Macroalgal extracts replace antibiotics in sustainable aquaculture production

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Abstract

Intensification in aquaculture has increased challenges related to infectious diseases, prompting the search for alternatives to traditional antibiotic treatments, which often result in chemical residues, environmental pollution, and antimicrobial resistance. This review evaluates marine macroalgae and terrestrial plant extracts as sustainable antimicrobial agents, focusing on their extraction methods, phytochemical composition, and efficacy. Marine algae, particularly brown and red species, contain unique bioactive compounds such as sulfated polysaccharides, phenolics, and pigments. These extracts demonstrate potential as growth promoters and immunostimulants; however, safety is paramount, as studies on zebrafish have revealed teratogenic effects at high concentrations. Research confirms enhanced growth performance in tilapia and shrimp fed diets supplemented with algal extracts, including improved feed conversion ratios and specific growth rates. The immunomodulatory properties of these extracts activate defense mechanisms, such as increased lysozyme activity and elevated hemocyte counts. Additionally, macroalgal extracts help preserve post-harvest seafood quality by inhibiting spoilage and oxidation. Key challenges for commercial application include standardizing extraction procedures, establishing safety thresholds, and determining optimal dosing levels. Overall, plant and seaweed extracts present a promising alternative to antibiotics by enhancing growth, immunity, and disease resistance in aquaculture species. Their efficacy depends on extraction techniques, bioactive compound profiles, and precise dosing to avoid toxicity. Further research is necessary to standardize protocols and evaluate long-term effects, representing a sustainable strategy to improve aquaculture productivity while mitigating the risks of antimicrobial resistance.

Keywords: Phytogenic feed additives, Marine macroalgae, Immunostimulation, Antimicrobial resistance, Sustainable aquaculture

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Introduction

The global aquaculture industry has rapidly expanded to become the world's fastest-growing food production sector. To meet the rising demand for protein, aquaculture now supplies approximately half of all fish and shellfish consumed worldwide. However, intensified production has degraded the environments of culture systems, increasing the vulnerability of aquatic animals to infectious diseases. These infections result in significant economic losses, exceeding $6 billion annually in the shrimp sector alone (Stentiford *et al*., 2012; Bharath *et al*., 2023). Traditional management of aquatic diseases has relied heavily on chemotherapy and synthetic antibiotics. However, their overuse has resulted in the accumulation of chemical residues in aquatic tissues, environmental pollution, and, critically, the development of antibiotic resistance (AftabUddin *et al*., 2021; Lu *et al*., 2022). The transfer of resistance genes to human pathogens poses a significant public health threat, leading international organizations to impose restrictions on antibiotic use in aquaculture (Schar *et al*., 2020). Therefore, sustainable and eco-friendly alternatives to synthetic antimicrobials are urgently needed.

Phytogenic feed additives derived from terrestrial medicinal plants and marine macroalgae (seaweeds) show significant promise due to their bioactive compounds. These natural products contain polysaccharides, phenolics, flavonoids, alkaloids, terpenoids, and pigments, which exhibit antimicrobial, anti-inflammatory, antioxidant, and immunostimulatory properties (Reverter *et al*., 2014; Van Hai, 2015). Marine macroalgae are of particular interest because of their abundance and unique bioactive components, such as sulfated polysaccharides (e.g., fucoidan and alginate), which are absent in terrestrial plants.

This review evaluates the efficacy of plant and seaweed extracts in aquaculture as growth promoters, immunostimulants, and antibacterial agents. Although studies have highlighted the benefits of specific plants, a comparative analysis of solvent extraction methods and the mechanisms by which these extracts influence host physiology and pathogen virulence remains lacking. This review addresses this gap by synthesizing recent findings on extraction methodologies, nutritional enhancement, immunological modulation, and the synergistic potential of phytochemicals combined with antibiotics. This study reviews 23 key research articles (2011–2024) to evaluate the efficacy and safety of phytogenic extracts as immunostimulants. This dual assessment is essential for standardizing the use of phytogenics in aquafeeds to enhance health and ensure the welfare of cultured organisms.

Phytochemical profiling and extraction of marine and terrestrial plants

The effectiveness of botanical additives in aquaculture depends on their chemical composition, which is greatly influenced

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by the extraction method. Marine macroalgae including green, brown, and red varieties and terrestrial medicinal plants produce a diverse array of secondary metabolites that serve as defenses against environmental stressors. These metabolites constitute the bioactive foundation for their therapeutic applications in aquaculture (Dominguez, 2013). Phytochemical screenings reveal distinct profiles among algal species. For example, the ethanolic extract of the green seaweed *Ulva reticulata* contains alkaloids, flavonoids, saponins, tannins, phenols, and steroids, with significant concentrations of phenols and flavonoids contributing to its antioxidant activity (Tarigan *et al*., 2023). Studies on Moroccan macroalgae have shown that brown algae, such as *Bifurcaria bifurcata* and *Fucus spiralis*, possess higher polyphenol content than green algae like *Ulva rigida*. Polar solvents, including methanol and ethanol, are generally more effective than non-polar solvents for extracting phenolic compounds, resulting in higher antioxidant capacities. Solvent selection also affects extract toxicity. Although some extracts demonstrate high bioactivity, their safety must be thoroughly evaluated. The ethanolic extract of *U. reticulata* was classified as non-toxic in Brine shrimp lethality tests, indicating its potential safety for aquaculture applications (Chernane *et al*., 2014). In contrast, the methanolic extract of *Enteromorpha linza* exhibited larvicidal activity against *Artemia salina*, suggesting the presence of potent bioactive compounds that require careful dosing. These compounds inhibit bacterial enzymes, including beta-lactamases, which explains their biological activity. Characterizing these chemical profiles is essential for developing effective feed additives (Tarigan *et al*., 2023).

Toxicity, safety, and dose response

While phytogenics provide documented benefits, their "natural" origin does not guarantee safety. Determining toxicity thresholds is essential, as some plant extracts contain antinutritional factors or toxins that can cause teratogenic effects or mortality at high concentrations. This section reviews preclinical toxicity assessments of algal extracts using the zebrafish model. González-Penagos *et al*. (2024) evaluated the toxicity of *Sargassum* spp. ethanolic extract in zebrafish embryos by exposing them to concentrations ranging from 0.01 to 400 mg/L. The median lethal concentration (LC50) was determined to be 251 mg/L. Notably, malformations such as edema, scoliosis, and eye deformities were observed at concentrations as low as 10 mg/L. Transcriptomic analysis revealed downregulation of genes associated with the nervous system and visual perception, alongside upregulation of detoxification genes, including those encoding cytochrome P450 enzymes. These findings underscore the extract's potential teratogenicity and toxicity at higher doses. Yadav *et al*. (2024) evaluated the acute and subchronic toxicity of methanolic extract of Sargassum tenerrimum in adult zebrafish and SH-SY5Y cells. The in

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vitro IC50 was 140.014 µg/mL. The acute in vivo toxicity (96 hours) had an LC50 of 504.669 mg/L. However, subchronic toxicity over 14 days increased, with the LC50 decreasing to 404.196 mg/L. Histopathological analysis at 800 mg/L revealed liver vacuolization and brain inflammation. The study concluded that the extract exhibits dose- and time-dependent toxicity, being safe only at lower concentrations. Toxicity studies emphasize the importance of precise dosing of algal extracts in aquaculture. Due to their narrow therapeutic index, it is essential to determine both the no observed effect level and the effective dose to prevent mortality, malformations, and organ damage caused by excessive concentrations or prolonged exposure.

Enhancement of growth performance and feed utilization

In aquaculture, growth performance is a critical economic indicator, and functional feed additives are commonly used to improve the feed conversion ratio (FCR) and specific growth rate (SGR). Plant and algal extracts are thought to enhance growth by supplying essential nutrients and promoting gut health through the stimulation of digestive enzyme secretion and improved nutrient absorption. This section reviews the effects of various macroalgal extracts on the growth parameters of shrimp and fish (Table 1).

Table 1: Summary of studies on growth performance and feed utilization.

Study subject	Extract/additive	Experimental design	Key results	Reference
Nile Tilapia (*O. niloticus*)	*Gracilariopsis lemaneiformis* (Red seaweed) ethanolic extract	8-week feeding trial; 0%, 5%, 10%, 15% inclusion in RAS system.	15% inclusion yielded highest weight gain (51.5g) and best FCR (1.15).	(Shahabuddin *et al*., 2024)
White Shrimp (*L. vannamei*)	9 Macroalgae spp. (inc. *Acanthophora spicifera*) powder	28-day trial; 5% dietary inclusion.	All algae improved growth; *A. spicifera* showed highest SGR and weight gain.	(Zhang *et al*., 2023)
Tiger Shrimp (*P. monodon*)	*Sargassum polycystum* acidic polysaccharide	50-day trial; 0-2000 mg/kg supplementation.	2000 mg/kg dose significantly enhanced weight gain and specific growth rate.	(Victoriano-Blancia *et al*., 2022)
Zebrafish (*Danio rerio*)	*Ulva intestinalis* powder	8-week trial; 0-1% inclusion.	Increased growth-related gene expression (GH, IGF-1) at 1% inclusion.	(Rouhani *et al*., 2022)

Recent studies demonstrate positive correlations between algal supplementation and growth. For example, Shahabuddin *et al*. (2024)

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found that Nile tilapia (*Oreochromis niloticus*) fed a diet containing 15% red seaweed (*Gracilariopsis lemaneiformis*) extract exhibited the highest mean weight gain and lowest FCR in an 8-week trial, indicating improved nutrient utilization and metabolic efficiency. Similarly, Zhang *et al*. (2023) showed that supplementing white shrimp (*Litopenaeus vannamei*) diets with 5% macroalgae powder, particularly the red alga *Acanthophora spicifera*, significantly increased weight gain and specific growth rate SGR compared to controls. Victoriano-Blancia *et al*. (2022) also found that *Penaeus monodon* fed diets supplemented with acidic polysaccharides extracted from the brown seaweed *Sargassum polycystum* exhibited significantly enhanced weight gain and specific growth rates after 50 days, suggesting that specific polysaccharide fractions can effectively promote growth. Studies demonstrate that incorporating macroalgae into aquaculture diets enhances growth performance and feed efficiency. In Pacific white shrimp (*L. vannamei*), co-feeding with *Ulva clathrata* significantly improved growth rates, with isotope analysis confirming the assimilation of algal carbon and nitrogen, thereby complementing commercial feeds (Gamboa-Delgado *et al*., 2011). Similarly, supplementation with *Ulva lactuca* and *Gracilaria vermiculophylla* in *L. vannamei* diets resulted in high apparent digestibility coefficients (78–82%) for dry matter and crude protein, indicating that these macroalgae lack significant anti-nutritional factors (Anaya-Rosas *et al*., 2017). This enhanced digestibility and feed efficiency support both animal health and the economic sustainability of aquaculture by reducing feed costs.

Macroalgal and plant extracts can enhance aquaculture growth by increasing the SGR and reducing the FCR in crustaceans and finfish. These benefits, observed with both crude powders and extracted polysaccharides, likely result from improved nutrient absorption and the presence of bioactive compounds. Although optimal inclusion levels vary, these extracts hold significant potential for advancing aquatic animal cultivation.

Modulation of non-specific immune responses

Aquatic invertebrates rely on innate immunity, whereas fish utilize both innate and adaptive immune responses to defend against pathogens. Key indicators of immune function include lysozyme activity, total hemocyte count (THC), respiratory burst activity, and the prophenoloxidase (proPO) system. Phytogenic extracts, which are rich in glucans, bacteria-like compounds, and polyphenols, can serve as immunostimulants by activating these pathways (Table 2). Studies demonstrate the immunomodulatory effects of algae in aquatic species. Rouhani *et al*. (2022) found that supplementation with *Ulva intestinalis* upregulated Lyz and IL-1β gene expression in zebrafish, with 1% inclusion yielding the highest mucosal lysozyme activity and immunoglobulin levels, suggesting stimulation of both the

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mucosal barrier and systemic immunity. In shrimp, Zhang *et al*. (2023) showed that *A. spicifera* significantly increased THC, phagocytic activity, and respiratory burst activity in *L. vannamei*, upregulating proPO system and antimicrobial peptide gene expression, indicating hemocyte priming. Similarly, Victoriano-Blancia *et al*. (2022) reported that polysaccharides from *S. polycystum* enhanced THC and serum antibacterial activity in *P. monodon* in a dose-dependent manner, suggesting that acidic polysaccharides mimic pathogen-associated molecular patterns (PAMPs) to trigger immune defenses.

Table 2: Antimicrobial and immunostimulatory efficacy of plant extracts against aquatic pathogens.

Extract source	Pathogen / target	Method of application	Observed outcome	Immune parameter affected	Reference
Gracilaria sp.	*V. parahemolyticus*	Combined with Carbenicillin	Reduced MIC of antibiotic (Synergy)	Inhibition of VarG beta lactamase	(Lu *et al*., 2022)
Padina tetrastromatica	*V. parahaemolyticus*	Oral (5 g/ kg	Reduced mortality (10% vs 60% control)	Increased THC, PO activity, O_2 production	(AftabUddin *et al*., 2021)
Bifurcaria bifurcata	Spoilage bacteria (lipolytic/proteolytic)	Ice medium inclusion	Inhibited growth of psychrotrophs	Reduced lipid oxidation	(Miranda *et al*., 2021)
Ulva reticulata	General toxicity test	Exposure to *Artemia salina*	Low toxicity (LC 50: 480 ppm)	Safe for physiological application	(Tarigan *et al*., 2023)
Enteromorpha linza	*A. salina*	Methanol extract exposure	100% mortality	High cytotoxicity (potential parasite control)	(Kim and Choi, 2017)

A study have shown that methanolic extracts from the brown seaweeds Padina tetrastromatica and Sargassum ilicifolium significantly enhance shrimp immunity by increasing THC, PO activity, and superoxide anion production. These immune responses lead to higher survival rates when shrimp are challenged with *Vibrio parahaemolyticus* (AftabUddin *et al*., 2021). Similarly, red seaweed extracts exhibit immunomodulatory effects in Nile tilapia, elevating hemoglobin levels and improving the blood plasma refractive index, an indicator of overall health. The spleen somatic index, a measure of immune organ health, also improves, suggesting enhanced oxygen transport and increased production of immune proteins (Shahabuddin *et al*., 2024). This immune enhancement is often attributed to polysaccharides such as alginate and fucoidan present in seaweed extracts, which activate pattern recognition receptors on immune cells. This activation triggers the release of

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antimicrobial peptides and reactive oxygen species (ROS), effectively "priming" the immune system for a faster and more effective response to pathogens, thereby reducing mortality without the use of antibiotics (Thanigaivel *et al*., 2023). *In vitro* study by Cavallo *et al*. (2013) demonstrated that lipid extracts from *Gracilariopsis longissima* and *Chaetomorpha linum* strongly inhibited fish pathogenic Vibrio species (*Vibrio ordalii*, *Vibrio vulnificus*, and *Vibrio alginolyticus*) using the disc diffusion method, suggesting the presence of potent antimicrobial compounds within these algae. Miranda *et al*. (2021) found that aqueous and ethanolic extracts of *Bifurcaria bifurcata* significantly inhibited microbial growth (psychrotrophs and lipolytic bacteria) and reduced lipid oxidation in chilled Hake (*Merluccius merluccius*) during storage, indicating that the antimicrobial properties of these algae can extend shelf life post-harvest.

Extracts from the red seaweed *Gracilaria* sp. enhance the efficacy of beta-lactam antibiotics against resistant *Vibrio* strains. Checkerboard assays demonstrated that combining *Gracilaria* sp. extract with carbenicillin synergistically reduced the minimum inhibitory concentration (MIC) for *V. parahaemolyticus* and *Vibrio cholerae* by inhibiting metallo-beta-lactamases, specifically the VarG enzyme. Unlike synthetic inhibitors, *Gracilaria* sp. likely inhibits this enzyme through allosteric interactions or active site blocking rather than metal chelation. This suggests that plant extracts can restore the effectiveness of conventional antibiotics, potentially allowing for lower dosages and reducing the selection pressure for resistance (Lu *et al*., 2022). This dual approach of direct enzyme inhibition and antibiotic synergy offers a versatile disease management strategy, particularly for multidrug-resistant bacterial infections prevalent in aquaculture. By targeting virulence factors or resistance mechanisms, these extracts may also reduce the evolutionary pressure on pathogen populations compared to traditional bactericidal methods (Defoirdt *et al*., 2011). Plant and algal extracts enhance cellular responses and upregulate immune gene expression, thereby strengthening the nonspecific immune system and increasing resistance to pathogens. *Ulva* and *Sargassum* species, in particular, are especially effective in stimulating these immune pathways across various aquatic taxa.

Application of natural preservatives to maintain post-harvest quality

Plant extracts provide a natural alternative to synthetic preservatives for post-harvest seafood preservation. A study on chilled hake (*M. merluccius*) have demonstrated the effectiveness of brown alga (*B. bifurcata*) extracts in extending shelf life. Both aqueous and ethanolic extracts, when incorporated into ice, significantly inhibited spoilage organisms including psychrotrophic, proteolytic, and lipolytic bacteria and slowed chemical spoilage. The lipophilic, antioxidant-rich ethanolic

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extract was particularly effective at inhibiting lipid hydrolysis, while the phlorotannin-rich aqueous extract suppressed secondary lipid oxidation. This preservation mechanism involves the gradual release of bioactive compounds from the ice, which scavenge free radicals and disrupt bacterial membranes. This method preserves nutritional quality and sensory attributes, thereby enhancing product value without the use of synthetic additives (Miranda *et al*., 2021).

Conclusion

Phytogenic compounds derived from marine macroalgae and terrestrial plants present promising alternatives to antibiotics in aquaculture by enhancing production through growth promotion, improved feed efficiency, and immune modulation. Marine algae, particularly brown and red species, contain potent immunostimulatory compounds such as sulfated polysaccharides. However, their narrow therapeutic window, as evidenced by toxicity in zebrafish, requires species-specific dosing and comprehensive safety assessments. Challenges remain in standardizing extraction methods, ensuring batch-to-batch consistency, and determining optimal inclusion levels across different species and production systems. Variability in bioactive compound profilescaused by seasonal, geographical, and processing factors necessitates stringent quality control measures. Additionally, the economic viability of large-scale implementation requires thorough assessment. Future research should focus on elucidating the mechanisms of immunomodulation, conducting long-term safety assessments, and developing standardized, cost-effective extraction protocols. Investigating synergistic combinations of phytogenic compounds and creating protective delivery systems for feed processing are essential for practical applications across diverse aquaculture systems.

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