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Review

A review on the application of herbal medicines in the disease control of aquatic animals

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ABSTRACT

In recent years, the aquaculture industry has been significantly affected by the breakout of disease, especially viral and bacterial disease. The chemical and antibiotic drugs are highly toxic, and can result in drug resistant pathogenic microbes. Thus, their use is now restricted or banned in some countries. In contrast, herbal compounds added to aquaculture feeds can prevent and control diseases of aquatic animals and they are known for their safety, low toxicity, and minimal environmental impacts. Research has shown that herbal medicine has an important role in enhancing the immune function of aquatic animals (e.g., fish, shrimp, and crabs), and effectively promotes antiviral, antibacterial, antiparasitic activities of the immune system. Currently, many researches are focusing on the immunological role of specific extracts from individual herbs, allowing precision medication and a reduction in development costs. This study reviewed the application of herbal medicine in the prevention of disease in aquaculture, highlighting its potential as a more environmentally friendly approach to prevent disease in aquaculture.

1. Introduction

An herb is a plant or tissue of a plant that is used for its scent, flavor, or therapeutic properties. Herbal medicines exclusively comprise plants or their extractions, and are sold as tablets, capsules, powders, teas, extracts, and fresh or dried plants. Humans use herbal medicines to maintain or improve their health (Mosihuzzaman, 2012), and to treat various diseases (Pinn, 2001; Ho et al., 2002), and such use is being increasingly extended to improve the health and disease resistance of farmed animals (Lin and Panzer, 1994; David and Luseba, 2010). Herbal medicines have the advantages of low price, low toxicity, and few adverse effects, and are unlikely to result in drug resistance. Moreover, some ingredients of herbal medicine not only have antibacterial and antiviral effects, but also immune-promoting effects, which can significantly enhance the disease resistance of animals and improve their immune function (Lin and Panzer, 1994; Cutter, 2000; Alagawany et al., 2019a). Such medicines can be used to treat many viral, bacterial, and metabolic diseases that are difficult to treat using chemical drugs and antibiotics (Li and Peng, 2013; Alagawany et al., 2019b; Abd El-Hamid et al., 2019). Given the frequent occurrence of disease in the aquaculture industry and the environmental deterioration caused by the resulting treatments, the use of chemicals and antibiotics is increasingly restricted by governments and, thus, herbal feed additives have become a focus of research and development. Since the 1990s, the role of herbal medicines as aquatic feed additives to prevent and treat disease has attracted increasing research attention (Citarasu, 2010; Valladão et al., 2015).

Herbal medicines contain active ingredients, such as glycosides, organic acids, polysaccharides, alkaloids, tannins, and flavonoids (Pan et al., 2011). These active ingredients are closely related to many functions of aquatic animals, such as the immune function, metabolism and growth performance. Advantages of herbal additives include few adverse effects, little residue, little, if any, environmental pollution, and no drug resistance or drug-induced diseases. Given that they are natural products, they are also easy for animals to tolerate. Thus, herbal medicine additives have gradually replaced chemical synthetic drugs and hormones as feed additives, also rendering the farmed products safer for human consumption.

2. Antiviral effect of herbal medicines

Most current antibiotics and other drugs have no obvious effect on the treatment of viral pathogens. However, many herbs and their extracts can induce a strong resistance to viruses and have no significant adverse effects on the aquatic animals (Table 1). Herbal medicines mainly inhibit viral infection and replication via their immunoactive

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Table 1
The important aquatic pathogens that was controlled by many kinds of herbal medicines.

Important pathogens	Herbal medicines	References
White spot syndrome virus (WSSV)	*Cynodon dactylon*	Balasubramanian et al., 2007; Balasubramanian et al., 2008
	hesperetin	Qian and Zhu, 2018
	epigallocatechin-3-gallate (EGCG)	Wang et al., 2017; Wang et al., 2018
	Gardenia jasminoides	Huang et al., 2019a
	Genipin	Huang et al., 2019b
	Agathi grandiflora	Bindhu et al., 2014
Grass carp reovirus (GCRV)	EGCG	Wang et al., 2016; Wang et al., 2018
	Magnolia officinalis	Chen et al., 2017
Aeromonas hydrophila	*Andrographis paniculata*	Luo et al., 2006; Palanikani et al., 2019
	sanguinarine	Ling et al., 2016
	Urtica dioica	Ngugi et al., 2015
	gallnut bait	Jiang and Zhen, 2006
	Ficus carica	Wang et al., 2016
	Psidium guajava	Gobi et al., 2016
	Cucurbita mixta	Musthafa et al., 2017
	Korean mistletoe	Choi et al., 2008
	Astragalus membranaceus	Ardo et al., 2008
Vibrio alginolyticus	*Toona sinensis*	Hsieh et al., 2008
	Cinnamomum camphora	Yeh et al., 2009
	Avicennia marina	Dhayanithi et al., 2015
Streptococcus spp.	*Astragalus membranaceus*	Abarike et al., 2019
	Rosmarinus officinalis	Abutbul et al., 2004; Zilberg et al., 2010
	Sophora flavescens	Wu et al., 2013
	Mentha piperita	de Souza Silva et al., 2019
	Aristolochia debilis, Panax ginseng, Spatholobus suberectus	Guo et al., 2019
	Camellia sinensis	Doan et al., 2019
	Elephantopus scaber	Doan et al., 2019
	Pimenta dioica	Yılmaz and Ergün, 2014
	clove basil, ginger	Brum et al., 2019
Dactylogyrus spp.	*Semen aesculi*	Liu et al., 2010
	Radix angelicae	Wang et al., 2011
	Rosmarinus officinalis	Zoral et al., 2017
	Euphorbia fischeriana	Zhang et al., 2014
	Dioscorea zingiberensis	Jiang et al., 2014
	Gracillin	Luo et al., 2016
Ichthyophthirius multifiliis	*Toddalia asiatica*	Shan et al., 2014
	Artemisia annua	Wu et al., 2017
	Zingiber officinale	Fu et al., 2019
	Lippia alba	Soares et al., 2016
	Melaleuca alternifolia	Valladão et al., 2016; Baldissera et al., 2017
wheelworm	*azadirachtin*	Wu et al., 2003
	Sophora flavescens	Zhang et al., 2005

compounds. For example, *Astragalus membranaceus* (Kallon et al., 2013; Guo et al., 2014), *Lonicera japonica* (Chang et al., 1995), *Euphorbia humifusa* (Chang et al., 2016), and *Radix isatidis* (Zhou and Zhang, 2013) have significant inhibitory effects on viral replication. Herbal medicine can also indirectly inhibit viral infection by inducing the host to produce a series of interferons or by improving its nonspecific immune level (Choi et al., 2017).

As crustaceans don't have an adaptive immune system and can't use vaccines to prevent diseases, there are more and more studies focus on the use of herbal antiviral drugs. White spot syndrome virus (WSSV) infects many crustaceans, including shrimp, causing mass mortalities and devastating production losses to shrimp farming over many areas (Escobedo-Bonilla et al., 2008). The ethanol extract from the leaves of *Pongamia pinnata* protected *Penaeus monodon* against WSSV infection, whereby shrimps fed with 300 μg g^{-1} extract showed a survival rate of 80% (Rameshthangam and Ramasamy, 2007). Extracts of *Aegle marmelos*, *Momordica charantia*, *Phyllanthus urinaria*, *Lantana camara*, and *Cynodon dactylon* were fed to *Penaeus vannamei* as an immune additive (Balasubramanian et al., 2007); the strongest resistance against WSSV was recorded with extracts of *C. dactylon* and *M. charantia*, with survival rates after WSSV challenge of 100% (with 100 mg kg^{-1} of *C. dactylon* extract and 150 mg kg^{-1} *M. charantia* extract). Balasubramanian et al. also found that 2% water extract *C. dactylon* powder had a strong inhibitory effect against infection with WSSV, resulting in a 100% survival rate of *P. vannamei* after WSSV challenge (Balasubramanian et al., 2008). The methanolic extracts of five herbs, including *Acalypha indica*, *C. dactylon*, *Picrorhiza scrophulariiflora*, *Withania somnifera*, and *Zingiber officinale*, were added in feed at a rate of 2 g kg^{-1}, and resulted in an increase in the survival rate of *P. monodon* to 60% after WSSV challenge (Yogeeswaran et al., 2012). Feeding *P. monodon* with 1 g kg^{-1} leaf extract of *Clinacanthus nutans* effectively prevented yellow head virus disease (Direkbusarakom et al., 1996). Shrimps fed 800 mg kg^{-1} methanolic extracts of five different herbs (*C. dactylon*, *A. marmelos*, *Tinospora cordifolia*, *Picrorhiza kurooa*, and *Eclipta alba*) showed a 74% survival rate and a reduction in the viral load following WSSV challenge (Citarasu et al., 2006). The methanolic extracts of *Agathi grandiflora* at the concentration of 400 mg kg^{-1} can improve immunological parameters and had strong antiviral activity against WSSV. And *A. grandiflora* active principles reduced the cumulative mortality of 80% in *Fenneropenaeus indicus* (Bindhu et al., 2014). The green tea extract epigallocatechin-3-gallate (EGCG) also enhanced the survival rate of *Scylla paramamosain* after WSSV challenge as well as the anti-WSSV infection ability of crabs by inhibiting viral replication (Wang et al., 2017). EGCG also improved the innate immunity against, and reduced mortality from, WSSV infection in *Marsupeneaus japonicas* (Wang et al., 2018a, 2018b). In addition, hesperetin (50 mg kg^{-1}) enhanced immune parameters including hemocyte apoptosis, phenoloxidase and superoxide dismutase activity, and delayed and reduced the mortality of crayfish after WSSV challenge (Qian and Zhu, 2019). Extracts of *Gardenia jasminoides*, notably genipin, inhibited WSSV replication and improved the survival rate of WSSV-challenged and infected crayfish (Huang et al., 2019a). Genipin is a bioactive compound extracted from the fruit of *G. jasminoides*, and it could inhibit WSSV replication and reduce the mortality rate of WSSV-infected crayfish (Huang et al., 2019b).

As vaccine is the best way to prevent viral diseases, there are few studies on antiviral use of herbal medicine. The grass carp reovirus (GCRV) is an important viral pathogen of fish and is the main cause of grass carp hemorrhagic disease. EGCG inhibited grass carp reovirus infection by blocking the binding of reovirus to the laminin receptor (Wang et al., 2016a; Wang et al., 2018a, 2018b). Magnolol and honokiol from *Magnolia officinalis* showed strong antiviral immune responses against grass carp reovirus in *Ctenopharyngodon idella* kidney cells (Chen et al., 2017). Spring viremia of carp virus (SVCV) has been shown to infect a variety of fish species, resulting in significant mortality. Coumarin is a chemical compound found in a variety of different plants such as Tonka bean. Two coumarin derivatives (B4 and C2) showed strong antiviral activity against SVCV in epithelioma papulosum cyprinid (EPC) cells (Liu et al., 2017). A novel imidazole coumarin derivative, 7-(4-benzimidazole-butoxy)-coumarin, showed strong anti-SVCV activity and increased the survival rate of zebrafish (Shen et al., 2018). Saikosaponin D, a triterpene saponin derived from *Bupleurum falcatum*, at a dose of 6 mg kg^{-1} increased the survival rate of zebrafish by 36% and inhibited SVCV nucleoprotein and glycoprotein gene expression by > 90% in kidney and spleen (Shen et al., 2019). Infectious hematopoietic necrosis virus (IHNV), a member of the Rhabdoviridae family, causes infectious hematopoietic necrosis in salmonid fish, such as trout and salmon. A novel imidazole arctigenin derivative, 4-(8-(2-ethylimidazole)octyloxy)-arctigenin, significantly decreased the cytopathic effects and viral titers induced by IHNV in EPC cells (Hu et al., 2019a). The arctigenin-imidazole hybrid derivative 15, which has an eight carbon-long linker, inhibits the apoptosis and cellular morphological damage induced by IHNV and affects its early replication (Hu et al., 2019b). A crude extract of *Clinacanthus nutans* showed antiviral activity against cyprinid herpesvirus 3 in koi (*Cyprinus carpio koi*), with a 50% effective dose (ED50) from post-infection tests of 2.05 mg/mL and 2.34 mg/mL at 0 and 24 h, respectively (Haetrakul et al., 2018).

3. Antibacterial activities of herbal medicines

Bacterial diseases cause significant mortality in aquaculture animals. Some herbal medicines have specific antibacterial effects on pathogenic bacteria, such as *Astragalus membranaceus* (Xu et al., 2007), *Scutellaria baicalensis* (Zhao et al., 2016), *Andrographis paniculata* (Banerjee et al., 2017), *Allium sativum* (Harris et al., 2001), *Eucommia ulmoides* (Peng et al., 2014), *Zingiber officinale* (Sukumaran et al., 2016) and *Mentha piperita* (de Souza Silva et al., 2019). As everyone knows, the usage of antibiotics is easy to cause drug resistance and environmental pollution. The antibiotic and chemicals were found that they can reduce the innate immunity and the disease resistance of crayfish (Ma et al., 2019). For the above reasons, more and more studies on the use of herbal medicine against bacterial infection have been carried out (Table 1).

Aeromonas hydrophila, an opportunistic aquatic pathogen, causes several major diseases including skin ulcers and hemorrhagic septicemia. Feeding with 4% and 6% powdered *E. ulmoides* leaves improved the immune response of carp and enhanced their ability to resist *A. hydrophila* infection (Luo, 2002). Korean mistletoe extract also enhanced the immune stimulation and nonspecific immunity of Japanese eel (*Anguilla japonica*). After *A. hydrophila* infection, a 0.5% mistletoe concentration stimulated phagocytic activity, resulting in increased reactive oxygen intermediate (ROI) production (Choi et al., 2008). Adding *A. membranaceus* to the feed of *Oreochromis niloticus* significantly increased the phagocytic activity of blood cells, reducing the mortality rate of *O. niloticus* following *A. hydrophila* infection (Ardo et al., 2008). *Urtica dioica* promoted the immune function of *Victoria labeo*, resulting in a 95% survival rate of *V. labeo* challenged with *A. hydrophila* (Ngugi et al., 2015). Common carp (*Cyprinus carpio*) fed 0.5% and 1% gallnut additive prevented *A. hydrophila*-induced bacterial septicemia (Jiang and Zhen, 2006). Although l% and 2% *A. paniculata* additive fed to grass carp did not affect most of the dominant bacteria in the carp intestine, it did significantly reduce the number of *Aeromonas spp.* (Luo et al., 2006). *Ficus carica* polysaccharides used as immunostimulants are capable of enhancing immune responses and disease resistance against *A. hydrophila* in crucian carp (Wang et al., 2016b). Dietary supplementation with *Psidium guajava* leaf extract powder reduced the mortality and increased disease resistance in *Oreochromis mossambicus* following challenge with *A. hydrophila* (Gobi et al., 2016). Dietary supplementation with 10 mg kg^{-1} sanguinarine, an alkaloid from *Sanguinaria canadensis*, showed enhanced antibacterial efficacy against *A. hydrophila* in *C. carpio* (Ling et al., 2016). Additives from *Z. officinale* promoted immunological indicators, such as skin and mucosa, in Indian major carp (*Labeo rohita*), and improved resistance against *A. hydrophila* infection (Sukumaran et al., 2016). Adding *Mumiyo* to feed increased the activity of phenoloxidase and superoxide dismutase in *Macrobrachium rosenbergii*, resulting in reduced mortality following *A. hydrophila* infection (Musthafa et al., 2016). *Myrciaria dubia* extracts could also significantly improve the immune response of *O. niloticus* to *A. hydrophila*, including lysozyme activity, respiratory activity, serum bactericidal activity, total white blood cells, and direct agglutination (Yunis-Aguinaga et al., 2016). A *Cucurbita mixta* seed meal-enriched diet at 4 g kg^{-1} and 6 g kg^{-1} enhanced the growth performance, innate immunity, and disease resistance against *A. hydrophila* in *O. mossambicus* (Musthafa et al., 2017), whereas methanol extract from *Euphorbia hirta* improved the resistance of African catfish *Clarias gariepinus* to *A. hydrophila* (Sheikhlar et al., 2017). *A. paniculata* extracts were also effective against *A. hydrophila* infection in L. *rohita* by increasing the levels of hemoglobin and total erythrocyte-leucocyte counts, along with the phagocytic index (Palanikani et al., 2019).

Streptococcus spp., a kind of opportunistic pathogens that occur widely in aquaculture systems, can cause significantly mortality of farmed fish. A traditional herb, *Sophora flavescens*, enhanced the non-specific immune response and resistance to *Streptococcus agalactiae* in *O. niloticus* (Wu et al., 2013), whereas a traditional Chinese medicine (a mix of *A. membranaceus*, *Angelica sinensis*, and *Crataegus hupehensis* at a ratio of 1:1:1 on a weight basis) enhanced the growth, immune response, and resistance to *S. agalactiae* in *O. niloticus* (Abarike et al., 2019). *Rosmarinus officinalis* is a common medicinal herb with antimicrobial and antitumor properties. It was able to inhibit *Streptococcus iniae* growth and reduced the mortality rate of *O. niloticus* infected by *S. iniae* (Abutbul et al., 2004). Dietary supplementation with dried *R. officinalis* leaves also reduced the mortality of *O. niloticus* infected with *S. agalactiae* (Zilberg et al., 2010). The extracts of *Aristolochia debilis*, *Panax ginseng*, and *Spatholobus suberectus* were found to be useful for the treatment of *Streptococcus agalactiae* infection in Nile tilapia (Guo et al., 2019). The supplementation with the *Mentha piperita* essential oil (0.25%) increased the resistance of Nile tilapia after the challenge with *S. agalactiae* (de Souza Silva et al., 2019). Dietary supplemented with 2 g kg^{-1} *Camellia sinensis* extract increased the humoral and mucosal immunity and offered higher resistance against *S. agalactiae* infection in Nile tilapia (Van Doan et al., 2019). Dietary supplementation of 5 g kg^{-1} *Elephantopus scaber* extract enhanced the humoral and mucosal immunity and improved disease resistance of Nile tilapia against *S. agalactiae* (Doan et al., 2019). Dietary supplementation with essential oils of clove basil and ginger modulated the immune response and improved resistance to experimental infection with *S. agalactiae* in Nile tilapia (Brum et al., 2019). Dietary supplemented with *Pimenta dioica* at 10 g kg^{-1} would reduce the occurrence of *Streptococcal* disease in Mozambique Tilapia (Yılmaz and Ergün, 2014).

Vibrio spp. include halophilic bacteria that occur widely in marine environments; most are opportunistic pathogenic bacteria of mariculture animals, such as *Vibrio alginolyticus*, *Vibrio parahaemolyticus*, and *Vibrio harveyi*. Essential oil extracts from the leaves and branches of *Cinnamomum kanehirae* inhibited *V. alginolyticus* infection in *P. vannamei* (Yeh et al., 2009). Water extracts from *C. kanehirae* branches greatly reduced the sensitivity of *P. vannamei* to *V. alginolyticus*, and greatly improved the sensitivity of *P. vannamei* to *V. alginolyticus*, by increasing the phenoloxidase and hemocyte phagocytosis activity of *P. vannamei* (Yeh et al., 2009). The injection of rutin from *Toona sinensis* increased the activity of phenoloxidase and reduced the mortality of *P. vannamei* following *V. alginolyticus* infection (Hsieh et al., 2008). *Amphiprion sebae* fed with 1%, 2%, or 4% extracts from leaves of *Avicennia marina* showed survival rates of 70%, 80%, and 85%, respectively, following infection with *V. alginolyticus*, compared with 10% in the control group (Dhayanithi et al., 2015). Ngambi et al. found that saponins (from *Quillaja saponaria*) stimulated the immune response of *Portunus trituberculatus*, including phagocytic activity, total number of blood cells, and superoxide dismutase and phenoloxidase, and enhanced the immune defense of *P. trituberculatus* against *V. alginolyticus* (Ngambi et al., 2016). Juvenile greasy groupers (*Epinephelus tauvina*) fed a diet containing 100 or 200 mg kg^{-1} *Ocimum sanctum* showed reduced mortality rates of up to 5% following *V. harveyi* challenge (Sivaram et al., 2004). Among the screened herbal diets, *Ricinus communis* additives showed a high survival rate (58.88%) and low *V. parahaemolyticus* load in muscle and hepatopancreas tissues of *Penaeus indicus* (Immanuel et al., 2004). The traditional compound Chinese herbal medicine, San-Huang-San, improved the innate immunity of *P. vannamei* and enhanced its resistance to an acute hepatopancreatic necrosis disease (AHPND)-causing strain of *V. parahaemolyticus* (Zhai and Li, 2019).

The immune parameters of *Oplegnathus fasciatus* increased significantly with the addition of *Scutellaria baicalensis* and effectively reduced the mortality rate following infection with *Edwardsiella tarda* (Harikrishnan et al., 2011). Diets with extracts of *Psidium guajava* at 0.2% and 1.0%, or *Mimosa pudica* at 2.0% improved striped catfish health by enhancing the immune system and reducing mortality against *Edwardsiella ictaluri* challenge (Nhu et al., 2019). Kakoolaki et al. found that 200 mg kg^{-1} *Camellia sinensis* extract improved the blood immune index and lysozyme activity of *Mugil cephalus*, and enhanced resistance to *Photobacterium damselae* infection (Kakoolaki et al., 2016). *Centella asiatica* extract significantly increased the antimicrobial activity of *Tilapia nilotica* against *Flavobacterium columnare* (Rattanachaikunsopon and Phumkhachorn, 2010). Columnaris disease is caused by the Gram-negative bacterium, *Flavobacterium columnare*. *Ictalurus punctatus* fed with *Nigella sativa* seeds (5%) displayed a lower mortality rate after *F. columnare* challenge than those fed a control diet (Mohammed and Arias, 2016). The *Z. officinale* supplement (6 or 10 g kg^{-1}) could reinforce the non-specific immunity and diminish the vulnerability of *Oncorhynchus mykiss* to *Yersinia ruckeri* (Soltanian et al., 2019).

4. Antiparasitic effect of herbal medicines

Parasitic infections are responsible for mass mortalities of farmed fish and cause significant economic losses. Common aquatic insecticides, such as furazolidone and dipterex (chemical agents) and avermectin (antibiotics), have resulted in some drug-resistant parasites (Hien et al., 1997; Hallett et al., 2006). Herbal medicines do not significantly pollute the aquaculture environment, and are not toxic to humans, ensuring food safety. Although there are a few reports on the antiparasitic application of herbal medicines in aquaculture, these are not enough to meet the increasing demands of consumers in terms of food safety. Thus, the use of plant essential oils to treat parasites of farmed animals will help to improve the food safety of aquaculture animals (Fang et al., 2016; Ferreira et al., 2018; Chen et al., 2019). However, such use is challenged by the range of parasitic life-histories and developmental stages, making it more difficult to develop antiparasitic applications of herbal medicine.

Dactylogyrus, a monogenous fluke that lives on the gills of fish, is common in Asia and central Europe. It can cause gillitis, mucus hypersecretion, and accelerated respiration in fish. Methanolic and aqueous extracts of *Semen aesculi* can be exploited as a natural antiparasitic agent for the control of *Dactylogyrus intermedius* (Liu et al., 2010). An ethanol extract from *Radix angelicae* showed strong anthelmintic activity against *D. intermedius* in goldfish (Wang et al., 2011a). *C. carpio* supplemented with aqueous rosemary extract of *R. officinalis* showed strong anthelmintic activity against *Dactylogyrus minutus* infections (Zoral et al., 2017). The ethyl acetate extracts from *Euphorbia fischeriana* were effective against *Dactylogyrus vastator* in vitro. However, the effective dose was close to its toxic dose and, thus, this limits its practical application in aquaculture (Zhang et al., 2014). The active compound combinations between *Dioscorea zingiberensis* and *Ginkgo biloba* showed a highly synergistic anthelmintic effect against *Dactylogyrus* (Jiang et al., 2014). Gracillin, the main active compound of rhizome of peltate yam, showed the highest synergy rate (71.4%) and increased anthelmintic efficacies against *Dactylogyrus* infections using a goldfish model (Luo et al., 2016).

Ichthyophthirius multifiliis is one of the most common protozoan diseases encountered in tropical-fish aquariums. In vitro antiparasitic assays revealed the 100% effectiveness of chelerythrine and chloroxylonine from *Toddalia asiatica* against *Ichthyophthirius multifiliis* at a concentration of 1.2 mg L^{-1} and 3.5 mg L^{-1}, respectively. In vivo experiments demonstrated that fish treated with chelerythrine and chloroxylonine at 1.8 mg L^{-1} and 8.0 mg L^{-1} carried fewer parasites than the control fish (Shan et al., 2014). Oral administration with *Artemisia annua* at a concentration of 20 g kg^{-1} feed for 45 days provided strong protection against *I. multifiliis* infection (Wu et al., 2017). The 10-gingerol, isolated from the *Z. officinale* extract, at a concentration of 1 mg L^{-1} protecting grass carp from *I. multifiliis* (Fu et al., 2019). The efficacy in this trial against *I. multifiliis* in fish exposed to 150 mg L^{-1} *Lippia alba* essential oil was 50.3% (Soares and Neves, 2016). However, the concentrations that eliminate these ectoparasites are toxic for the hosts. *Melaleuca alternifolia* essential oil prevents oxidative stress and ameliorates the antioxidant system in the liver of silver catfish (*Rhamdia quelen*) naturally infected with *I. multifiliis* (Baldissera et al., 2017). The 53.33% of the fish severely infected by *I. multifiliis* survived after the treatment with *M. alternifolia* (50 μL L^{-1}) and the parasitological analysis has shown an efficacy of nearly 100% in the skin and gills, while all the fish in the control group died (Valladão et al., 2016).

The wheelworm is harmful to the fries of many species of cultured fish, and is parasitic on the body surface and gills. The effects of azadirachtin that is isolated from the neem tree (*Azadirachta indica*) against *Trichodina* sp. were confirmed in *Daino rerio* (Wu and Zhu, 2003). The median lethal concentrations of azadirachtin at 48 h and 96 h were 41.9 mg L^{-1} and 23.3 mg L^{-1}, respectively. The safe concentration of azadirachtin for fish was less than or equal to 2.3 mg L^{-1}. In addition, azadirachtin did not induce chromosomal mutations in the peripheral blood cells of carp, indicating that it shows no mutagenicity and no obvious toxicity to cultured fish. Pharmacological methods were also used to test the anti-wheelworm effect of *S. flavescens*, and the results showed that alkaloids extracted from *S. flavescens* effectively killed the wheelworm in the gills of fish (Zhang et al., 2005). The highest rate of mortality was achieved by using an ultrasonic method to extract the alkaloids from *S. flavescens*; such a method resulted in a higher content of matrine, indicating that this is the main active alkaloid in *S. flavescens* against wheelworm.

The anthelminthic activity of essential oil from *M. piperita* against monogeneans in *Arapaima gigas* was dose dependent, causing monogenean mortality after 30 min in in-vitro trials. However, the toxicity of the *M. piperita* essential oil and their influence on the histopathology of *A. gigas* is obvious in vivo (Malherios et al., 2016). The *M. piperita*, at a concentration of 40 mg L^{-1}, showed strong activity against monogenean parasites in *Nile tilapia* (de Oliveira Hashimoto et al., 2016). The 320 mg L^{-1} *Ocimum gratissimum* was demonstrated to cause 100% mortality of the monogenean *Cichlidogyrus tilapiae* gill parasite of *Nile tilapia* (Meneses, 2018). It was demonstrated that immersion in ginger extract offers an effective, alternative treatment against monogenean (*Gyrodactylus turnbulli*) infection in guppy (*Poecilia reticulata*) (Levy et al., 2015). Eugenol is the main component of *O. gratissimum*. The bath with 10 mg L^{-1} eugenol solution for 60 min is efficient for controlling monogenean gill infection in *Colossoma macropomum* (Boijink et al., 2015). Therefore, some herbal medicines might also be toxic to aquatic animals at the effective antiparasitic dose. Thus, it is necessary to determine the safe concentration of herbal medicines before determining the effective antiparasitic concentration (Wu and Zhu, 2003; Malherios et al., 2016).

5. Challenges and future perspectives

With our gradually improving understanding of the negative effects of antibiotics and chemicals and the growing importance of food safety, the development of “green” immune additives has become a top priority. Herbal medicine resources are not only abundant, cheap, and easy to obtain, but also show minimal toxicity and few adverse effects, leave relatively little residue, and almost no pollution. Some herbal medicines even show unique activity against a variety of pathogens, such as EGCG, *C. nutans*, *R. officinalis*, *A. membranaceus*, *S. flavescens*, *M. piperita*, *Z. officinale* (Table 2) and *Terminalia catappa* (Chitmanat et al., 2005). Traditional herbal medicine has been used in many countries for many years, but usually comprises multiple herbs with complex chemical profiles (Shi et al., 2018). Given the lack of understanding of its modality and a lack of standardization, there are significant challenges associated with regulating the safety of herbal medicines and for understanding their mechanisms of efficacy (Zhou et al., 2019). As seen with the discovery of artemisinin (Tu, 2011), the use of purified active ingredients to prevent and treat diseases will be the future for the application of herbal additives for disease prevention and treatment.

Table 2
The important herbal medicines used for controlling many kinds of aquatic pathogens.

Herbal medicines	Pathogens	References
epigallocatechin-3-gallate (EGCG)	WSSV	Wang et al., 2017; Wang et al., 2018
	grass carp reovirus	Wang et al., 2016
Clinacanthus nutans	Cyprinid herpesvirus 3	Haetrakul et al., 2018
	yellow head virus	Direkbusarakom et al., 1996
Rosmarinus officinalis	*Streptococcus iniae*	Abutbul et al., 2004
	Dactylogyrus minutus	Zoral et al., 2017
	Streptococcus agalactiae	Zilberg et al., 2010
Astragalus membranaceus	*Aeromonas hydrophila*	Ardo et al., 2008
	Streptococcus agalactiae	Abarike et al., 2019
Sophora flavescens	*Streptococcus agalactiae*	Wu et al., 2013
	Trichodinella ninuta	Zhang et al., 2005
Mentha piperita	*Streptococcus agalactiae*	de Souza Silva et al., 2019
	monogenean	de Oliveira Hashimoto et al., 2016
Zingiber officinale	*Aeromonas hydrophila*	Sukumaran et al., 2016
	Yersinia ruckeri	Soltanian et al., 2019

Given the reduced effectiveness of their ingredients, unpurified herbal medicines are used less regularly. Compound herbal medicines are not suitable for economic and environmental protection because of their high cost, many adverse effects and low efficacy resulting from the interaction of various herbal components. The content of active ingredients in natural herbs also varies across locations and with the seasons. For example, the antimicrobial activities of the essential oils of *R. officinalis* differed depending on the location and season (Celiktas et al., 2005). Compared with LD50 and other parameters, it is safer to measure the safe concentration of herbal medicine in terms of their cytotoxicity. Even EGCG, an extract of the well-known health drink, green tea, is cytotoxic to crab hemocytes at high concentrations (Wang et al., 2017). As the price of some herbs increases, the discovery of single purified compounds will have more application prospects compared with the whole herb or its extracts. Thus, research on the safety and mechanisms of action of disease-resistant herbs needs to be more thorough. Novel research has used *Artemia* spp. as a carrier to immunize aquatic animals orally with herbal medicines (Citarasu et al., 2003).

6. Conclusion

Most studies focus on antiviral or antimicrobial activity of herbal medicines in vivo or in vitro, with few studies on the effective components and target organs of herbal medicines. Different geographical regions and harvesting times can result in different efficacies of the same herbal medicine. At present, there are relatively few studies on the synergistic and antagonistic effects of different herbal medicines. For example, when *Coptis chinensis* was combined with *Forsythia suspensa*, the antimicrobial activity of *C. chinensis* was enhanced by six-fold (Wang et al., 2011b). It is now necessary to strengthen basic research into herbal medicine, to clarify the active ingredients and the mechanisms of common herbal medicines in aquaculture, and to conduct in-depth pharmacological and toxicological studies to guide their use in the treatment and even prevention of diseases in aquatic animals.

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Declaration of Competing Interest

The authors declared that they have no conflicts of interest to this work. We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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