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A Review on Medicinal Plants and Immune Status of Fish

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ABSTRACT

Nowadays, one of the limiting factors in aquaculture is infectious diseases which cause substantial economic losses worldwide. Antibiotics are mainly used to control these diseases even though they have several adverse effects on the environment and human life. In this context, researchers are trying to find an alternative to antibiotics, which should be eco-friendly and economically feasible for fish farmers. Medicinal plants can be used as an alternative to antibiotics, which have been showing promising possibilities in numerous fish health benefits including modulation of the fish immune system (one of the most commonly purported benefits). This review describes the immunomodulatory role of different medicinal plants to boost the immune system of fish, which might be effective to fight against infectious diseases.

INTRODUCTION

Aquaculture is a rapidly growing economic sector and a plethora of protein sources for human consumption (**Hayatgheib *et al.*, 2020**). However, diseases cause a 50% production loss of this industry (**Gabriel, 2019**). Antibiotics and 'traditional' chemical therapeutics are administered to minimize the economic impact (**Van Doan *et al.*, 2019; Lieke *et al.*, 2020**). However, the recurrent use of antibiotics in aquaculture system is not only hampering fish metabolism but also the environment and public health. This harmful effect allows horizontal gene transfer (HGT) of antibiotic resistance genes among diverse species with the collaboration of bacterial population, which leads to drug-resistant pathogens (**Watts *et al.*, 2017**). Vaccine is also used to treat the aquaculture diseases; however, it is relatively expensive and not effective for broad-spectrum use (**Plant & LaPatra, 2011**). As a result, alternative sustainable strategies followed by substitutes for antibiotics, vaccines, or other chemical therapeutics, are highly needed that are characterized as immunostimulants by a broad-spectrum activity, which contribute to fish growth mechanism, and more precisely, cost-effective, eco-compatible best quality products from aquaculture indeed (**Gabriel, 2019**).

Over the past two decades, it has been a common trend of using plant-derived supplements rather than chemical residues in aquaculture because of many factors: low cost, ready availability, fewer side effects in fish health and sustainable practice for aquatic environments (**Reverter *et al.*, 2014; Van Hai, 2015; Gabriel, 2019**). Plant-enriched diets contain bioactive plant components such as phenols, alkaloids, flavonoids, tannins, terpenoids, saponins, glycosides, and essential oils that enhance fish growth, stimulate immune parameters, and increase disease resistance (**Ghosh *et al.*, 2018**). If proper administration occurs, medicinal plant can be an alternative means of synthetic drugs in aquaculture (**Gabriel, 2019**).

This review literature is carried out to focus on the beneficial actions of different medicinal plants in aquaculture. Most specifically, how medicinal plant products modulate the immune response of the fish body. In addition, the current study was organized to address several expressions of immune profiling and disease resistance genes.

MEDICINAL PLANTS

Traditionally, people were strongly dependant on medicinal plants to prevent and treat diseases (**Tsabang *et al.*, 2016**). Several parts of medicinal plants like leaves, roots, rhizome, bark, bulbs, as well as seeds have been used as crude or extracting active compounds (**Zhang *et al.*, 2014**). They are recorded for a diverse range of biological activities such as: modulation of the immune response, growth promotion, antioxidant enhancing, antistress, digestion-stimulating, and gastroprotective effects (**Gabriel *et al.*, 2015**). Moreover, drug resistance features was rarely diagnosed in fish body systems due to diversity in molecular extracts of medicinal plants, which are biodegradable compared to synthetic drugs (**Reverter *et al.*, 2014**).

Application of medicinal plants in fish farming is mainly done by three established methods such as: oral administration, immersion or bathing, and injection (**Revertet *et al.*, 2014; Adel *et al.*, 2015a**). The oral application is the most common, economically suitable technique and less stressful for fish of any size, but least effective due to slow absorbance (**Bulfon *et al.*, 2015**). Immersion is more useful for a small fish size population (weight < 15 gm) and could be expensive as it requires a large amount of solution preparation (**Awad & Awaad, 2017**). The intraperitoneal injection method is very demanding and an effective way to provide an appropriate dose because an injection can act faster in the bloodstream and becomes functional. However, this method is difficult, labour-intensive, and not effective for fry and fingerlings (**Alexander *et al.*, 2010**). Medicinal plants can be administrated singly or in combination for treating diseases in fish. Studies have shown that using extracts from a combination of medicinal plants provides better benefits to hosts (**Jian & Wu, 2004**).

THE USEFULNESS OF MEDICINAL PLANTS ON FISH HEALTH

1.1 As growth promoters

Numerous studies confirmed that using medicinal plants as crudes, semi extracts or pure extracts stimulate appetite, promote weight gain (WG), and cause a specific growth rate (SGR) of fish species (**Awad and Awaad, 2017**). Generally, medicinal plants increase the digestive enzyme secretion, which leads to growth promotion and enhances an increase in the survival rate of fish (**Van Hai, 2015**). This suggestion was supported by **Shalaby *et al.*, (2006)** who observed that crude extracts of *Allium sativum* increased WG, SGR, and feed intake of the Nile tilapia (*Oreochromis niloticus*) as well. Crude powder of caraway showed a significant impact as a growth promoter for the Nile tilapia (**Ahmad and Abdel-Tawwab, 2011**). Noticeably, extracts of *Zingiber officinalis, Cynodon dactylon, Tridax procumbens, Piper longum,* and *Phyllanthus niruri* increased the retention rate of *Epinephalus tauvina* (**Punitha *et al.*, 2008**).

1.2 As immunostimulants

With the increasing demand for aquaculture in the fast-growing food sector, researchers have been heavily concerned to conduct studies on fish immune system (**Secombes & Wang, 2012**). Fish fed medicinal plants containing bioactive compounds, that act as immunostimulants, boost the specific and the non-specific immune response (**Ghosh *et al.*, 2018**). Since the immune system is a biological mechanism of protecting living organisms from pathogens, medicinal plants can boost up the immune responses of fish, which eventually increase their antipathogenic capability (**Bulfon *et al.*, 2015**). Therefore, medicinal plants help to reduce the losses of fish production before the occurence of any disease (**Awad & Awaad, 2017**). The application of medicinal plants were reported to improve the immunological parameters in many fishes, including lysozyme, phagocytic, respiratory burst, as well as complement activities, peroxidise, and anti-protease activities (Fig. 1). However, the activity of medical plants depends on dose, types of medicinal plants, as well as their active compounds and fish size.

1.2.1 Lysozyme activity

Lysozyme is an effective antimicrobial and antioxidant component that acts on the lytic action on peptidoglycan bacterial cell wall and control microbial growth (**Liu *et al.*, 2006**). It plays an important role to develop non-specific or innate immunity of fish and shellfishes (**Yang *et al.*, 2015**) since it stimulates and activates several complement components, neutrophils, and macrophages, which eventually cause phagocytosis of bacteria, parasite, and virus as an opsonin (**Harikrishnan *et al.*, 2011**). Notably, lysozyme are shown at the early developmental stages of fish when the specific immunity is yet to develop and fight against microorganisms at the larval stage (**Cecchini *et al.*,**

2000). The upregulation of serum lysozyme indicates the advancement of different humoral immunity that can protect the fish body from any kind of infection (**Harikrishnan *et al.*, 2010**). Several medicinal plants are reported to enhance lysozyme activity in fishes (Table 1).

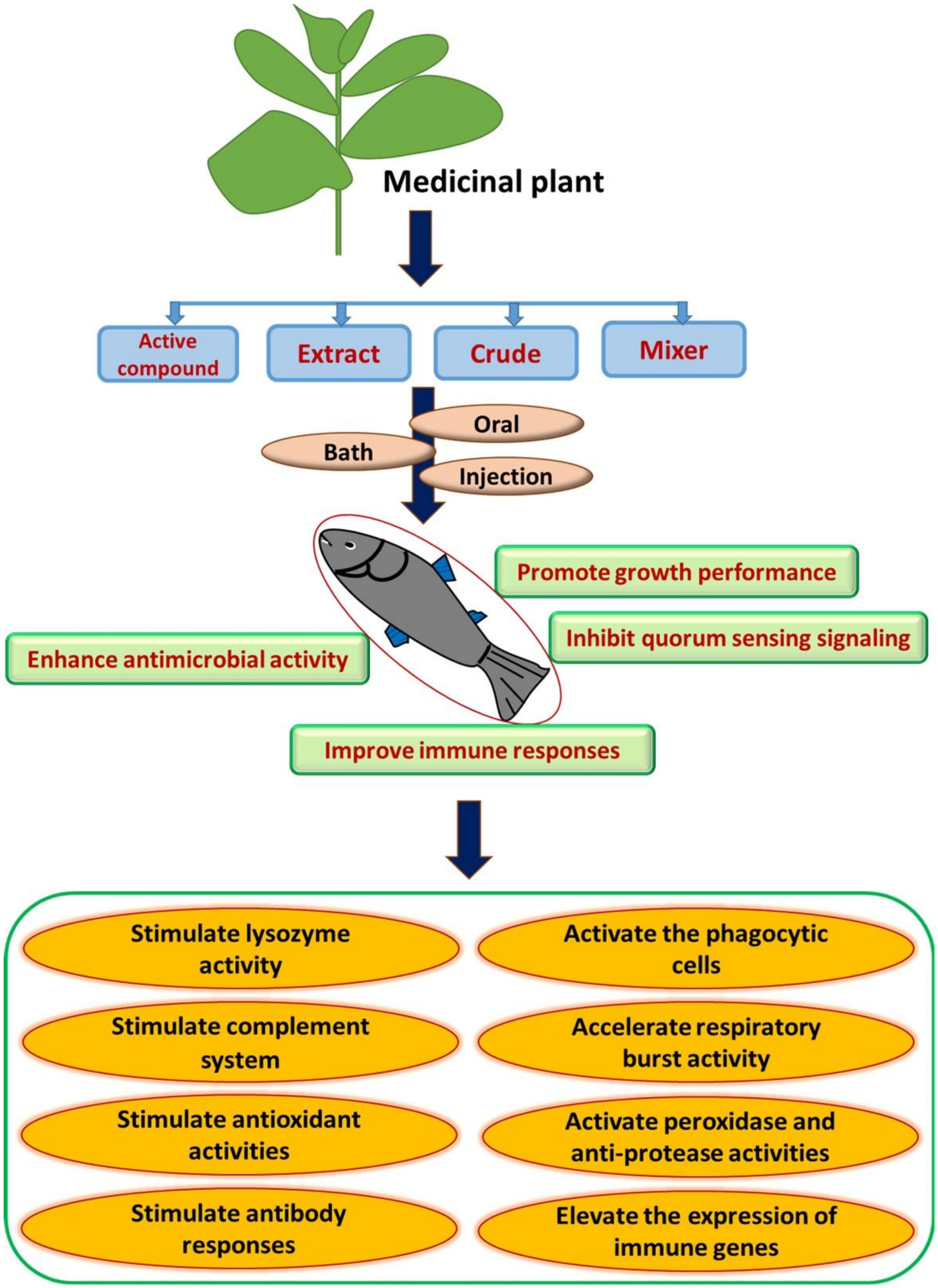

Fig. 1. Role of medicinal plants on immune status in fish.

1.2.2 Phagocytic and respiratory burst activity

Phagocytosis constitutes a primitive defence against invading pathogens and involves internalization, killing, and digestion of invading pathogens (**Harikrishnan *et al.,* 2011**). Oxidative burst activity occurs due to the stimulated production of reactive oxygen from phagocytes, which are responsible for killing bacteria and other pathogens during phagocytosis (**Carbone & Faggio, 2016**). It signals the active status of macrophage and neutrophil in the cell (**Talpur, 2014**). For vertebrates, phagocytosis is a fundamental defence mechanism, which is followed by the release of reactive oxygen species, such as superoxide anion (O_2-), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH), all of which are highly antimicrobial; the antioxidant enzyme (superoxide dismutase, SOD, catalase, and glutathione peroxidase) can protect cells from damage (**Messaoudi *et al.,* 2009**). The present study revealed that the phagocytic activity can be enhanced after dietary supplementation of several medicinal plants. Fish showed improved phagocytic and respiratory burst activity that lead to reduce susceptibility to pathogens due to various medicinal plants and their extract (Table 1).

1.2.3 Peroxidase and anti-protease activity

Peroxidases are the component of a large group enzyme that are clinically prominent and act as microbicidal agents, which not only utilize oxidative radicals to kill the pathogen but also used for ionic stability of immune cells. During the respiratory burst, it is mainly released by neutrophils. Anti-protease activities of serum are responsible for preventing proteolytic pathogen. Some medicinal plants were reported to elevate this activity in fish and showed higher survival against different pathogens (Table 1).

Table 1. List of medicinal plants and their extract used as immunostimulant.

Medicinal plants	Fish species	Dose	Impacts	Reference
Ethanolic extracts of propolis	*Oreochromis mossambicus*	2, 4 g kg^{-1}	Increase lysozyme and myeloperoxidase activity, total protein and disease resistance against *Streptococcus iniae*	**Acar (2018)**
Essential oil from orange peel (*Citrus sinensis*)		1, 3, and 5 g kg^{-1}		**Acar *et al.* (2015)**
Mucuna pruriens and *Cucurbita mixta* seed meal		2, 4 and 6 g kg^{-1}	Enchance lysozyme, phagocytic, respiratory burst, complement activity, weight gain, feed efficiency ratio and survival against *Aeromonas hydrophila*	**Musthafa *et al.* (2017, 2018)**
Cinnamon nanoparticles (CNP)	*O. niloticus*	3 g CNP kg^{-1}	Enhance antioxidant and digestive enzymes, activities, high survival against *A. hydrophila*	**Abdel-Tawwab *et al.* (2018a)**
Astragalus polysaccharides		1500 mg kg^{-1} diet	Improve growth performance, increase phagocytic, respiratory burst, lysozyme, bactericidal and amylase activity	**Zahran *et al.* (2014)**

Propolis and *Aloe barbadensis* (1:1)		0.5, 1.0 and 2%	Elevate serum lysozyme, phagocytic and antimicrobial activity	**Dotta *et al.* (2014)**
Green tea and Chinese herbal mixtures		0.5 – 2%	Increase lysozyme, peroxidase, superoxide dismutase activity and reduce mortality against *A. hydrophila*	**Tang *et al.* (2014)**
Peppermint (Metha piperita) plant extract	*Onchorhynchu -s mykiss*	0, 1, 2, 3%	Increase respiratory burst acitivity, total protein and protection against *Yersinia ruckeri*	**Adel *et al.* (2016)**
Ajwain (*Trachyspermum ammi*) and marjoram (*Origanum* sp.) extract		1-2%	Improve growth performance and lysozyme activity	**Ali *et al.* (2017)**
Lentinula edodes mushroom extract		1-2%	Decrease mortality rate against *Lactococcus garvieae* and increase lysozyme activity	**Baba *et al.* (2015)**
Ficuscarica polysaccharide	*Ctenopharyng-odon idella*	1.0%	Increase lysozyme and bactericidal activity	**Yang *et al.* (2015)**
Dill (*Anethum graveolens*) and garden cress (*Lepidium sativum*)	*Cyprinus carpio*	1-2 g kg^{-1}	Increase lysozyme, myeloperoxidae and survival rate against *A. hydrophila* and *Edwardsiella tarda*	**Bilen *et al.* (2018)**
Ginger (*Zingiber officinale)* and Garlic (*Allium sativum*)	*Lates calcarifer*	5, 10 g kg^{-1}	Increase phagocytic, respiratory burst, bactericidal and antiprotease activity, reduce susceptibility to *Vibrio harveyi*	**Talpur and Ikhwanuddin, (2012, 2013)**
Peppermint powder			Increase phagocytic, respiratory burst, bactericidal and antiprotease activity, elevate serum protein and globulin level, reduce susceptibility to *V. harveyi*	**Talpur (2014)**
Peppermint plant extract	*Rutilus frisii kutum* and *Salmo trutta*	1%, 2%, and 3% respiratory only	Increase blood leukocyte number, lysozyme, antimicrobial and respiratory burst activity	**Adel *et al.* (2015a, 2015b)**
Clove basil (*Ocimum gratissimum*) leaf extract	*Clarias gariepinus*	10, 15 g kg^{-1}	Increase intestinal villi length, absorption area, reduce cholesterol and glucose level, increase protein, antioxidant and survival against *Listeria monocytogenes*	**Abdel-Tawwab *et al.* (2018b)**
Plantagoasiatica and *Houttuynia cordata*	*Rachycentron canadum*	10, 20 g kg^{-1}	Induce phagocytosis, respiratory burst, lysozyme activity.	**Wu *et al.* (2016)**
Pontogammarus maeoticus extract	*Rutilus caspicus*	2%	Improve growth performance, feed intake salinity stress resistance, complement and lysozyme activity	**Rufchaei *et al.* (2017)**
Fenugreek (*Trigonella foenum graecum*)	*Sparus aurata*	5 and 10%	Increase haemolytic complement, peroxidase, antiprotease activity, enhance cellular and humoral immune parameters	**Guardiola *et al.* (2018)**

1.3 Enhance immune gene profile

Immune related genes, such as interleukin 1 (IL-1β), interleukin 8 (IL-8), tumour necrosis factor-α (TNF-α), heat shock proteins (Hsp), β-defensins, transforming growth factor-beta (TGF-β) were reported as a defence mechanism and to have a growth-promoting effect. IL-1β, IL-8, and TNF-α are early inflammatory cytokines secreted during inflammation (**Zou & Secombes, 2016**). IL-1β and IL-8 induce host immune response to pathogenic infection and play a pivotal role in invading microbial community that damages tissues and organs causing autoimmune diseases (**Engelsma *et al.,* 2002**), whereas TNF-α is important for rapid cellular proliferation, differentiation, and stimulation of other cytokines (**Wei *et al.,* 2009**).

Several authors revealed that medicinal plants modulate the immune gene profile in various fish species. The up-regulation of IL-1β and TNF-α was found in grass carp (*Ctenopharyngodon idella*) when supplemented with *Ficus carica* polysaccharide at 0.5 and 1.0 % of the basal diet for 21 days (**Yang *et al.,* 2015**). Supplementation of dietary apple cider vinegar (ACV) in zebra fish (*Danio rerio*) diet reflected the induction of gene expression of lysozyme and interleukin 8 (IL-8), whereas no significant changes were found for IL-1β and TNF-α expression level (**Ahmadifar *et al.,* 2019**).

On the other hand, olive leaf (*Olea europea*) showed dose and tissue dependent manner of immune gene expression in rainbow trout (*O. mykiss*). At low level of olive leaf extract, the expression of IL-1β, IL-8, and TNF-α in the spleen tissue was elevated, but higher level showed down regulation of the gene expression (**Baba *et al.,* 2018**). A significant increase in cytokine gene expression including IL-1β, IL-8, IL-10, TGF-β, and IL-12p40 in the head kidney was observed when rainbow trout was fed with caper (*Capparis spinosa*), though the TNF-α was downregulated (**Bilen *et al.,* 2016**). The intramuscular administration of flavonoids in *Heliotropium huascoense* showed induction of TNF-α, IL-1, IFN-α, IFN-γ, and TGF-β1 in the head kidney of Atlantic salmon, whereas flavonoids from *Heliotropium sinuatum* decreased the transcriptional expression of TNF-α, IL-1, and IL-12 (**Valenzuela *et al.,* 2018**). Hence, the effect of medical plants on fish immunity varies with the fish species and their immune organ, type of medicinal plants, and their concentrations.

1.4 Enhance antimicrobial activity

The medicinal plant extracts consisting of antimicrobial properties can be applied for the treatment of certain diseases caused by specific pathogens, including bacteria, viruses, fungi, or parasites (**Harikrishnan *et al.,* 2009**).

1.4.1 Antiviral activity

Lymphocystis disease virus (LDV), viral haemorrhagic septicaemia virus (VHSV), and aquabirnavirus (ABV) are the most frequent viruses that cause severe economic loss to the fish farmers (**Harikrishnan *et al.,* 2010**). Solvent extracts of *Punica granatum* against lymphocystis disease virus (LDV) for eight weeks significantly increase relative percent survival (RPS) in olive flounder (*Paralichthys olivaceus*) (**Harikrishnan *et al.*, 2010**). *Cynodondactylon* was used for the treatment of black tiger shrimp (*Penaeus monodon*) infected with white spot syndrome virus (WSSV), and resulted in neither fatality nor signs of infection compared to control groups, where 100% mortality was observed (**Balasubramanian *et al.*, 2008**).

1.4.2 Antibacterial activity

Several authors displayed the antibacterial functionality of medicinal plants against both gram-positive and gram-negative bacteria (**Van Hai, 2015**). Cinnamon showed an antagonistic effect in the Nile tilapia (*O. niloticus*) against *Aeromonas hydrophila* (**Ahmad *et al.*, 2011**). Extracts of *Punica granatum* was effective against methicillin-sensitive *Staphylococcus aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), *Escherichia coli* O157:H7, *Salmonela typhi*, and some *streptococci* strains (**Rani *et al.*, 2004; Braga *et al.*, 2005**).

1.4.3 Antifungal/antiparasitic activity

Prominent herbs also showed antifungal or anti parasitic effectiveness against certain fungal or parasitic strains in aquaculture. Ethanolic extracts of *Piper guineese* (fruits) and *Xylopia aethiopica* (seeds) showed antifungal activity against the fungus *Candida albicans* (**Okeke *et al.*, 2001**). Datura metal Linn (Thorn -apple) displayed a prominent effect against fungal fish pathogens, being the most active for treating *penicillium restrictum* fungal infection (**Madhuri *et al.*, 2012**).

1.5 Alternative to antibiotics

Previous studies proved that medicinal plants can be used as promising antibiotics for fish species by increasing immune status to resist diseases (**Van Hai, 2015**). *Azadirachta indica* stimulated the primary and secondary antibody responses in *O. mossambicus*, and could be alternative for antibiotics against the infection of *Citrobacter freundii* (**Thanigaivel *et al.*, 2015**). Similarly, *Ocimum sanctum* accelerates antibody production and disease resistance in the Nile tilapia against *A. hydrophila* infection (**Logambal *et al.*, 2000**). *Sargassum duplicatum* and *Sargassum wightii* could be used as a substitute for antibiotics to prevent white spot syndrome virus disease in black tiger prawns (**Immanuel *et al.*, 2010**). For treating enteritis in grass carp, a combination of four herbs could be used as an alternative to antibiotics (**Choi *et al.*, 2014**).

1.6 As quorum sensing inhibitor

Quorum sensing (QS) or Quorum signalling (QS) is the inter and intraspecific communication system of bacteria that allows bacterial adhesion and growth, virulence properties, antibiotic resistance, biofilm maturation, and so on (**Defoirdt *et al.*, 2008**). There has been a growing interest to inhibit QS signalling due to the increasing rate of bacterial drug resistance (**Defoirdt *et al.*, 2008**). A broad spectrum of secondary metabolites (flavonoids, phenols, phenolic acids, saponins, coumarins, tannins, quinones, terpenoids, alkaloids, and polyacetylenes) synthesized by medicinal plants, proved to have a significant effect on the QS system of *Escherichia coli*, *Staphylococcus aureus*, and *Chromobacterium violaceum* (**Bouyahya *et al.*, 2017**). Moreover, the substance of essential oil produced by aromatic plants sustained an active effect against certain bacterial strains of *Salmonella*, *Listeria*, *Pseudomona*s, *Staphylococcus*, and *Lactobacillus* sp. Additionally, extract from the *Terminalia bellerica* plant hindered the QS communication system of *P*. *aeruginosa* (**Ganesh & Rai, 2018**).

FUTURE STUDIES

Medicinal plants possess a complex chemical composition suitable for the treatment of multifactorial diseases, showing potential effects on growth and survival, making plants a suitable alternative to antibiotics (**Srivastava *et al.*, 2014**). However, many antinutritional factors are also found in medicinal plants like tannin, phytic acid, trypsin inhibitor, lectins, saponins, alkaloids, and antigenic compounds (**Mohanta, 2012**). Sometimes the rate of development and feed efficiency in the fish body recorded a decrease due to anti-nutritional, which contain an inappropriate ratio of amino acid (**Hansen & Hemre, 2013**). Therefore, research is necessary to minimize the side effects of antinutritional components and enrich the products for best use.

Several studies explained that the efficiency of different medicinal plants strongly depends on various fish species and additional factors like dosage, method of extraction and types of extracts, route of administration, and other physiological aspects (**Harikrishnan *et al.*, 2011**). Therefore, more studies are required to optimize the dosage application to standardize medicinal plant applications for immune response. Moreover, the effects of medicinal plants on the different life stages of fishes (i.e. fry, fingerlings, juveniles, preadults, and adults) are detected except for infancy. Consequently, future studies are recommended for this aspect.

In conclusion, this review reveals the advantages of medicinal plants in aquaculture as immunostimulants and alternatives to antibiotics, or chemotherapeutic agents. For the sustainability of the growing fish industry, it is vital to find a more feasible and well-developed protocol for using medicinal plants in aquaculture. For the large-scale fish industries, commercially produced medicinal plants are highly recommended.

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