A Review on the Application of Phytogenics as Feed Additives for Aquatic Animals

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Abstract

Feed preparation is the most expensive part of the aquaculture industry. In recent years, studies have been conducted on the utilization of plants' wastes and by-products (such as peel, pulp, and kernels) as phytogenetic materials and sources of protein and nutrients for preparing feed in the aquaculture industry, which have yielded promising results. These wastes are recycled by processing as feed additives and returned to the feed chain, and because they are waste products of plants and fruits, prepared phytogenic feed additives cannot be regarded as feed sources for humans. In the future, there will be large quantities of fruit and vegetable waste, which have the potential to be recycled and returned to the feed chain by being processed as additive feed for aquatic animals. Phytogenics encompass a wide range of substances that can be classified based on plant origin, the processing method, and composition but generally found in the form of herbs and spices, or as plant extracts, essential oils, and oleoresins. The phytogenic properties of plants are related to the various secondary metabolites produced by them. These metabolites are used as growth and appetite stimulants. Furthermore, these metabolites induce the secretion of bile and other digestive enzymes. They are not a threat to the environment, and their benefits as substitutes for antibiotics have been promising. The antioxidant, anti-cancer, analgesic, antimicrobial and antiparasitic effects of these products have been proven so far but the main function reported for these compounds in the host is to improve gastrointestinal microbiota and immune function (modulating cytokine production by epithelial cells). However, the mechanisms of action of these products are not yet completely understood, and further studies are needed to divulge the potential side effects of phytogenic substances on the host, the environment, and on gastrointestinal microbiota. Understanding these mechanisms will ensure us about the safety of these herbal additives for fish, consumers, and the environment. Despite some applications of plant materials in aquaculture, their widespread use for feed preparation is still limited due to the lack of sufficient knowledge on the mechanisms of action of phytogenic materials. So, a better understanding of the effects of these compounds, which are derived from plant and fruit wastes, on the host's physiology will provide us with the opportunity to use these substances more widely in the aquaculture industry. In the present review, we discuss the studies conducted on the use of phytogenic materials as feed additives for aquatic animals, as well as their effects, advantages, and disadvantages.

Keywords: Phytogenics, Feed Additives, fish, shrimp, immunesystem, growth performance

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Introduction

Phytogenic feed additives or phytobiotics are among the functional feed additives that have been widely studied in recent years. Phytogenic feed additives are non-destructive bioactive compounds of the environment derived from plants, including herbs, spices, essential oils, and extracts. Glycyrrhizin, liquiritin, glabridin, polysaccharides, flavonoids, alkaloids, anthraquinone, saponin, and azadirachtin are among the active ingredients in these phytogenic compounds (Bhujel *et al*., 2017). Acids, alcohols, aldehydes, acyl esters, sulfur-containing compounds, coumarins, and homologues of polypropanoid are other studied molecules (Yang *et al*., 2015). A wide range of phytogenics in farmed aquatic animals have been studied mainly due to their properties including improved taste in feed, increased growth, stimulated immune system, improved intestinal microbiota, antimicrobial, antiparasitic and antiviral activities.

Global aquaculture production (including aquatic plants) is 110.2 million tons, with an initial sales value of 243.5 billion dollars. Total production includes 80.0 million tons of edible fish and 30.1 million tons of aquatic plants (Bharathi *et al*., 2019). According to the FAO, global aquaculture production is estimated to reach 80 million tons by 2050. The aquatic feed contains 50 to 80 percent of rearing costs, and successful aquaculture depends on a balanced diet and low-cost production. As a result, one of the most important challenges for aquaculture producers is providing adequate and inexpensive nutrients to achieve the ideal growth rate and non-destructive to the environment. The use of low-protein feeds and low amounts of nutrients lead to inefficient use of nutrients. As a result, increased feed intake increases susceptibility to disease and increases production costs. The production of more waste also causes damage to the environment (Goncalves and Santos, 2015).

The presence of endemic pathogens and pandemic diseases constantly endangers aquaculture farmers around the world to achieve a balanced production system. The prevalence of fish diseases is one of the main limitations for the development of aquaculture (FAO, 2020). In the past, antibiotics were used to prevent these problems. But today, producers are looking for alternative ways due to the increasing awareness of consumers about environmental problems and bacterial resistance to the indiscriminate use of antibiotics against zoonotic pathogens. A significant number of studies have focused on the search for antibiotic alternatives with similar antimicrobial and growth-promoting effects without causing residues, bacterial resistance, and potential side effects for animals. Functional feed additives are an alternative to antibiotics and in addition to nutritional value have health benefits for animals (Korzekwa *et al*., 2016; Waagbø and Remø, 2020). This study aimed to investigate the effects of phytogenic feed additives on aquatic nutrition as an alternative strategy for antibiotics to achieve sustainable aquaculture.

Classification of phytogenic compounds

Phytogenic feed additives are classified into three main groups, which include sensory additives, technological additives, and zootechnical additives. Some of these additives have more than one positive effect, but they can not be precisely classified in one of the above groups (Karásková *et al*., 2015).

Sensory additives

This group of additives usually stimulates the appetite through the effect they have on the taste or color of feed (such as plant pigments). The most commonly used sensory additives are carotenoid pigments, which are sourced from carrots, chlorella, marigolds (Tagetes erecta L.), or lutein (Karásková *et al*., 2015). Astaxanthin is one of the known carotenoids in aquatic animals. The use of astaxanthin improves the color of fish fillets (Teimouri *et al*., 2013). Other studies on carotenoid pigment include increased redness in goldfish and carp (Hancz *et al*., 2003), production of vivid colors (including blue and green) in marine invertebrates (Davies, 2009), and increased redness in dwarf gourami (Baron *et al*., 2008). However, the instability and high cost of natural carotenoids have limited the use of these compounds (Englmaierová *et al*. 2014).

Technological additives

This classification refers to a group of additives that affect the technological aspects of the feed. These additives do not directly affect the nutritional value of the feed, but may indirectly affect the nutritional value of the feed by improving maintenance or hygienic properties, such as mycotoxin contaminants in feed (Pandey *et al*., 2019).

Zootechnical additives

These additives improve the nutrient status and livestock production. These compounds provide specific nutrients and help to use the nutrients in the diet more effectively (Pandey *et al*., 2019). These additives include immune regulators, digestive stimulants, and growth stimulants of non-microbial origin, and substances that enhance the quality of animal products. These additives are divided into three subgroups: Immunosuppressive compounds (oligosaccharides, especially beta-glucans that stimulate the activity of cells, enzymes, and other factors involved in immunity), compounds that improve production performance or quality of livestock products (cinnamaldehyde and turmeric) They are effective in improving digestion and absorption of nutrients) and compounds that reduce oxidative stress (polyphenols, carotenoids, betalains, and curcumin, which are effective in reducing the level of free radicals (ROS)) (Karásková *et al*., 2015). The use of these feed additives in aquaculture can be a powerful solution to limit nitrogen depletion in the environment by improving feed efficiency, saving nutrients, and using proteins, and helping manage fish health (Goncalves and Santos, 2015). According to reports, Feeding with phytogenic feed additives including AROMEX® ME Plus and FRESTA® F Plus, oregano, anise, and citrus peel essential oils reduced excreted ammonia in feed animals (Veit *et al*., 2011; Hong *et al*., 2012).

The role of phytogenics in aquatic growth performance

In recent years, rations containing fish (FM) and fish oil have been used more selectively due to reduced availability and simultaneous price increases, while many efforts are being made to find alternative protein sources for profitable and sustainable aquaculture (FAO, 2018; Slater *et al*., 2018). Plant products have been proposed as an alternative to FM in aquatic feed due to their low cost, availability, and high protein (Gatlin *et al*., 2007; Olsen and Hasan, 2012). But the use of plant products is the cause of problems such as high levels of anti-nutritional factors in plant proteins, lack of essential amino acids, lower digestibility, high levels of insoluble carbohydrates, and high fiber, which reduces the palatability of these plant proteins compared to animal proteins (Hardy, 2010), and leads to reduced growth in fish and shrimp that feed on plant protein (De Francesco *et al*., 2004; Enterria *et al*., 2011; Montero *et al*., 2005; Peres and Oliva-Teles, 2006; Sudaryono And Evans, 1999; Zhu *et al*., 2013a). The use of dietary supplements has been suggested to compensate for the problems caused by replacing FM with a diet containing phytogenic plant proteins. According to studies, phytogenic compounds improve nutrient retention and growth function in aquatic organisms (Karásková *et al*., 2015; Encarnação, 2016). Induction of secretion of digestive enzymes is one of the mechanisms of phytogenics in increasing growth performance which stimulates appetite and thus increases feed intake and conversion efficiency (Wenk 2003; Liu *et al*. 2011). For example, spices such as peppers (such as capsaicin and piperine) and other essential oils containing cinnamaldehyde stimulate amylase production (Steiner and Syed 2015). Phytogenic additives (especially essential oils) increase the taste and smell of feed, increase palatability and thus increase fed consumption (Kroismayr *et al*., 2006). This is probably due to the antioxidant effects of phytogenic compounds, which help maintain the quality of the diet and prevent the spread of unpleasant odors (Franz *et al*., 2010; Solà-Oriol *et al*., 2011). However, there is little evidence to increase the palatability of diets containing phytogenic compounds in fish and shrimp (Giannenas *et al*., 2012; Volpatti *et al*., 2013).

The role of phytogenics in the growth of cold water fish

Giannenas *et al*. (2012) reported that using phytogenic additives including carvacrol and thymol showed no significant difference in feed intake in the diet of Rainbow trout (*Oncorhynchus mykiss*) compared to control diets. But in fish fed with carvacrol and thymol, feed efficiency increased significantly compared to fish fed with the control diet. In the study of Giannenas *et al*. (2012), feeding on diets fortified with carvacrol and thymol improved feed efficiency. But it did not affect fish weight gain compared to the control group. The study by Peterson *et al*. (2014) has not reported the weight gain of trout fed with the commercial phytogenic supplement Digestarom® P.E.P. MGE.

The role of phytogenics in the growth of warm water fish

Zheng *et al*. (2009) evaluated the effect of carvacrol and thymol separately in combination with each other and combination with oregano essential oil in canal catfish. The results of this study showed that fish that consumed oregano essential oil, and fish that used carvacrol alone or a combination of thymol and carvacrol gained more weight than fish in the control group. In a study by Ceulemans *et al*. (2009) on the nutrition of Nile tilapia (*Oreochromis niloticus*) with a diet containing a mixture of plant extracts and natural emulsifying agents, feed conversion and protein consumption efficiency were more favorable than control diets. The use of sweet potato skin in the di*et al*so improved growth performance and nutritional efficiency in Nile tilapia (Omoregie *et al*., 2009).

The role of phytogenics in shrimp growth

The research by Goncalves and Santos (2015) is one of the studies on the effect of phytosanitary additives on shrimp growth performance. Based on the results of this study, the use of commercial phytogenic feed additive Digestarom® P.E.P. MGE in the diet containing small amounts of fish increased weight, increased feed conversion ratio, and growth rate compared to shrimp that did not use dietary supplements. In another study, papaya leaves increased protein digestion, feed conversion ratio, and growth in *Penaeus monodon* shrimp larvae (Peñaflorida, 1995). In addition, a significant increase in digestive enzymes (amylase, protease, and lipase) and better feed conversion efficiencies were observed in Post-larvae of P. monodon fed with enriched Artemia with ginger (*Zingiber officinale*) (Venkatramalingam *et al*., 2007).

The role of phytogenics in the improvement of immune system function

Numerous studies have reported the use of phytobiotics in aquaculture to stimulate the activity of immune system components (Rao *et al*., 2006; Sahu *et al*., 2007; Ardó *et al*., 2008). Antioxidant effect of phytogenic mechanisms in improving immune function. The antioxidant activity of phytogenic compounds is due to their ability to destroy free radicals, inhibit reactive oxygen species (ROS) and other oxygen radicals produced in cells and tissues.

However, high concentrations of these compounds have been reported to exhibit peroxidation antagonistic effects (Llana-Ruiz-Cabello *et al*., 2015). Phytogenic compounds are involved in modulating the expression of proinflammatory and anti-inflammatory cytokines by disrupting NF-κB signaling pathways mediated by TLR and MAPK (Somensi *et al*., 2019; Zhou *et al*., 2014; Wu *et al*., 2017; Liu *et al*., 2019). In this regard, several studies have shown that phytochemical compounds including curcumin (Shehzad *et al*., 2011), caffeic acid phenyl ester (CAPE) from bee propolis (Lee *et al*., 2010), epicatechin (Bahia *et al*., 2008), grape seed extract and grape brand (GSGME) (Gessner *et al*., 2013), Cinnamaldehyde (Wondrak *et al*., 2010) and Purple Potato Anthocyanins (Hwang *et al*., 2011) Increase the expression or transfer of Nrf2 and reduce or inhibit NF-κB activation. Plant compounds that alter the Nrf2 and NF-κB pathways can protect the host against oxidative stress, reduce inflammation, and ultimately improve animal health and growth performance. Lectin-mediated pathways are another mechanism by which phytogenic compounds can improve the immune system (LaFrentz *et al*., 2012) because lectins can activate complement and are involved in improving innate immunity (Ourth *et al*., 2007).

The role of phytogenics in improving the immune system of cold water fish

Numerous studies have been performed on the effect of phytogenic additives on improving the immune system function in cold-water fish (especially rainbow trout). In the study of Giannenas *et al*. (2012) on the effect of feeding rainbow trout with carvacrol and thymol (although the fish were not sick in the challenges) a significant increase in the activity of glutathione-based enzymes (glutathione reductase, glutathione-S-transferase), an increase in lysozyme levels and catalase activity and a significant decrease in serum nitric oxide (NO) were observed. These results indicate the effect of phytogenic additives on intrinsic safety parameters. In the study of Gulec *et al*. (2013), the use of feed containing vegetable oils (*Thymus vulgaris* and *Foeniculum vulgare*) significantly increased the amount of total protein, albumin, cholesterol, triglycerides, bilirubin, K Na, Ca, Mg, and decreased plasma glucose and chlorine levels in rainbow trout exposed to *Yersinia ruckeri*.

The role of phytogenics in improving the immune system of warm water fish

According to the results of Yin *et al*. (2006), the extract of Milkvetch root increased phagocytosis of leukocytes and lysozyme activity in the Nile tilapia. In another study, Asimi and Sahu (2013) investigated the effect of feeding on extracts of thyme (Thymus vulgaris), rosemary (*Rosmarinus officinalis*), and fenugreek (*Trigonella foenum graecum*) on Mozambique tilapia (*Oreochromis mossambicus*). They observed increased phagocytic activity, increased white and red blood cells, and increased hematocrit levels. In addition, they reported an increase in plasma lysozyme and myeloperoxidase activity after infection with *Streptococcus iniae*. In *Labeo rohita*, the root extract of *Withania somnifer* increased Nitro blue tetrazolium levels, phagocytic cell activity, lysozyme activity, and total immunoglobulin levels (Sharma *et al*., 2010). Also, Indian ginseng root extract (Ashwagandha) stimulated the immune system and reduced stress caused by low pH and iron toxicity in water (Laltlanmawia *et al*., 2019). Injection of Astragalus polysaccharides (APS) increased IL-1β mRNA levels in a dose-dependent manner in the renal head and regulated TNF-α transcription in the gills and spleen (at high concentrations of APS). TNF-α mRNA was also significantly increased in the renal head (at low concentrations of APS) and regulated Lysozyme-C mRNA levels in gills (at low concentrations of APS) and spleen (at moderate concentrations of APS) in common carp (*Cyprinus carpio*) (Yuan *et al*., 2008). According to Nahak and Sahu (2014), the use of basil aerial part extract in feed increases RBC, WBC, serum protein, and hematocrit (at concentrations of 2.5 and 5%) and decreases serum glucose (at 5%) in Walking catfish (*Clarias batrachus*) and this compound acts as a strong immune stimulant.

The role of phytogenics in improving the immune system of shrimp

The increase in survival rate is one of the most important effects of increased immunity due to the use of phytogenic compounds in shrimp. For example, the increase in survival rate in the post-larvae of *Penaeus indicus* shrimp (Immanuel *et al*., 2004; Citarasu, 2010) and the improvement in the survival rate of *Litopenaeus vannamei* shrimp have been reported as a result of the use of herbal supplements (Yu *et al*., 2008). It has also been reported that the mixture of Chinese herbal supplements increases nonspecific immunity in shrimp (Luo, 1997; Chansue *et al*., 2000). He *et al*. (2017) have reported the increased immunity in *Litopenaeus vannamei* shrimp as a result of using stout camphor extract (Yeh *et al*., 2009) and a combination of organic acids (citric acid and sorbic acid) and essential oils (thymol and vanillin) as dietary supplements. The study by Kesselring *et al*. (2021) showed that feeding a diet low in FM and phytogenic supplementation increased the total number of hemocytes (THCs) and red blood cells compared to a diet high in fish (FM). According to similar studies, the decreased FM levels typically affect shrimp defense mechanisms and reduce hemocytes (Van de Braak *et al*., 2002). Also, a low-FM diet with phytogenic supplementation reduced ALT and LDH activity levels compared to the low-FM diet group which shows that the use of phytogenic supplements improves the health status of *L. vannamei* by reducing the risk of cell damage and tissue necrosis.

The role of phytogenics in increasing mucosal immunity

Mucosal safety in aquatic animals has been considered by many researchers in recent years due to its diversity and characteristics. Mucosal-associated lymphoid tissue (MALT) immunity is divided into Gut-associated lymphoid tissue (GALT), Skin-associated lymphoid tissues (SALT), and Gill-associated lymphoid tissue (GIALT) (Lazado and Caipang, 2014). Mode of action of phytogenics at the level of the main mucosal lymphoid tissues in fish is depicted in Figure 1. In addition, the effect of phytogenics against fish pathogenic organisms is suggested in Figure 2.

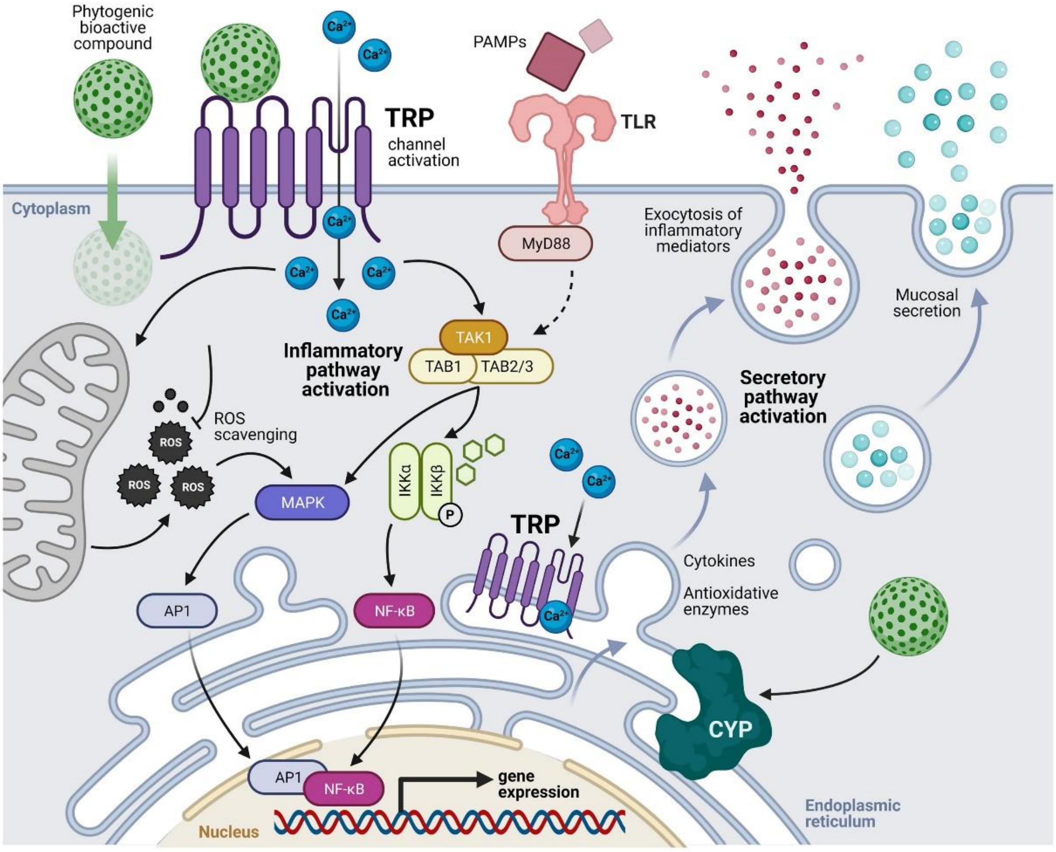

Figure 1: Suggested mechanisms of cell activation by the transient receptor potential (TRP) cation channels mediated by phytogenics' bioactive compounds in mucosal-associated lymphoid tissues (MALTs). Bioactive compounds activate TRP channels leading to intracellular Ca^{2+} increase and non-canonical activation of the TAK complex. In parallel, stimulation by pathogen-associated molecular patterns (PAMPs) may facilitate the activation of TLR and TRP signaling pathways. TLR, toll-like receptors; MyD88, myeloid differentiation primary response 88; TAK, transforming growth factor beta (TGFβ) activated kinase; TAB, TGFβ activated kinase binding protein; ROS, reactive oxygen species; NF-*k*B, nuclear factor kappa-B; IKK, inhibitor of NF-*k*B kinase; MAPK, mitogen-activated protein kinase; AP1, activator protein 1; CYP, cytochromes P450; P, phosphorylation (Firmino *et al.*, 2021).

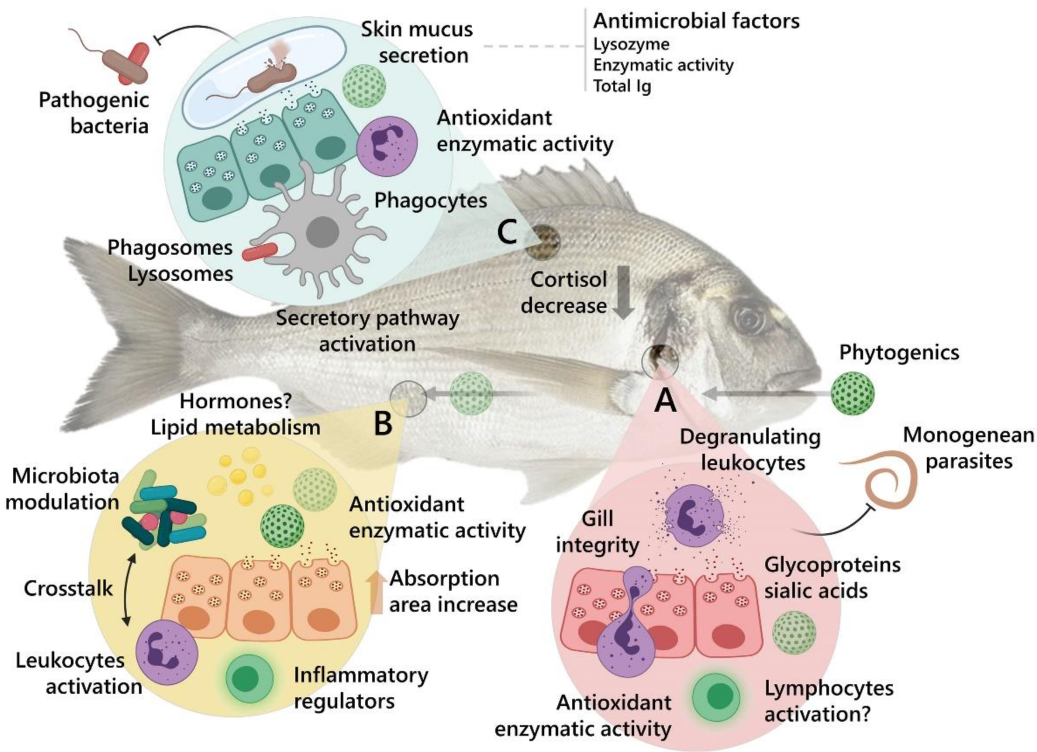

Figure 2: Summary of the proposed mode of response induced by phytogenic bioactive compounds in fish mucosal tissues. The effects against representative types of common pathogens on the most studied mucosal-associated lymphoid tissues in fish so far are represented in the figure. (A) Gills. (B) Gut. (C) Skin. Gilthead seabream (*S. aurata*) was used in the figure as a representative aquaculture-relevant fish (Firmino *et al*., 2021).

Figure 1 Suggested mechanisms of cell activation by the transient receptor potential (TRP) cation channels mediated by phytogenics' bioactive compounds in mucosal-associated lymphoid tissues (MALTs). Bioactive compounds activate TRP channels leading to intracellular Ca^{2+} increase and non-canonical activation of the TAK complex. In parallel, stimulation by pathogen-associated molecular patterns (PAMPs) may facilitate the activation of TLR and TRP signaling pathways. TLR, toll-like receptors; MyD88, myeloid differentiation primary response 88; TAK, transforming growth factor beta (TGFβ) activated kinase; TAB, TGFβ activated kinase binding protein; ROS, reactive oxygen species; NF-*k*B, nuclear factor kappa-B; IKK, inhibitor of NF-*k*B kinase; MAPK, mitogen-activated protein kinase; AP1, activator protein 1; CYP, cytochromes P450; P, phosphorylation (Firmino *et al*., 2021).

The role of phytogenics in increasing skin mucosal immunity

The skin plays a key role as the first line of defense against various pathogens in fish (Hoseinifar *et al*., 2017). Most studies on the effects of phytogenic additives on skin mucosal immunity have shown an increase in skin mucosal immune markers or increased antibacterial activity of skin mucosa (Heyman *et al*., 2015; Adel *et al*., 2015a; Adel *et al*., 2015b; Gholamhosseini *et al*., 2020; Heydari *et al*., 2020; Kurian *et al*., 2020; Mirghaed *et al*., 2020; Mohammadi *et al*., 2020; Paknejad *et al*., 2020; Rashidian *et al*., 2021; Yousefi *et al*., 2021). Lysozyme, alkaline phosphatase, complement and protease activities, total immunoglobulin, and protein content in fish skin mucosa are markers that have been evaluated and have antibacterial potential in vitro against pathogens. Unfortunately, few studies have attempted to identify the underlying mechanisms that regulate the immune system (Firmino *et al*., 2021).

The role of phytogenics in increasing gill mucosal immunity

Studies on the effects of phytogenic feed additives on gill structure and function are very limited. Some studies have reported the protective effects of these compounds in reducing histopathological lesions of the gills due to exposure to toxic elements or pathogens (Vickers, 2017; Khafaga *et al*., 2020; El Euony *et al*., 2020). According to the results of Yuan *et al*. (2008), injection of astragalus polysaccharides (APS) had no effect on IL-1β mRNA level in the gills but regulated TNF-α and Lysozyme-C mRNA transcription at high and low doses of APS in the gill of common carp (*Cyprinus carpio*).

The role of phytogenics in increasing gastrointestinal mucosal immunity

The gastrointestinal tract (especially the intestine) is mainly composed of physical, chemical, immunological, and microbiological components. Therefore, it is a selective barrier between the host and its surrounding environment (Yegani and Korver, 2008). As a result, any damage or disruption of its normal function suppresses immune responses and reduces animal productivity (McDevitt *et al*., 2006). In recent years, the study of phytogenic compounds' effect on mucosal immunity has become necessary due to the importance of the mucosal barrier in defending fish against the invasion of pathogens (Yu *et al*., 2020).

Studies on the effect of phytogenic substances on the intestine include evaluation of changes in morphoanatomical parameters such as improved integrity, increased length, width, and the number of goblet cells (Abdel-Latif *et al*., 2020; Heluy *et al*., 2020; Ferreira *et al*., 2016; Abdel-Tawwab *et al*., 2018; Vickers, 2017; Araruna *et al*., 2020), modulation of intestinal lymphocyte count (Hernández *et al*., 2016; Valladao *et al*., 2017), improvement in the level of humoral immune markers such as lysozyme (Sutili *et al*., 2016), improvement in the activity of antioxidant enzymes (Hoseini and Yousefi, 2019; Reyes-Cerpa *et al*., 2018), reducing the expression of proinflammatory genes such as tnfa and tnfb (Zhang *et al*., 2020) and modulation of intestinal microbiota composition (Zhang *et al*., 2020; Mousavi *et al*., 2016; Araruna *et al*., 2020). The positive effects of phytogenetics on the morphology of small intestinal tissues and villi increase nutrient digestibility (Steiner and Syed, 2015). Other effects of phytogenics on the gastrointestinal tract include stimulating gastrointestinal secretions and increasing mucus production as a result of increasing the number of goblet cells in the intestine (Goncalves and Santos, 2015). The bacterial status of the gastrointestinal tract changes under the influence of genetic factors, feeding habits, and the environment (Austin, 2006; Wong and Rawls, 2012; Gómez and Balcázar, 2008). However, the intestinal bacterial community and the metabolites produced by them have significant effects on the host health status by modulating the immune system and affecting metabolism (Bento *et al*. 2013; Lazado and Caipang, 2014). Limited studies have examined the effects of phytogenics as feed additives on intestinal microbiota in fish. Previous studies have focused on the effect of these plant substances as dietary ingredients instead of additives and their effect on microbial communities of fish intestines (Ringø *et al*., 2008; Silva *et al*., 2011; Reveco *et al*. 2014; Zarkasi *et al*., 2017). Studies on the microbial flora of the gastrointestinal tract are often limited to identifying lactic acid bacteria. Therefore, evaluation of the feed additives' effects on mucosal tissues using the results of these studies is not complete and acceptable and leads to incorrect conclusions. Also, some studies have not reported any effect of phytogenics on mucosal parameters (Valladão *et al*., 2019; Navarrete *et al*., 2010; Vickers, 2017; Hernández *et al*., 2015; Vazirzadeh *et al*., 2019). The use of phytogenic compounds as food additives in non-optimal doses and their negligible effect on the bacterial composition of fish intestines is one of the main causes (Sutili *et al*., 2018).

Studies on the effect of phytogenic food additives on the gastrointestinal mucosa are divided into two main groups: the effect on the microbial flora and the intestinal histomorphology. Modification of intestinal microbial flora has been considered by Hongbai *et al*. (2004) using different Chinese plants in carp, Ran *et al*. (2016) using a commercial mixture of thymol and carvacrol in hybrid tilapia (*O. niloticus* x *O. aureus*), and Giannenas *et al*. (2012) using phytogenic supplementation containing thymol and carvacrol in rainbow trout. According to a study by Sutili *et al*. (2016) using gradient gel electrophoresis (DGGE) analysis, the use of American basil (*Ocimum americanum*) essential oils with food did not affect the intestinal microbiome in *Sciaenops ocellatus*. In the study by Navarrete *et al*. (2010) using temperature gradient gel electrophoresis (TGGE) analysis, a diet containing thyme-derived essential oil supplement (Thymus vulgaris) showed no effect on the intestinal bacterial composition of rainbow trout. In the study of Bello *et al*. (2012), an increase in the height and width of the villi and the depth of crypt was observed in *Clarias gariepinus* fed with onion residues and walnut leaf.

Also, according to Goncalves and Santos (2015), the use of commercial phytogenic additives Digestarom® P.E.P. MGE in a low-fish diet improved the structure of midgut microvilli compared to shrimp that did not use dietary supplements.

The role of phytogenics in inhibiting microbial pathogens

The antimicrobial properties of phytogenic compounds vary according to the location of hydroxyl or alkyl groups and the release properties of lipopolysaccharides (Yang *et al*., 2015). About phenolic terpenoids, the hydroxyl group and the presence of non-localized electrons are important elements for their antimicrobial function (Lambert *et al*., 2001; Ultee *et al*., 2002). Hellander *et al*. (1998) also reported that thymol and carvacrol have a high ability to degrade outer membranes .This function is mainly due to their ability to release lipopolysaccharides. Phytogenics penetrate the bacterial membrane due to their lipophilic properties and disrupt the structure and function of bacteria by expanding the membrane, increasing membrane fluidity and permeability, disrupting membrane proteins, inhibiting respiration, and altering ion transport. (Firmino *et al*., 2021). These compounds also play a role in reducing infection by detecting and accumulating microbial pathogens through lectin-mediated pathways (Ourth *et al*., 2007; LaFrentz *et al*., 2012). Other mechanisms of phytogenics as antibacterial compounds include inhibition of flagellin synthesis, inhibition of bacterial movement, depletion of ATP reservoirs, elimination of proton stimulus, inhibition of quorum sensing (QS), and reduction of bacterial biofilm formation (Kachur and Suntres, 2020).

Quorum Sensing (QS) is involved in regulating a wide range of different physiological processes of bacteria, especially in aggravating factors that are important during the pathogenic process (Greenberg, 2003; Vendeville *et al*., 2005; Xavier and Bassler, 2003; Defoirdt *et al*., 2013). In this regard, there is evidence for the ability to disrupt QS by various phytogenic compounds including alfalfa seed extract (Vikram *et al*., 2010), plants (Koh and Tham, 2011), and essential oils (Bjarnsholt *et al*., 2005; Choo *et al*., 2006; Zhou *et al*., 2013). Unfortunately, the use of QS inhibition strategies to control bacterial infections is unknown in aquaculture (Yang *et al*., 2015). The first report on aquatic animals was made by Manefield *et al*. (1999) on furanone extracted from the Australian microalgae (*Delisea pulchra*). Based on the results of this study, this combination increased the survival of shrimp larvae exposed to pathogens such as *V. campbellii*, *V. harveyi,* and *V. parahaemolyticus* (Defoird *et al*., 2007). Organic compounds such as cinnamaldehyde and its derivatives have also been reported to be effective against *V. harveyi* in Brine shrimp (Niu *et al*., 2006; Brackman *et al*., 2008) and *Macrobrachium Rosenbergii* larvae (Pande *et al*., 2013).

The role of phytogenics in inhibiting microbial pathogens in cold water fish

Studies on the effect of phytogenetics on increasing the resistance of cold-water fish to bacterial pathogens are much less than warm-water fish, and studies have been limited to rainbow trout. In a study by Menanteau-Ledouble *et al*. (2015), the use of a commercial phytogenic food additive (containing oregano, anise, and citrus oils) increased the survival of rainbow trout (*Onchorhynchus mykiss*) exposed to *Aeromonas salmonicida* in three forms of Intraperitoneal injection, immersion in bacterial solution and living with infected fish. According to these results, the highest effect of phytogenics in protecting fish from pathogens was in the form of immersion. Also, according to Gulec *et al*. (2013), fortification of the diet with oils extracted from *Thymus vulgaris* and *Foeniculum vulgare* can increase the resistance to *Yersinia ruckeri* in rainbow trout by increasing the levels of some biochemical parameters and electrolytes.

The role of phytogenics in inhibiting microbial pathogens in warm water fish

Most studies have been performed on the effects of phytogenics on increasing the resistance of tilapia to bacterial diseases. Numerous studies have reported increased resistance of tilapia to *Aeromonas hydrophila* challenge due to the use of phytogenic compounds which include studies by Jayathirtha and Mishra (2004) using *E. officinalis* supplement, El Deen and Razin (2009) using crude garlic extract (*Allium sativum*), and mugwort (*Artemisia vulgaris*), Gbadamosi *et al*. (2016) using *Moringa oleifera*, and Pachanawan *et al*. (2008) using dry leaf powder and ethanolic extract of *Psidium guajava*. Asimi and Sahu (2013) in the study of feeding with extracts of thyme (Thymus vulgaris) rosemary (*Rosmarinus officinalis*) and fenugreek (*Trigonella foenum graecum*) extracts in Mozambique tilapia (*Oreochromis mossambicus*) and Zilberg *et al*. (2010) in the study of feeding with *Rosmarinus officinalis* extracts in Nile tilapia reported increased resistance and decreased fish mortality after infection with *Streptococcus iniae*.

Numerous studies have been performed on catfish, including the effect of using garlic peel (Allium sativum) on increasing resistance to *Aeromonas hydrophila* infection in the fingerlings of African catfish (Thanikachalam *et al*., 2010). Zheng *et al*. (2009) also evaluated the effect of carvacrol and thymol separately, in combination with each other and combination with oregano essential oil in canal catfish. In this study, fish were challenged with this diet for 8 weeks and then with *Aeromonas hydrophila*. After challenge with *A. hydrophila*, the lowest mortality was observed in the group fed with oregano and then the fish fed with thymol and carvacrol. In another study, Peterson *et al*. (2015) found that feeding with a commercial phytogenic feed additive (Digestarom® PEP MGE; containing the essential oils of carvacrol, thymol, anethole, and limonene) increased survival rates in juveniles of canal catfish (*Ictalurus punctatus*) exposed to *Edwardsiella ictalurid*. Other studies on warm-water fish include Minomol (2005) on the effect of *Emblica officinalis* on reducing the incidence of microbial infection *in Carassius auratus* and the results of Volpatti *et al*. (2013) on-resistance of European sea bass fed carvacrol against *Vibrio anguillarum*.

The role of phytogenics in inhibiting microbial pathogens in shrimp

There are also studies on the protective effect of nutrition with phytogenes exposed to bacterial pathogens in shrimp. According to Goncalves and Santos (2015), the use of a diet containing the commercial phytogenic compound Digestarom® P.E.P. MGE increased resistance and decreased mortality in shrimp exposed to *Vibrio parahaemolyticus*. Also, according to the report of Yatip *et al*. (2018), the use of fermented Japanese soy extract (Natto) in the diet led to a reduction in mortalities due to *Vibrio harveyi* in white leg shrimp *Penaeus vannamei*.

The role of phytogenics in inhibiting viral pathogens

The antiviral effects of plant compounds are mainly due to the inhibition of virus transcription, reducing its proliferation in host cells and thus increasing the innate immune response (Syahidah *et al*., 2015). In this regard, few studies have been performed on the effect of phytogenic food additives in inhibiting viral pathogens in aquatic animals, which is limited to shrimp. The shrimp farming industry is currently facing several episodic viral diseases. White spot syndrome (WSSV) virus causes 100% mortality in shrimp farms (Selvam *et al*., 2020). In this regard, according to Yogeeswaran *et al*. (2012), the use of *Withania somnifera* (Yogeeswaran *et al*., 2012) and phytogenic supplementation ™ Phytocee (Selvam *et al*., 2020) as a dietary supplement increases the survival of shrimp exposed to White spot disease. However, the results of studies show the antiviral effects of medicinal plants on aquatic viruses and the extensive research capacity to investigate the effects of these plant compounds as food additives in vivo.

For example, in vitro studies include Micol *et al*. (2005) report on the inhibitory effect of olive leaf extract (Olea europaea) on Viral hemorrhagic septicemia (VHSV) and the effect of eighteen Thai plant extracts (*Cassia alata*, *Clinacanthus* spp., *Clinacanthus nutans*, *Calophyllum inophyllum*, *Hura crepitan*, *Glinus oppositifolis*, *Momordica cha rantina*, *Ocimum sanctum* (white), *Ocimum sanctum* (red), *Phyllanthus reticulatus*, *Phyllanthus urinaria*, *Phyllanthus acidus*, *Orchocarpus siamensis*, *Phyllanthus amarus*, *Phyllanthus debelis*, *Psidium guajava*, *Tinospora crispa* and *Tinospora cordifolia*) on CHSE-214 cells were reported in vitro against infectious hematopoietic necrosis virus (IHNV), *Oncorhynchus masou* virus disease (OMV) and Infectious pancreatic necrosis (IPNV) (Direkbusarakom *et al*., 1996). Also in the study of Harikrishnan *et al*. (2010) Intraperitoneal injection of aqueous, ethanolic, and methanolic extracts of *Punica granatum* leaves increased resistance to lymphocystis disease virus (LDV) in Olive flounder (*Paralichthys olivaceus*). According to Novriadi and Haw (2015), immersion of tiger grouper (*Epinephelus fuscoguttatus*) in herbal solution © AquaHerb increased fish resistance to iridovirus infection.

The role of phytogenics in inhibiting parasitic pathogens

Most of the studies on the effect of plant compounds on parasites in aquatic animals have been related to external parasites and the preferred prescription method is immersion due to the lack of proper implementation of prevention methods in aquaculture farms (Reverter *et al*., 2014). Numerous studies have been done on the inhibitory effects of plant compounds on parasites including *Gyrodactylus turnbulli* (Fridman *et al*., 2014), *Anacanthorus penilabiatus* (Martins *et al*., 2002), *Neobenedenia* sp. (Militz *et al*., 2014), *Ichthyophthirius multifiliis* (Zhang *et al*., 2013), *Dactylogyrus intermedius* (Wu *et al*., 2011) and *Gyrodactylus kobay ashii* (Zhou *et al*., 2017). However, limited studies have reported the effects of phytogenic dietary supplements on the prevention and control of parasitic diseases. Existing mechanisms are involved in improving immune function (especially mucosal immunity). Some studies in tilapia have reported a protective effect of phytogenes against Trichodina infection. According to a study by El Deen and Razin (2009), the use of crude garlic extract (*Allium sativum*) and mugwort (*Artemisia vulgaris*) controlled Trichodina's disease in Nile tilapia. Chitmanat *et al*. (2005) showed that the use of garlic and Indian almond extract (*Terminalia catappa*) reduces Trichodina infection in tilapia. Chansue and Tangtrongpiros (2005) also reported that the addition of dried almond leaves (*Terminalia catappa*) could kill monogenic parasites in *Carassius auratus*. According to Fridman *et al*. (2014), the use of the aqueous extract of garlic (*Allium sativum*) in the diet of guinea fowl (*Poecilia reticulata*) infected with *Gyrodactylus turnbulli* and *Dactylogyrus* sp. significantly reduced the mean prevalence and severity of parasites. Militz *et al*. (2013) showed that the use of garlic supplements as prophylaxis leads to a significant reduction in infection of *Neobenedenia* sp. (Monogenea: Capsalidae) in farmed barramundi (*Lates calcarifer*).

The role of phytogenics in improving the quality of fish carcasses

Carcass composition including fat and protein are factors that have been evaluated in some studies as a result of feeding with phytogenic food additives in aquatic animals. The results of Peterson *et al*. (2014) study on catfish fillets fed with phytogenic feed additive (Digestarom® PEP MGE) showed less fillet fat (31.3 vs. 35.9) and slightly higher fillet protein (62.4 vs. 61.2%). Less fat in seafood is beneficial because it reduces waste, increases efficiency, reduces bad taste, and reduces storage problems. Also in the study of rainbow trout, the stability of lipids against oxidative damage and the activity of glutathione-based enzymes in the fillets of both thymol-treated fish and carvacrol-treated fish improved (Giannenas *et al*. 2012). The results of these studies show that herbal supplements may have a beneficial effect in reducing fillet fat, increasing protein deposition, and increasing carcass antioxidant activity. However, the results of studies in some cases show the lack of phytogenic compounds' effect on improving carcass quality. According to the results of Zheng *et al*. (2009), feeding canal catfish with carvacrol and thymol separately, in combination with each other and combination with oregano essential oil did not affect carcasses and fillets among the control and treatment groups.

Prospects for the future

The world's population today is about seven billion and will reach nine billion by 2050. Feeding the world's population by 2050 will be a major challenge. Therefore, aquaculture will replace fishing and most of the required protein will be provided from aquatic sources (Costello *et al*., 2020). The use of antibiotics and chemicals as stimulants for the growth and treatment of diseases in aquaculture has raised concerns in many countries. These compounds cause environmental pollution and are dangerous to human health. In 2022, several countries and the European Union (EU) will ban the use of antibiotics on farms. This ban indicates the need to develop alternative therapies (More, 2020). The use of herbal compounds is one of these alternative therapies that have attracted a lot of attention in recent years. The global market for phytogenic food additives is estimated at $ 753 million in 2020 and is projected to reach $ 1.098 million by 2025 (Firmino *et al*., 2021). Herbal compounds can be effective alternatives, especially for the prevention of diseases caused by bacteria and parasites in aquatic animals. However, studies on this subject have shown varying degrees of effectiveness, and the use of phytogenic compounds to control parasites through immersion has had limited success. The reason for this can be attributed to factors such as extraction methods, part of the plant that is used as raw material, the concentration of additives, prescription method, and storage conditions before feeding, which greatly affects their performance (Reverter *et al*. 2014). Determining the optimal dose in the use of phytogenic compounds is also very important because it increases losses if inappropriate doses are used (Ikhwanuddin *et al*., 2014). Further studies are also needed to determine the quality, bioactive components, and classification of the chemical composition of these phytogenics to be used to develop standard extraction protocols, determine prescribing methods and determine the optimal dose in fish and crustaceans (Reverter *et al*., 2014). The fastest way to use phytogenic compounds is by injection, but this method is very troublesome and stressful in fish and crustaceans. Therefore, feeding prescription is the most appropriate and available method (Yoshida *et al*., 1995). One of the valuable initiatives that will help develop the use of these phytogenic compounds in the future is the stabilization of various phytogenic compounds such as volatile essential oils using methods such as matrix-encapsulation. This allows these compounds to remain active in more parts of the gastrointestinal tract (GIT) and their positive effects are not limited to a small part of the GIT (Goncalves and Santos, 2015).

Despite numerous reports of the benefits of using phytogenic compounds in experimental studies, inconsistencies in their effects on host growth and systemic safety and a lack of understanding of how they work in intestinal health and intestinal microbiota have led to limitations in the use of these compounds in aquatic animals. Generally, further studies are needed to introduce and develop sustainable prevention strategies to use phytogenic compounds to enhance host immunity, stress resistance, and the prevention of pathogenesis in aquaculture.

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