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REVIEW

Natural antimicrobials to mitigate the impact of *Enterocytozoon hepatopenaei*-caused hepatopancreatic microsporidiosis in shrimp aquaculture

Nor Asma Husna Yusoff . Joey Joe Yee Ng . Heri Prasetyoning Tias . Mochammad Sultan Syah Apendi . Farizan Abdullah . Ahmad Najmi Ishak . Marina Hassan

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Abstract Hepatopancreatic microsporidiosis (HPM), caused by *Enterocytozoon hepatopenaei* (EHP), has resulted in significant financial losses in aquaculture worldwide. This disease can infect a wide range of hosts, including both freshwater and brackish water aquatic animals. The most common clinical signs of EHP infection include reduced feeding, growth retardation, lethargy, soft shells, an empty midgut, and chronic mortality in severe cases. Currently, antibiotics are used as prophylactic agents to manage microsporidiosis in aquaculture. However, the use of antibiotics has contributed to the development of antibiotic-resistant bacteria, and antibiotic residues may pose risks to public health. As a result, natural antimicrobials are being explored as alternative solutions to mitigate the impact of microsporidiosis, offering farmers safer and more sustainable options for maintaining the health of aquaculture species. This review elaborates on the life cycle, characteristics, physiological signs, and histopathological alterations of microsporidian infection in shrimp. It also discusses transmission and biochemical impact of EHP infection in shrimp aquaculture. Finally, it examines recent approaches for controlling EHP, with a focus on the potential use of natural antimicrobials as alternatives to chemical treatments and antibiotics, which are rarely addressed in previous review papers, underscore the significance and novelty of this study.

Keywords Antibiotics . Aquatic diseases . Fungal . Natural antimicrobials . Microsporidiosis . Sustainable aquaculture

Introduction

Food security is a major global concern today, and aquaculture is considered one of the most effective methods for providing affordable and sustainable sources of protein for human consumption (Kumar et al. 2023). The shrimp farming industry significantly contributes to the gross domestic product (GDP) of several developing Asian countries, producing 5, 812.2 tonnes globally in 2023 that accounting for 51.7 % of total crustacean production (11, 237 tonnes) (FAO 2022; Madesh et al. 2023). Among shrimp species, whiteleg shrimp (*Penaeus vannamei*) is a preferred candidate for aquaculture due to its appealing taste, rapid growth, and high nutritional value (Zhu et al. 2022). However, since 2009, hepatopancreatic microsporidiasis (HPM), caused by *Enterocytozoon hepatopenaei* (EHP) (Tourtip et al. 2009), now reclassified as *Ecytonucleospora hepatopenaei*) (Wang et al. 2023) has emerged as one of the most contagious and

Nor Asma Husna Yusoff . Joey Joe Yee Ng . Farizan Abdullah . Ahmad Najmi Ishak . Marina Hassan (✉)
Institute of Tropical Aquaculture and Fisheries, Universiti Malaysia Terengganu, 21300 Kuala Nerus, Kuala Terengganu, Terengganu, Malaysia
e-mail:marina@umt.edu.my

Heri Prasetyoning Tias
Faculty of Fisheries and Marine, Universitas Airlangga, Surabaya, Jawa Timur 60115, Indonesia

Farizan Abdullah
Faculty of Science and Marine Environment, Universiti Malaysia Terengganu, 21300 Kuala Nerus, Kuala Terengganu, Terengganu, Malaysia

economically damaging diseases in the global shrimp industry (Geetha et al. 2022). In addition to *Penaeus monodon* (Dhar et al. 2023) and *P. vannamei* (Cao et al. 2023; Kim et al. 2022; Suryakodi et al. 2022), EHP has been reported in other shrimp species, including *Penaeus stylirostris* (Tang et al. 2015), *Palaemon carinicauda* (Jiang et al. 2022; Xu et al. 2023), *Macrobrachium rosenbergii* (Wang et al. 2022), *Artemia salina* (Karthikeyan and Sudhakaran 2020), and the crayfish *Procambarus clarkii* (Ling et al. 2024). The emergence of EHP has led to market declines due to increased shrimp mortality and growth retardation (Madesh et al. 2023). Infection rates are positively correlated with stocking density, and in severe cases, farmers may lose nearly all of their investment (Geetha et al. 2022). EHP outbreaks have been reported in several Asian countries, including China, Brunei, Vietnam, India, Indonesia, Korea, Venezuela, Thailand, and Malaysia (Dhar et al. 2023; Geetha et al. 2022; Hou et al. 2021; Han et al. 2020; Marimuthu et al. 2021; Patil et al. 2021; Rajendran et al. 2016; Tang et al. 2017; Tangprasittipap et al. 2013; Wan Sajiri et al. 2021).

EHP is a microsporidian parasite of the genus *Enterocytozoon* that infects shrimp hosts. It was first reported in 2009 in Thailand (Tourtip et al. 2009) and was later identified in China, Malaysia, Indonesia, and Vietnam, primarily infecting *Penaeus vannamei* (Varela-Mejías et al. 2019). Initially, phylogenetic analysis identified the strain as *Enterocytozoon bieneusi*, but subsequent histopathological and transmission electron microscopy (TEM) studies revealed distinct ultrastructural characteristics of the *Enterocytozoonidae* family, leading to its classification as a new species, EHP (Tourtip et al. 2009). More recently, due to observed biological and geographical variations, EHP has been reclassified as *Ecytonucleospora hepatopenaei* (Wang et al. 2023). EHP hampers shrimp growth by disrupting key metabolic processes, leading to lipid peroxidation and tissue damage (Cao et al. 2023). It specifically targets the hepatopancreas and midgut, impairing nutrient absorption and disturbing cellular homeostasis. This includes dysregulation of antioxidant enzyme expression, glucose and lipid metabolism, and genes involved in growth (Cao et al. 2023; Han et al. 2020).

To date, synthetic drugs such as oxytetracycline, florfenicol, and trimethoprim have been commonly used in shrimp hatcheries and farms to control disease transmission. However, they are growing concerns about their safety, environmental persistence, and the risk of promoting antimicrobial resistance (Bondad-Reantaso et al. 2023). In response, the use of natural antimicrobials has gained increasing attention due to their sustainability, cost-effectiveness, and low toxicity, as many of these compounds are classified as Generally Recognized as Safe (GRAS) (Rani et al. 2025). Despite this growing interest, relatively few reviews have explored the recent potential of natural antimicrobials in combating EHP specifically or in enhancing shrimp immune responses; therefore, this gap highlights the importance and novelty of the present review.

Life cycle of EHP

Approximately 57 % aquatic environments are known to host EHP, most of which exhibit a direct life cycle that does not require an intermediate host for transmission or completion (Bojko and Stentiford 2022; Wang et al. 2023). EHP spores are typically oval or round, measuring approximately 1.67 µm in length and 0.96 µm in width, and feature an extruded polar tube in germinated forms (Jaroenlak et al. 2018; Tang et al. 2016; Wang et al. 2023;). Transmission occurs primarily via oral ingestion or contaminated food or water, and may also occur vertically from broodstock to offspring (Terry et al. 2004). Multiple shrimp species have been reported to be infected by EHP, including *L. vannamei, P. monodon,* and *M. rosenbergii* (Jiang et al. 2023). In addition to shrimp, other aquatic organisms such as polychaetes, crabs, false mussels, and *Artemia* have been identified as potential hosts or carriers, complicating efforts to control the spread of EHP in aquaculture systems (Desrina et al. 2020; Krishnan et al. 2021; Mani et al. 2022; Munkongwongsiri et al. 2022; Wan Sajiri et al. 2023).

Figure 1 illustrates the life cycle of EHP within the shrimp hepatopancreas. Briefly, the life cycle of EHP consists of three main stages: merogony, sporogony, and spore maturation. EHP replicates within the cytoplasm and infected host cells via spore formation and nuclear proliferation (Newman 2018). Merogony is the proliferative phase, during which cells divide initially by binary fission, followed by multiple rounds of nuclear division (Wang et al. 2023). Sporogony follows, characterized by the formation of electron-dense discs in the cytoplasm, which develop into polar filaments. Concurrently, dense secretions thicken the plasma membrane, and sporoblasts begin to form. Both merogonial and sporogonial plasmodia develop directly

within the cytoplasm of hepatopancreatic epithelial cells and exhibit strong nucleophilicity toward host cell nuclei (Wang et al. 2023). As the life cycle progresses, the sporoblast's spore wall gradually thickens, resulting in the formation of mature spores which is the infectious stage of EHP (Wang et al. 2023). These mature spores are surrounded by distinguishable interfacial envelopes, measuring approximately 1.65 μM in length and 0.92 μM in width, and must transfer into the new host cell cytoplasm in order to initiate infection and complete the life cycle (Bundurus et al. 2023; Wang et al. 2023).

Characteristics and histopathological changes of microsporidian infection in shrimp

In shrimp infected with microsporidian species, physiological abnormalities typically become apparent 20 to 60 days, particularly during the post-larval stages PL10 to PL12. Common symptoms include a sudden reduction in feeding, lethargy, uneven shrimp sizes within the same pond, and occasional mortality (Cao et al. 2023; Wang et al. 2023). In advanced stages of infection, shrimp often exhibit stunted growth, midgut discoloration, floating whitish fecal strings, and chronic mortality (Aranguren et al. 2020; Wang et al. 2023). Research by Jiang et al. (2022) and Chen et al. (2018) showed that the hepatopancreas is more susceptible to EHP infection than other tissues such as the intestine, hemolymph, gills, and muscles. These studies also reported that waterborne transmission is the most rapid route of infection, causing significant tissue damage within just 72 hours. Collins et al. (2022) reported that infection by *Ameson pulvis* in *Necora puber* led to the replacement of muscle fibres in the skeleton and heart with spores; in severe cases, spores were also detected in the haemolymph. Schuster et al. (2024) described a microsporidium infecting the brain of the red swamp guppy (*Micropoecilia picta*), where spores were observed grouped or scattered in regions such as the optic tectum and diencephalon. Meanwhile, Ding et al. (2025) discovered *Potaspora macrobrachium* infecting the muscle fibers of the oriental river prawn (*Macrobrachium nipponense*), often accompanied by haemocyte aggregation. Other recent studies on microsporidia infections in various aquatic hosts highlighting associated characteristics and morphological changes are summarized in Table 1.

Recent findings on EHP infections in other aquatic hosts are also included in similar Table 1 to emphasize the main focus of this review. For example, Couch et al. (2022) identified *Enterocytozoon schreckii* infection in the intestines of *Oncorhynchus tshawytscha*, leading to the loss of intestinal folds, dysplasia, and complete epithelial degradation. Ling et al. (2024) observed that EHP infects both the intestine and hepatopancreas of *Procambarus clarkii*, resulting in a discoloured, atrophied hepatopancreas and necrosis of intestinal epithelial cells. In general, EHP-infected shrimp present with pale or discoloured hepatopancreas and intestines due to lipid depletion (Ding 2021; Wu et al. 2022), whereas infected crayfish often develop an opaque exoskeleton (Ling et al. 2024). The proliferative stages of EHP are closely associated

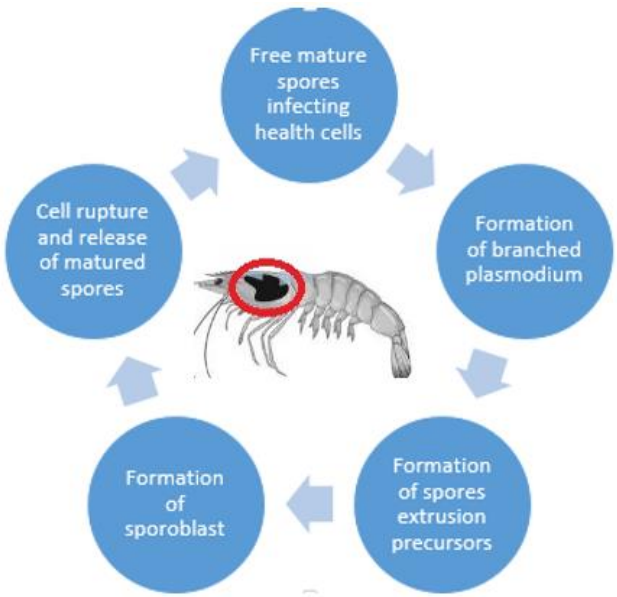

Fig. 1 EHP life cycle in shrimp hepatopancreas

with host lipid droplets, suggesting the parasite relies on host lipids for its development (Ling et al. 2024). As an intracellular parasite, EHP primarily develops in the nutrient-rich hepatopancreas of its host; and once attached to the basement membrane of hepatopancreatic cells, EHP induces epithelial detachment and consumes host nutrients, ultimately leading to energy depletion, cell fragmentation, and death (Desrina et al. 2020). Histological analysis of EHP-infected shrimp typically reveals regular or irregular basophilic inclusion bodies within the cytoplasm, with or without visible spores (Tourtip et al. 2009). Additional histological changes include mild to severe sloughing of epithelial cells in the gastrointestinal tract and hepatopancreatic tubules, commonly accompanied by various developmental stages of EHP within the cytoplasm (Aranguren et al. 2017; Wang et al. 2023). According to Wang et al. (2023), EHP infects all types of hepatopancreatic epithelial cells including reserve (R), fibrillar (F), blister (B), and embryonic (E) cells with infections most concentrated in the proximal and middle regions of the hepatopancreatic tubules, and less frequently in distal regions. Cao et al. (2023) reported similar histopathological findings, including hepatopancreatic tubular atrophy and epithelial shedding containing mature spores.

The severity of hepatopancreatic damage was found to be positively correlated with the duration and intensity of EHP infection. By day 20 post-challenge, extensive structural damage to the hepatic tubules

Table 1 List of some recent findings on microsporidia infection in aquatic hosts

Microsporidian species	Host	Infected organ	Identified spore size	Morphological and histopathological findings	References
Ameson earli sp.	Atlantic blue crab, *Callinectes sapidus*	Muscle	2.0 – 3.0 µM × 1.6 µM	Whitish skeletal muscle with spores and presporogonic stages in host cytoplasm.	Sokolova et al. (2023)
Pseudohepatspora borealis	Jonah crab, *Cancer borealis*	Hepatopancreas	1.48 µM × 1.00 µM	Microsporidian parasites in host cytoplasm enlarged and developed into small xenomas.	Bojko et al. (2023)
Ameson pulvis	Velvet swimming crab, *Necora puber*	Skeletal muscle tissues.	n.m	Muscle fibers in skeleton and heart replaced by spores; in severe cases, spores also found in hemolymph from damaged tissues.	Collins et al. (2022)
Ameson portunus	Gazami crab, *Portunus trituberculatus*	Skeletal muscle cells.	1.4 µM × 1.0 µM	Opaque, chalky-white muscle with two white bands on the swimming leg propodus.	Wang et al. (2017)
Areospora rohanae	Southern king crab, *Lithodes santolla*	Walking limb and abdomen	2.8 µM × 2.2 µM	White, xenoma-like lesions in pereopod soft tissues and abdominal epidermal/connective tissues.	Stentiford et al. (2014)
Potaspora macrobrachium	Oriental river prawn, *Macrobrachium nipponense*	Hepatopancreas	n.m	Degraded microsporidian cells and mature spores observed among muscle fibers, often with hemocyte aggregation.	Ding et al. (2024)
Hepatospora eriocheir	Chinese mitten crab, *Eriocheir sinensis*	Hepatopancreas	n.m	Pale hepatopancreas with enlarged epithelial cells, dark deposits, and host mitochondria near *H. eriocheir* meronts.	Ding (2018)
Agmasoma penaei	White shrimp, *Litopenaeus setiferus*	Ovarian tissues	2.7 - 4.2 µM × 1.5 - 2.7 µM	White cyst-like structures and amorphous tissue masses beneath the carapace.	Sokolava et al. (2015)
Swamp guppy microsporidium (OR398664)	Red swamp guppy, *Micropoecilia picta*	Brain	3.9 - 5.9 µM long	Microsporidia found in brain regions, including optic tectum and diencephalon; spores grouped or scattered, with no xenoma formation.	Schuster et al. (2024)
Enterocytozoon schreckii	Chinook salmon, *Oncorhynchus tshawytscha*	Intestine	2.0 - 2.5 µM × 1.5 – 2.0 µM	Lower intestine showed loss of folds, epithelial erosion, and presence of spores and sporoblasts in host cytoplasm.	Couch et al. (2022)
Myosporidium ladogensis n. comb.	Burbot, *Lota lota*	Skeletal muscle	4.3 µM × 2.3 µM	Meronts and sporophorous vesicles (SPVs) developed in host cytoplasm; capsule-like structures formed around some cells. No plasmodium observed	Jones et al. (2020)
Heterosporis lessepsianus n. sp.	Lizardfish, *Saurida lessepsianus*	Abdominal cavity, skeletal muscles and mesenteric tissues.	3.8-6.5 mm in diameter	Infections appeared as whitish cysts in the abdominal cavity, muscle, and mesenteric tissue, forming tumor-like masses that caused tissue hypertrophy.	Quraishy et al. (2019)
Ecytonucleospora hepatopenaei (previously known as EHP)	Red swamp crayfish, *Procambarus clarkii*	Hepatopancreas and intestine	n.m	Discolored, atrophied hepatopancreas with emptied intestine; necrosis, tissue damage, and ruptured tubules; intestinal epithelial cell necrosis.	Ling et al. (2024)
Cambaraspora faxoni	Crayfish, *Faxonius virilis*, *Faxonius rusticus*, *Procambarus spiculifer*	Muscle and heart tissue, and develops within a sporophorous vesicle.	3.22 µM × 1.45 µM	White musculature visible through ventral cuticle; spores at various stages within vesicles in skeletal muscle and heart.	Stratton et al. (2023)
E. hepatopenaei	Polycahete worms, *Marphysa* sp., *Dendronereis* sp., and *Nereis* sp.	Muscle	n.m	Localized disruption of circular muscle layers.	Krishnan et al. (2021)
E. hepatopenaei	Polychaete worms, *Dendronereis* spp., and *Marphysa* spp.	Intestine	n.m.	Enlarged, basophilic nuclei and hypertrophy of intestinal epithelial cells.	Desrina et al. (2020)
Steinhausia mytilovum	Mediterranean mussel, *Mytilus galloprovincialis*	Gonad	2.8 – 3.0 µM long	Inflammation with hemocyte encapsulation, tissue damage, degenerated oocytes, and enlarged spores in capsules.	Carella and Vico (2023)

n.m: not mentioned

and basement membrane was observed, along with spore clusters within epithelial cells (Cao et al. 2023). Dhar et al. (2023) reported abnormal nuclei in R-cells of the hepatopancreatic tubules in *Enterocytozoon* spp.-infected *P. vannamei* from Latin America. This contrasts with findings by Stentiford et al. (2007), who observed microsporidian infections localized within the nuclei of hepatopancreatic epithelial cells in *Cancer pagurus*, affecting R, F, and E cells, but not B cells. Tourtip et al. (2009) also noted that worsening infections lead to epithelial cell atrophy and detachment. In jelly prawns (*Acetes sibogae australis*), Diggles et al. (2022) observed various plasmodial developmental stages within hepatopancreatic cells during severe EHP infections, with uninucleate trophonts budding into the tubule epithelium. Moreover, EHP compromises the shrimp's immune system, making it more vulnerable to secondary infections, particularly from *Vibrio* spp. Although EHP infections does not always result in high mortality, it significantly reduces shrimp growth performance that will reduce their size, with soft shells, and poor appearance, thereby lowering their market value (Bundurus et al. 2023). Often, farmers fail to notice HPM disease-related signs early and continue to provide feed as usual, which results in significant loss when mass mortality happens (Patil et al. 2021).

Transmission and biochemical impact of EHP infection in shrimp

EHP can spread horizontally through various vectors, including contaminated feed, cannibalism, bait, residues of infected shrimp, and aquaculture water contaminated with EHP spores. While Tangprasittipap et al. (2013) initially suggested that EHP could not be transmitted horizontally, later studies by Tang et al. (2016) and Desrina et al. (2020) demonstrated that EHP infection is indeed associated with the occurrence of white feaces syndrome (WFS), as transmissible condition. Wan Sajiri et al. (2023) reported the presence of various macrofauna species from the phylum of Arthropoda, Mollusca, and Chordata, as potential EHP carriers in shrimp ponds, with prevalence ranging from 14.81 to 74.70 %. A separate study by Mungkongwongsiri et al. (2022) identified the false mussels (*Mytilopsis leucophaeata*) as a passive carrier of EHP. Similarly, Krishnan et al. (2021) noted that the polychaete worms may act as passive carriers by ingesting EHP-contaminated feed or sediments.

Chaijarasphong et al. (2021) proposed that EHP-induced growth retardation may occur through activation of the ATP sink mechanism, which drains the host's cellular energy. Ning et al. (2019) further suggested that overexpression of shrimp hormones such as methyl farnesoate and farnesoic acid *O*-methyltransferase combined with reduced levels of esterase-like carboxylesterase-1 and upregulation of ecdysteroid-regulated-like protein, may impair the ecdysis process, thereby contributing to stunted growth. Cao et al. (2023) reported that EHP infection also leads to suppression of the glycolysis and TCA (Tricarboxylic acid) cycles, activation of gluconeogenesis, and disruption of growth-related genes. Additionally, EHP-induced hepatopancreatic microsporidiasis (HPM) can trigger oxidative stress by increasing levels of lipid peroxidation (LPO) products and malondialdehyde (MDA), which may lead to mortality in severe cases (Cao et al. 2023). Wu et al. (2022) observed a significant depletion of storage lipids and downregulation across the lipid metabolic network in EHP-infected *L. vannamei* (e.g., unsaturated fatty acid biosynthesis, elongation and degradation of fatty acids, metabolism of alpha-linolenic acid metabolism, sphingolipid metabolism, and glycerolipid metabolism), which eventually will contribute to impaired growth and reduced productivity in infected shrimp.

Recent approaches to control EHP and the potential of natural products

The use of chemicals and antibiotics in shrimp aquaculture can lead to several adverse effects, including the development of antimicrobial resistance genes, environmental toxicity due to sediment accumulation and poor absorption, and the presence of toxic residues that may be transferred to humans. Additionally, such use can result in consignment rejections due to unclear or non-compliant regulatory status (Citarasu et al. 2022; Sanandakumar 2002). Vaccination has previously been considered a promising alternative to antibiotics and synthetic drugs for disease prevention in shrimp farming. However, challenges such as short duration of immunity, high cost, risk of virulence reversion, thermal instability, and the need for complex administration techniques have limited its practical application particularly among farmers practicing extensive or semi-intensive systems (Citarasu et al. 2022).

Several studies have investigated synthetic and antibiotic-based approaches for controlling EHP. For example, Aldama-Cano et al. (2018) revealed that EHP spores frozen at -20 °C for more than 2 hours, or exposed for 15 minutes to certain chemicals such as 15 mg/L KMnO4, 40 mg/L 65 % active chlorine or 20 % ethanol, lost their ability to form budding bodies and could no longer proliferate. Benzimidazole derivatives such as albendazole and fumagillin have also been shown to interfere with the intracellular development of microsporidia (Costa and Weiss 2001). In another study, Jiang et al. (2023) found that EHP-infected *Exopalaemon carinicauda* injected with 0.3 µg/L of sodium nitroprusside showed significantly reduced EHP copy numbers and less hepatopancreatic damage after 3 days. Salachan et al. (2017) demonstrated that viable EHP spores lost their activity following exposure to 20 ppm calcium hypochlorite (90 % concentration) for 24 hours over a 10-day period. While these studies confirm the effectiveness of inactivating EHP *in vitro*, no drug has yet been proven effective against EHP *in vivo*, due in part to the parasite's thick wall composed of chitin and proteins, and its intracellular parasitism (Prasertsri et al. 2009).

In recent years, alternative treatments for HPM caused by EHP have gained attention. Sangklai et al. (2024) reported that c-type lysozyme (LvLyz-c) can disrupt the EHP endospore layer and degrade chitin, thereby reducing spore germination rates. Arumugam et al. (2025) identified several beneficial gut probiotics such as *Bifidobacterium* spp., *Lactobacillus* spp., *Bacillus* spp., *Akkermansia muciniphila*, and *Lactococcus* spp., in EHP-infected *P. vannamei* that appeared to enhance mucin layer thickness and stimulate the host's innate immune responses, thereby improving overall immunity. These findings were supported by Li et al. (2024), who also reported that *Bifidobacterium* sp. and *Lactococcus* sp. significantly reduced EHP loads and improved hepatopancreas and intestinal morphology EHP-infected *E. carinicauda*. Xu et al. (2023) described a recombinant crustin-like peptide, EcCrustin2, with broad-spectrum antibacterial activity *in vitro*, showing potential for use against bacterial and EHP infections. Additionally, Bakar et al. (2024) reported that the inclusion of cinnamon essential oil in the functional diet of *P. vannamei* in super-intensive culture systems improved specific growth rates, enhanced resistance to acute hepatopancreatic necrosis disease (AHPND), and resulted in reduced EHP detection in the culture systems.

Although research is limited, plant-based compounds have also shown promise for EHP control. Table 2 summarizes recent findings on the application of natural antimicrobials for the control of EHP disease in shrimp aquaculture. For example, Ning et al. (2021) demonstrated that linolenic acid could act as a metabolic modulator to control HPM. Kongplong et al. (2023) supported this finding, reporting that administering 5-aminolaevulinic acid and linolenic acid to EHP-infected shrimp improved hepatopancreas function. In our previous study, we observed that *Melaleuca cajuputi* leaf extract at 48.6 mg/L caused significant damage to the EHP spore membrane while remaining below the LC_{50} threshold, indicating safety for use in *L. vannamei* (Ng et al. 2025). Furthermore, Bundurus et al. (2023) evaluated the effectiveness of a natural antimicrobial product called AuraAqua (Aq), a mixtue of citrus and olive extracts along with other food-

Table 2 A list of previously reported natural antimicrobial treatments used against EHP in shrimp aquaculture

Sources / types; Natural agents	Shrimp species	Reported effects	References
Plant extract; *Melaleuca cajuputi* leaf extract	*L. vannamei*	Damaged EHP spores at 48.6 mg/L; safe below LC_{50} for *L. vannamei*	Ng et al. (2025)
Gut microbiota enhancers; Probiotics (e.g., *Bifidobacterium*, *Lactobacillus*, and *Bacillus* spp.)	*P. vannamei*	Improved immune response, mucin layer, and reduced EHP load.	Arumugam et al. (2025) and Li et al. (2024)
Host-derived immune enzyme from *L. vannamei*; c-type lysozyme (LvLyz-c)	*L. vannamei*	Altered EHP spore wall permeability and reduced germination rate.	Sangklai et al. (2024)
AuraAqua (Aq); A mixture of citrus and olive extract blend + food-grade materials	*P. vannamei*	Reduced EHP spore germination and decreased the secretions of lysozymes, crustins, and penaeidins. The best treatment was at 0.5 % w/w for 24 and 48 hours.	Bundurus et al. (2023)
Plant-derived oil; Cinnamon essential oils	*P. vannamei*	Improved shrimp growth rate, reduced EHP detection and protection against AHPND.	Bakar et al. (2024)
Antimicrobial peptide; EcCrustin2 (recombinant crustin-like peptide)	*P. carinicauda*	Exhibited broad-spectrum antibacterial activity, potential against EHP	Xu et al. (2023)
Natural plant polyphenols (quercetin, rutin, and caffeic acid); Aqueous neem extract, *Azadirachta indica* leaf	*L. vannamei*	40 mg/L application for 15 days reduced EHP spore load, improved shrimp immunity, and survival.	Madesh et al. (2023)
Natural metabolic intermediate; 5-Aminolaevulinic acid (5-ALA)	*L. vannamei*	Supplementation of 60 ppm of 5-ALA/kg pellets for 21 days helped to restore hepatopancreas function in infected shrimp. Also experienced less percentage of atrophic tubules and larger areas of the vacuoles in the B-cells.	Kongplong et al. (2023)
Omega 3-fatty acid; Linolenic acid (LNA)	*P. vannamei*	Inclusion of 2.4 g LNA/kg in feed for 30 days improved shrimp growth with increased non-specific immunity responses; and increased hepatopancreas functions.	Ning et al. (2021)
Natural signaling molecule / NO donor; nitric oxide (NO)	*E. carinicauda*	Use of 0.3 µg/L for 1- 4 days reduced EHP copy number and hepatopancreas damage in *E. carinicauda.*	Jiang et al. (2023)

grade components against EHP. They revealed that the concentrations raging from 0.1 to 0.5 % (w/w) significantly reduced EHP spore activity within 24 to 48 hours, with the 0.5 % formulation demonstrating the highest efficacy. This study also reported improved shrimp survival post-infection, attributed to increased expression of antioxidant enzymes such as catalase (CAT) and superoxide dismutase (SOD) in gut tissue and reduced H_2O_2 activation.

Conclusion

The methods described above offer several alternatives to using chemicals and antibiotics for controlling EHP in shrimp aquaculture. However, their application and management can still be improved to maximize effectiveness. One promising approach is the development of shrimp diets enriched with biologically active compounds that enhance digestion and strengthen immune responses. Adding probiotics and prebiotics can also improve gut health by preventing the attachment of harmful microbes, thereby reducing the severity of HPM. Even so, continuous monitoring, strict biosecurity measures, and good pond management practices remain essential for preventing EHP infections. Regardless of the control strategies used, rapid and sensitive detection methods such as molecular diagnostics and histopathology are critical for early warning, helping to prevent the spread of disease and reduce losses in aquaculture production.

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Conflicts of interest The authors declare no competing interests.

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