and

Table 3 Immunostimulatory effects of *Phyllanthus* extracts on various aquatic species

Aquatic species	Extract	Dosage (mg kg^{-1})	Immunostimulation	Ref.
Oreochromis niliioticus	Ether extract of *P. emblica*	20	~85%	111
Oreochromis mossambicus	Water extract of *P. niruri*	20	~90%	90
Litopenaeus vannamei	Water extract of *P. amarus*	10	~78%	11
Penaeus monodon	Ethanol extract of *P. emblica*	20	~70%	53
Macrobrachium rosenbergiti	Leaf powder of *P. emblica*	15	~88%	112

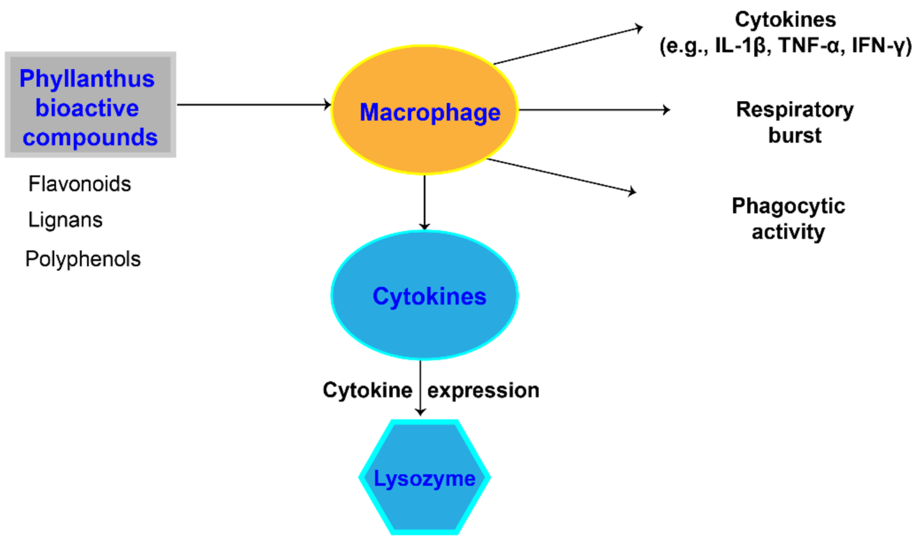

Fig. 3 Immunomodulatory pathways of *Phyllanthus* bioactive compounds in aquatic species.

immunity-related genes of *Hsp70*, *COX-2*, *cMnSOD*, and *Bax*, illustrating a broad-spectrum immunoregulatory function.[59] Moreover, naringenin significantly suppressed the growth of *Edwardsiella tarda* and disrupted quorum sensing in *Vibrio cholerae*, indicating both direct antimicrobial and host-targeted effects.[11,12]

Rutin, a glycosylated quercetin derivative from *P. emblica* and *P. amarus*, boosted total hemocyte counts and modulated immune parameters in *Fenneropenaeus chinensis* at dietary levels of 1 g kg^{-1}. Although minimal immunostimulation was observed in pathogen-free environments, rutin shows potential as a prophylactic immunomodulator when disease pressure is high.[67,108] Similarly, caffeic acid enhanced innate immune responses in *Oreochromis niloticus* by upregulating *IL-1β*, *TNF-α*, *IFN-γ*, and *HSP70*, while increasing the phagocytic index, respiratory burst activity, and catalase levels in serum comparable to antibiotic-based interventions.[100]

Furthermore, chlorogenic acid, when administered to *L. vannamei* under low salinity and nitrite stress, enhanced survival *via* increased GSH-Px and CAT activities, and upregulated immune-relevant genes (*GN*, *CAT*).[92] Chlorogenic acid also blocked horizontal transmission of WSSV in shrimp by inducing apoptosis and inhibiting viral transcription in hemocytes and gill tissues.[78] In *Micropterus salmoides*, chlorogenic acid modulated the expression of IL-8, TNF-α, and SOD, pointing to its dual role as an immunoregulator and anti-inflammatory agent.[106]

Notably, hypophyllanthin, a lignan from *P. urinaria*, at concentrations of 7.5 μM, activated immunological pathways in *Pangasianodon hypophthalmus*, enhancing resistance to microbial challenge.[14] On the other hand, ferulic acid improved immune markers in *Macrobrachium nipponense*, including lysozyme activity and interleukin expression, at dietary levels of ~180 mg kg^{-1}, contributing to both innate and adaptive immunity.[109,110]

These data support the development of *Phyllanthus* spp. immunostimulants as functional feed additives that confer disease resilience, reduce antibiotic reliance, and enhance the immunocompetence of farmed species under intensive aquaculture conditions.

4.3. Antimicrobial and antiviral properties

Aquatic animal health is constantly challenged by bacterial and viral pathogens that compromise survival and productivity. To this end, phytochemicals isolated from *Phyllanthus* species have emerged as potent antimicrobial and antiviral agents with multifunctional mechanisms, including quorum sensing inhibition, disruption of membrane integrity, and suppression of pathogen virulence gene expression. Specifically, *Phyllanthus* polyphenols and tannins bind to membrane phospholipids and destabilize the lipid bilayer, leading to increased membrane permeability, leakage of cellular contents (ions, proteins, nucleic acids), and eventual bacterial lysis.[12,83] Lignans such as phyllanthin intercalate with bacterial DNA or inhibit DNA gyrase/topoisomerase enzymes, blocking replication.[15] Flavonoids can inhibit ribosomal function, disrupting protein synthesis and metabolic pathways.[107] Regarding antiviral mechanisms, tannins, polyphenols, and saponins can bind to viral envelope glycoproteins or host cell receptors, blocking virus attachment and entry into host cells.[113] *Phyllanthus* phytochemicals modulate intracellular signaling pathways (*e.g.*, MAPK, NF-κB) essential for viral replication. Lignans and flavonoids can directly inhibit viral polymerases and proteases, interfering with genome replication and viral protein synthesis. *Phyllanthus* extracts also enhance the expression of antiviral cytokines such as interferon and interferon-stimulated genes, strengthening the host's antiviral state.[114]

Quercetin, commonly extracted from *P. urinaria*, *P. emblica*, and *P. acidus*, demonstrated strong activity against *Vibrio parahaemolyticus* with MIC values as low as 0.8 μM and notable inhibition of motility (15.9–23.6%).[63] Its mechanism involves downregulation of *flaA* and *flgL*, two flagellar genes crucial for bacterial biofilm formation and colonization in host tissues.[65] Additionally, quercetin exerted synergistic effects when used in preservation of *Litopenaeus vannamei*, maintaining color, lipid stability, and microbial load during cold storage.[115]

Naringenin, apart from its immunomodulatory actions, inhibited *Edwardsiella tarda* at 200–400 μM,[12] and significantly reduced biofilm-associated virulence in *V. cholerae* by modulating quorum sensing regulatory genes such as *gbpA*, *vpsA*, *rbmA*, and *mbaA*.[116]

Kaempferol, at concentrations of ≥20 mg L^{-1}, suppressed *Microcystis aeruginosa* growth, achieving up to 69.2% inhibition of *Anabaena* after 96 h at a concentration of 50 mg L^{-1},[57] indicating its potential to control harmful algal blooms that threaten aquaculture environments. Moreover, kaempferol displayed antiviral activity against Ictalurid herpesvirus 1 by suppressing transcription and protein synthesis of viral genes.[107]

Chlorogenic acid and caffeic acid, abundant in *P. amarus* and *P. emblica*, exhibited inhibitory effects on WSSV replication. In *Procambarus clarkii*, chlorogenic acid at a concentration of 50 mg kg^{-1} inhibited WSSV in hemocytes and gills by >94%, through enhanced apoptosis and modulation of innate immunity.[78] Chlorogenic acid also reduced WSSV horizontal transmission and upregulated antioxidant and anti-inflammatory gene responses.[117]

Rutin, a quercetin glycoside, inhibited *Aeromonas hydrophila*, *Staphylococcus aureus*, and *Aspergillus ochraceus*, with MICs ranging from 35–1000 μg mL^{-1}. Notably, its antifungal activity against *A. ochraceus* was comparable to commercial disinfectants.[70]

Methyl gallate, found in *P. urinaria* and *P. emblica*, displayed MICs of 31.25 μg mL^{-1} against *Edwardsiella tarda*,[12,83] and disrupted bacterial membranes by collapsing cytoplasmic pH and membrane potential, ultimately impairing ATP generation.[83] Its quorum sensing inhibitory effects on *A. hydrophila* include suppression of virulence regulators (*ahyR*, *fleQ*) and promotion of anti-virulence gene expression (*litR*, *fleN*).[114]

Betulin, a triterpenoid from *P. urinaria*, showed significant *in silico* binding to VP28, a key structural protein of WSSV, suggesting its potential to block viral attachment and entry.[113] Experimentally, it inhibited growth of *E. coli*, *V. cholerae*, and *Pseudomonas aeruginosa* at a concentration of 20 mg mL^{-1}.[97]

Collectively, these bioactive agents act on multiple microbial targets, including structural proteins, signaling systems, and metabolic enzymes, rendering *Phyllanthus* spp. compounds attractive alternatives to synthetic antimicrobials. Their dual functionality as both therapeutic and prophylactic agents offers a novel strategy for pathogen control in sustainable aquaculture.

4.4. Antioxidant and hepatoprotective effects

Oxidative stress is a major contributor to impaired growth, immune dysfunction, and hepatocellular injury in aquaculture species, particularly under conditions of environmental or dietary stress. Phytochemicals extracted from *Phyllanthus* species exhibit potent antioxidant and hepatoprotective properties, acting through free radical scavenging, modulation of redox-related enzymes, and gene regulatory pathways. Polyphenols enhance the activity of endogenous antioxidant enzymes such as SOD, CAT, and (GSH-Px), thereby reducing oxidative stress induced by reactive oxygen species (ROS). By lowering ROS levels, polyphenols prevent oxidative damage to liver cell membranes and protect hepatocytes from injury. Additionally, they exert hepatoprotective effects through inhibition of lipid peroxidation, modulation of serum liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and suppression of inflammation (Fig. 4).

Caffeic acid, found in *P. urinaria* and *P. emblica*, enhances antioxidant defenses in multiple fish species. In *Oreochromis niloticus*, dietary supplementation at 5 g kg^{-1} significantly upregulated key antioxidant enzymes including SOD, CAT, and GSH-Px, while boosting immune gene expression (*IL-1β*, *TNF-α*, *IFN-γ*) and improving survival against *Aeromonas veronii* infection.[100] Similar effects were observed in *Huso huso*, where caffeic acid enhanced digestive enzyme activity and growth hormone expression, suggesting its dual role in metabolic enhancement and liver protection.[99]

Chlorogenic acid exerts dose-dependent hepatoprotection by suppressing inflammatory cytokines (*IL-1*, *TNF-α*, *IL-6*) and elevating redox regulators (SOD, GSH-Px, CAT) in hepatocytes exposed to ammonia toxicity.[105,117] In *Micropterus salmoides*, CGA reduced malondialdehyde accumulation while upregulating *APOA1*, *HSL*, and *ATGL*, genes involved in lipid metabolism, further indicating its role in mitigating hepatic lipid dysregulation under high-fat diets.[106]

Quercetin protected *Scomberomorus commersoni* muscle and liver tissues from metal ion-induced lipid peroxidation, achieving 32.6–44.2% inhibition even under Fe^{2+} and Cu^{2+} exposure.[89] Quercetin also maintained hematological and histopathological normalcy in *Salmo gairdneri* fed at levels up to 5%, highlighting its safety and bioactivity in long-term use.[118]

Myricetin and ellagic acid, polyphenols present in *P. acidus* and *P. niruri*, exhibited even stronger lipid peroxidation suppression, with ellagic acid achieving 75.7–83.9% inhibition in heavy metal-contaminated fish tissues.[89] These compounds

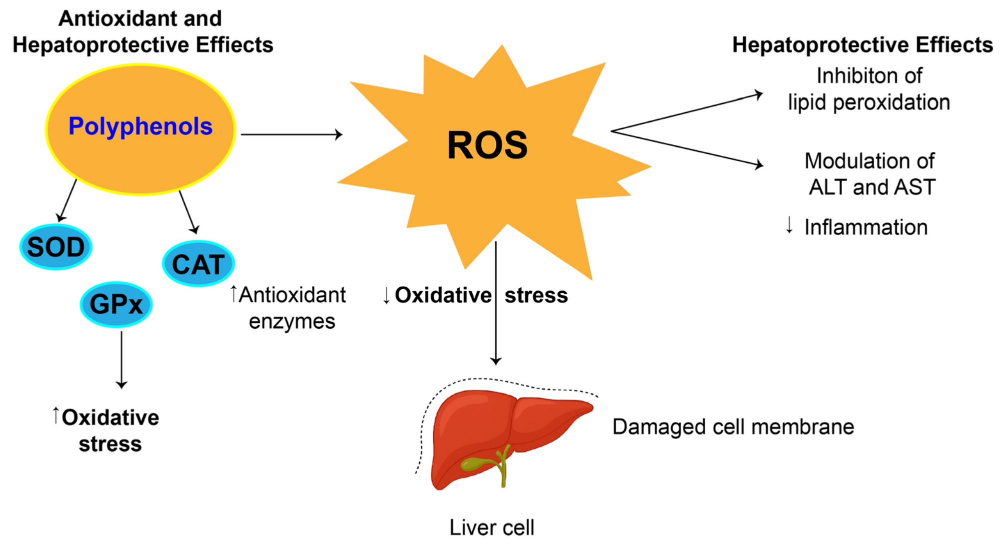

Fig. 4 Antioxidant and hepatoprotective mechanisms of *Phyllanthus* polyphenols in aquatic species.

preserved mitochondrial function and stabilized membrane integrity, likely *via* direct ROS scavenging and iron chelation.

Ferulic acid, widely distributed in *Phyllanthus* species, conferred robust hepatoprotection in *Megalobrama amblycephala* under LPS-induced stress. Oral gavage at 50–100 mg kg^{-1} body weight significantly enhanced GSH-Px levels and enzymatic activities (SOD, GST, GR), while downregulating proinflammatory cytokines.[98] In *Oreochromis niloticus*, ferulic acid mitigated liver damage under thermal stress by suppressing *HSP70* and upregulating *INF-γ*, *IL-1β*, and *TNF-α*.[119]

4.5. Environmental and water quality improvement effects

In addition to their direct physiological benefits to aquatic species, several *Phyllanthus* spp. phytochemicals have demonstrated capacity to enhance aquaculture environmental quality through algal bloom suppression, biofilm inhibition, and the development of biodegradable antimicrobial packaging systems.

Kaempferol exhibited strong allelopathic effects on cyanobacteria. At a concentration of 50 mg L^{-1}, kaempferol inhibited *Microcystis aeruginosa* growth by nearly 40% within 96 h, and suppressed *Anabaena* spp. by 69.2%.[57] Such activity holds potential for mitigating harmful algal blooms (HABs), a major cause of fish kills and dissolved oxygen depletion in pond systems.

Caffeic acid and chlorogenic acid were successfully incorporated into edible biofilms and packaging membranes to reduce microbial contamination and lipid oxidation in aquaculture products. Caffeic acid-enhanced gelatin-based films demonstrated 20-fold improved antioxidant capacity and 6-fold increase in antibacterial activity compared to controls, prolonging the shelf-life of stored fish.[120] Similarly, chitosan-grafted chlorogenic acid membranes inhibited *Pseudomonas fluorescens* biofilms by 71.64% and disrupted EPS production by over 60.72%.[121]

Protocatechuic acid and gallic acid, polyphenols isolated from *P. emblica* and *P. urinaria*, were incorporated into gelatin–chitosan composite films, showing strong free radical scavenging capacity, low water permeability, and broad-spectrum antimicrobial activity against *E. coli* and *S. aureus* during refrigerated storage of seafood.[85,91] These biopolymeric materials offer sustainable alternatives to plastic packaging in aquaculture value chains.

At the cellular level, chlorogenic acid improved waterborne ammonia detoxification by upregulating hepatocellular antioxidant genes and downregulating inflammatory cytokines in catfish exposed to ammonia concentrations of 0.23 mg L^{-1}.[117] This suggests that phytocompound supplementation could mitigate ammonia toxicity, one of the most prevalent environmental stressors in intensive aquaculture.

Additionally, lauric acid, extracted from *P. urinaria*, demonstrated microbiota-modulatory effects in *Portunus trituberculatus*, improving gut barrier function and enhancing the abundance of beneficial bacterial taxa such as *Actinobacteria* and Rhodobacteraceae, while reducing *Vibrio* load.[122] These findings point toward a prebiotic role of phytochemicals in shaping pond microbiome health and reducing opportunistic pathogen proliferation.

Collectively, the application of *Phyllanthus* spp. compounds extends beyond organism-level benefits to encompass holistic environmental management strategies, supporting water quality improvement, sustainable waste reduction, and the development of green aquaculture technologies.

5. Opportunities, challenges, and future research directions

The growing integration of *Phyllanthus* spp. phytocompounds in aquaculture opens new frontiers for sustainable fish and shrimp farming, driven by mounting pressure to reduce reliance on antibiotics, synthetic antioxidants, and

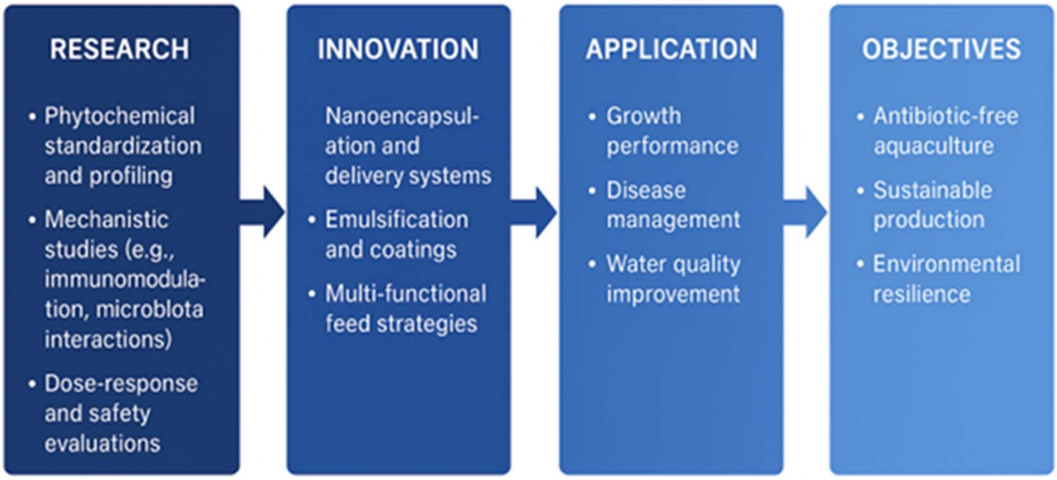

Fig. 5 Research–innovation–application roadmap for *Phyllanthus* spp. utilization in sustainable aquaculture.

environmentally detrimental feed additives. Their multifunctional properties of immunostimulation, growth promotion, antioxidant protection, and environmental amelioration position them as next-generation, bio-based solutions to meet the nutritional and ecological demands of modern aquaculture.

Opportunities lie in the valorization of native *Phyllanthus* species across tropical and subtropical regions. The broad-spectrum bioactivity of compounds such as kaempferol, chlorogenic acid, quercetin, and naringenin, demonstrated through both *in vitro* and *in vivo* models, offers the potential for the formulation of standardized phytogenic feed additives, biopreservatives, and antimicrobial films. Moreover, the capacity of certain phytocompounds to modulate gut microbiota, improve fillet quality, and suppress algal blooms suggests cross-domain applications spanning health, nutrition, and environmental remediation.

However, several challenges must be addressed to translate these findings into scalable commercial applications. First, phytochemical variability due to varied *Phyllanthus* species, geography, harvest season, and extraction method limits reproducibility. Second, the pharmacokinetics and bioavailability of these compounds in aquatic organisms remain poorly characterized, complicating dosage optimization. Third, large-scale production, regulatory approval, and cost-competitiveness compared to synthetic alternatives present formidable barriers. Furthermore, there is a paucity of longitudinal studies validating safety, efficacy, and ecological impact over production cycles.

To overcome these constraints, future research should pursue interdisciplinary and translational approaches. Omics-based techniques (metabolomics, transcriptomics, microbiomics) should be deployed to map host–compound interactions and elucidate molecular mechanisms of action. Novel delivery systems, such as encapsulation or nanoformulations, may enhance compound stability and bioavailability. Field-scale trials across species and farming systems are imperative to validate laboratory findings under real-world conditions. Additionally, life-cycle assessment (LCA) and techno-economic analyses will be crucial in informing policy and guiding industrial adoption (Fig. 5).

6. Conclusions

This review highlights the multifaceted potential of *Phyllanthus* species as a valuable source of bioactive compounds for sustainable aquaculture. *Phyllanthus* spp. phytochemicals such as kaempferol, naringenin, quercetin, caffeic acid, and chlorogenic acid exhibit demonstrable efficacy in enhancing growth performance, modulating immune responses, protecting hepatic tissues, destroying microbes and viruses, and improving environmental quality in aquatic farming systems. Nevertheless, commercial applications of *Phyllanthus* spp. remain constrained by challenges in standardization, bioavailability, and regulatory acceptance. Future research should prioritize mechanistic elucidation, formulation optimization, and large-scale validation under diverse aquaculture conditions.

Author contributions

Conceptualization: N. T. N. T., B. T. P. T.; investigation: N. T. N. T., P. T. M. H., N. T. P. T., V. D. N., T. H. B., V. T. P., D. T. P., B. T. P. T.; data curation: N. T. N. T., P. T. M. H., N. T. P. T., V. D. N., T. H. B., V. T. P., D. T. P., B. T. P. T.; validation: N. T. N. T., B. T. P. T.; project administration: B. T. P. T.; writing-original draft: N. T. N. T., D. T. P., B. T. P. T.; writing-review and editing: N. T. N. T., P. T. M. H., N. T. P. T., V. D. N., T. H. B., V. T. P., D. T. P., B. T. P. T. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

None to declare.

Data availability

No primary research results, software, or code have been included, and no new data were generated or analysed as part of this review.

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