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AQUACULTURE STUDIES

REVIEW

An Extensive Review on the Use of Feed Additives Against Fish Diseases and Improvement of Health Status of Fish in Turkish Aquaculture Sector

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Abstract

Aquaculture is the second-fastest-growing sector in the world after informatics and its. Average growth of aquaculture is annually ~8.8% over the last 30 years. Turkey has great potential in terms of fish production and the number of fish farms started to increase rapidly. Fish production in intensive culture conditions has enlarged possible threats of contagious disease outbreaks due to high stocking densities, water quality or environmental gradient, etc., as well as the combination of all these factors together. Depending on animal husbandry situations and organizational conditions, gradation of the aquatic surroundings and outbreaks of bacteriological diseases may well cause production losses around 30-40% in aquaculture facilities. Some fish diseases reported most repeatedly in Turkish aquaculture facilities are *Vibriosis*, *Furunculosis*, *Streptococcosis, Lactococcosis*, *Aeromonas septicemia*, *Yersiniosis*, *Photobacteriosis* and *Flavobacteriosis*. Antibiotics, disinfectants and chemotherapeutics used for the prevention and treatment of diseases result in residual antibiotics and chemicals in fish products, microorganisms resistant to antibiotics and damages to the aquatic environment and human health. This situation has led researchers to use alternative feed additives in fish diets such as medicinal plant, herbal extracts, phytochemicals, plant secondary metabolites, immunostimulants and probiotics. This review includes research conducted in Turkey between the years 2001 and 2020, and aims to summarize the findings regarding the use of medicinal plant, herbal extracts, phytochemicals, plant secondary metabolites and immunostimulants in fish feed to prevent and treat diseases, improve immunity, increase disease resistance, and reduce stress in fish towards a better management and best aquaculture practice for the sustainability of the growing aquaculture industry in the region and worldwide.

Introduction

Aquaculture represents one of the most commercially traded products in the world food industry, showing an annual increase of nearly ~8.8% over the last 30 years (FAO, 2018). In Turkey, rainbow trout (*Oncorhynchus mykiss*) is the most produced species in inland waters, whereas European sea bass (*Dicentrarchus labrax*) and gilthead sea bream (*Sparus aurata*) production stands out in the marine environment. As of 2019, trout harvest from freshwater and marine facilities yielded 116.053 and 9.692 tons, respectively, whereas sea bream and sea bass harvest from marine cage farms in Turkey reached around 99.730 and 137.419 tons, respectively (TUIK, 2019).

Fish production in intensive culture conditions has enlarged possible threats of contagious disease outbreaks due to high stocking densities, water quality or environmental gradient, underwater acoustic noise beyond ambient audio level from machines in recirculating systems, etc., as well as the combination of all these factors together. Depending on animal husbandry situations and organizational conditions, gradation of the aquatic surroundings and outbreaks of

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bacteriological diseases may well cause production losses around 30-40% in aquaculture facilities. Some fish diseases reported most repeatedly in Turkish aquaculture facilities are *Vibriosis*, *Furunculosis*, *Aeromonas septicemia*, *Streptococcosis, Lactococcosis, Yersiniosis*, *Photobacteriosis* and *Flavobacteriosis*.

Antibiotics and chemotherapeutics are frequently chosen for the control of several infectious diseases in culture systems (Ozturk & Altinok, 2014). There are 41 licenced drugs used in fish farm facilities in Turkey (Yarsan, 2013, Aksit, 2016). Out of these drugs, 15 contain florfenicol, 9 sulfadiazina+trimetoprim, 12 oxytetracycline, 2 enrofloxacin, 2 amoxicillin and 1 oxolinic acid (Yarsan, 2013).

The use of antibiotics and chemotherapeutics in aquaculture facilities is associated with residual complications in the nearby vicinity and the human body, as well as antibiotic-resistant pathogenic strains (Capkin et al., 2017; Yilmaz et al., 2018a). Additionally, resistance may be acquired by genes, which are placed on transportable elements of environmental, human, or other animals (pets)-origin of existing microorganisms that could be transported to the bacteria isolated from fish (Capkin et al., 2015).

Above mentioned detrimental effects have caused global concern in terms of the needs for biologically-safe feeding strategies in fish culture. Hence, fish diets used in aquaculture facilities could be improved with dietary incorporation of immunostimulants, organic acids, herbal extracts, medicinal plant, phytochemicals, plant secondary metabolites, essential oils and probiotics as feed additives. Many reports have documented the effect of β-glucans (Dugenci & Candan, 2001; Sahan & Duman, 2010), levamisole (Ispir & Dorucu, 2005), medicinal plants (Dugenci et al., 2003; Gultepe et al., 2014; Diler et al., 2017a; Akyüz et al., 2018; Almabrok et al., 2018; Amhamed et al., 2018; Diler and Gormez 2019; Yilmaz and Er 2019; Bilen et al., 2020a; Öntaş et al., 2020), plant syrups (Yilmaz et al., 2018b, Yilmaz, 2019c; Yilmaz, 2020), spices (Yilmaz et al., 2013a; Yilmaz et al., 2013c; Yilmaz & Ergun, 2014; Yilmaz et al., 2015a; Yilmaz et al., 2016; Gullu et al., 2016; Altunoglu et al., 2017; Savaşer et al., 2019), natural compounds (Yilmaz et al., 2015b; Acar, 2018a), organic acid (Yilmaz et al., 2019a), mushrooms (Ulukoy et al., 2016), yeast autolysates (Guven and Yalcın 2017), essential and plant oils (Acar et al., 2015; Arslan et al., 2018; Acar, 2018b; Altınterim et al., 2018; Altınterim & Aksu 2019; Acar et al., 2019; Baba et al., 2016b; Kıvrak & Didinen 2017; Diler et al., 2017b; Diler et al., 2017c; Yilmaz, 2019b; Kesbic, 2019a; Kesbic, 2019b; Parrino et al., 2019; Gultepe, 2020; Kesbic et al., 2020b), and anthocyanin (Yilmaz 2019d) as immune stimulators and health improvers in fish species (Table 1).

This study focuses mainly on the effects of different feed additives on fish, with special reference to hematology, serum biochemistry, nonspecific immunity, antioxidant status, stress responses, disease resistance and immune related gene expression. The results of this review are, therefore, aimed to provide remarkable information for the preparation of a "Standard Feed Additive Inoculation Protocol" and focus on several research gaps in fish production that might help to improve feeding strategies towards "Best Aquaculture Practice" for the sustainability of the growing aquaculture industry in Turkey as well as all around the world, both at laboratory and field levels.

Aeromonas spp.

Aeromonas hydrophila and *Aeromonas veronii* are among the bacteria that cause motile *Aeromonas septicemia* in fish (Austin & Austin, 2016). *Camellia sinensis* seed powder (Er & Kayıs, 2015), *Capparis spinosa* methanolic extract (Bilen et al., 2016a), *Avena sativa* water extract (Baba et al., 2016a), *Zingiber officinale* powder (Sahan et al., 2016), *Anethum graveolens* and *Lepidium sativum* methanolic extracts (Bilen et al., 2018), *Malva sylvestris* methanolic extract (Bilen et al., 2020b) and *Pleurotus ostreatus* methanolic extract (Bilen et al., 2016b) were administered to fish diets and found to increase protection against *A. hydrophila* (Table 2). Considering these earlier reports in terms of ecological approach (non-metanolic extraction) and the best RPS values, *Avena sativa* water extract (Baba et al., 2016a) with a value of 67 RPS and *Camellia sinensis* seed powder (Er & Kayıs, 2015) with a value of 100 RPS are remarkable ones.

There was merely one report showing 5 g/kg of caffeic acid supplement diets, adequately improved the enhanced nonspecific immune responses, up-regulated the immune and antioxidant related genes and disease resistance of fish against *A. veronii* (with a value of 57.89 RPS) in Turkey (Yilmaz, 2019a).

Yilmaz et al. (2020a) reported that L-alliin and oleuropein improved serum biochemistry parameters and immunological parameters of rainbow trout. Similary, Yilmaz et al. (2020c) investigated the nonspecific immune responses, health status and effect on growth performance of fish by testing black mulberry syrup in tilapia. The authors confirmed the highest RPS value (68.75%) in the fish fed with black mulberry syrup by 2%.

Aeromonas salmonicida are known as the causative agent of furunculosis. Yonar et al. (2019) reported that the curcumin powder administration, especially at 2% and 4%, effectively enhanced the nonspecific immune responses and disease resistance to *A. salmonicida* subspecies *achromogenes* in rainbow trout, and the highest RPS value (76.67%) was determined in the group fed with curcumin powder feed contribution by 2%.

Streptococcus spp.

Streptococcal disease is caused by three major species of facultative anaerobic encapsulated Gram-positive streptococci. *Streptococcus iniae*, *S. agalactiae* and *S. dysgalactiae* are in charge of disease in more than 30 freshwater, estuarine and marine fish species worldwide (Lee, 2015). *Streptococcus iniae* is perhaps the most significant because of its virulence across a broad range of hosts, global distribution, economic impact and zoonotic risk (Agnew et al., 2007; Gauthier, 2015).

Yilmaz et al. (2013b) indicated that rosemary, thyme or fenugreek powders increased disease resistance against *Streptococcus iniae* in tilapia fry (Table 3).

In another study, cumin can be used as a feed additive as an immunostimulant during feeding of Mozambique tilapia (*Oreochromis mossambicus*) and it can be recommended as an alternative to antibiotics to control streptococcal disease in tilapia culture (Yilmaz et al., 2012; Yilmaz et al., 2013c).

A different study revealed that the management of 400 mg/kg *Tribulus terrestris* extract, which are rich in flavonoids in a diet for Mozambique tilapia fry for 45 days and they improved disease resistance against *S. iniae* (Yilmaz et al., 2014).

Similarly, Yilmaz and Ergun (2014) stated that pimenta can be used as a substitute to antibiotics in the control of streptococcal disease in tilapia culture. The highest survival rate (80%) was recorded in 10 g/kg pimenta powder fed fish, and the lowest survival rate (38%) was recorded in fish fed the control feed. Acar et al. (2015) reported that the highest RPS value (51.92) was found in the fish fed 1% sweet orange peel (*Citrus sinensis*). In addition, a plenty of studies have been reported on the use of feed additive against *Streptococcus* spp. infection (Table 3).

Vibrio anguillarium

Disases that are caused by *Vibrio* spp. are known to influence a wide range of wild and farmed fish species around the world, with reports in marine and brackish water environments, as well as in freshwater conditions (Woo & Bruno, 2017; Gudding et al., 2014). *V. anguillarium* affects more than 50 diverse saltwater and freshwater fish species worldwide (Frans et al., 2011). Increased disease resistance against *V. anguillarium* was found in rainbow trout, gilthead seabream and European seabass when fed diets supplemented with *Vaccinium myrtillus*, *Glycyrrhize glabra*, *Echinacea angustifolia* (Terzioglu & Diler, 2016), *Salvia officinalis*, *Origanum vulgare* (Diler et al., 2017c), and *Artemisia vulgaris* (Diler et al., 2018a), respectively (Table 4). Among these studies, the best RPS value with 66.67% at the end of experimental infection with *V. anguillarum* was detected in fish fed diets containing *Cotinus coggygria* leaf powder (Bilen et al., 2013).

Yersinia ruckeri

Infection with *Yersinia ruckeri*, a member of the family Enterobacteriaceae causes Yersiniosis in fish. The term "yersiniosis" is identical with enteric redmouth disease (ERM), a disease of fish caused by overt infection with *Y. ruckeri*.

ERM was first reported in the late 1950s when it was affecting rainbow trout in the Hagerman Valley of Idaho (Woo & Bruno, 2017). Yersiniosis is now endemic across all the major salmonid farming areas of the world (Horne & Barnes, 1999).

Gulec et. al., (2013) reported that dietary supplementation with thyme and fennel oils increased disease resistance in rainbow trout against *Y. ruckeri* (Table 5).

The oral administration of trans-cinnamic acid for 60 days in rainbow trout diet enhanced the haematological, serum biochemical and non-specific immune responses, improved immune-related gene expression as well as increased disease resistance (with a value of 50 RPS) against *Y. ruckeri* (Yilmaz & Ergun, 2018).

Similarly, the highest RPS value (42.09%) was detected in the group with 20% rosehip (*Rosa canina*) added (Sahan et al., 2017). It was observed that olive leaf ethanolic extract (Baba et al., 2018), pomegranate seed oil (Acar et al., 2018) and orange peel (Gultepe, 2020) reduced mortality in rainbow trout after challenge with *Y. ruckeri* (Table 5).

Lactococcus garvieae

In 1985, the genus Lactococcus was reported as a separate genus from Streptococcus. The original isolation of the *L. garvieae* was made from bovine mastitis (Schleifer et al., 1985; Teixeira et al., 1996; Collins et al., 1983).

The disease was described as a hyperacute systemic disease in rainbow trout (Eldar & Ghittino, 1999). It can be separated into 3-distinct groups, based on RAPD analysis: Spanish, Portuguese, English and Turkish isolates formed one group, French and Italian formed a second, whilst Japanese formed a distinct third group (Ravelo et al., 2003).

Baba et al. (2017) examined the effects of argan oil, achieved from *Argania spinosa*, on pre- and post-challenge immuno-haematological and biochemical responses of the Nile tilapia (*Oreochromis niloticus*). For this purpose, the fish were comprising fed diets of 0, 0.5%, 1% or 2% argan oil for 45 days and then, fish were challenged with *L. garvieae*. The highest RPS of 52.0% against *L. garvieae* were recorded in the fish fed on argan oil at 1 % (Baba et al., 2017).

In another study with rainbow trout, the effects of the addition of olive pomace oil to assess the antioxidant activity and disease resistance were investigated (Yilmaz et al., 2020b). It was determined that the group fed with on 4% olive pomace oil had the highest RPS (43.86%) (Yilmaz et al., 2020b). Moreover, rainbow trout were fed the different doeses of *O. onites* essential oil (0.125, 1.5, 2.5 and 3.0 mL/kg) for 90 days, and 3.0 mL/kg diet showed no mortality after challenged with *L. garvieae* (Diler et al., 2017b).

Similarly, RPS values 55% was reported in study against *L. garvieae* in rainbow trout fed 2 % supplemented *Lentinula edodes* (medicinal mushroom) water extract (Baba et al., 2015) (Table 6).

Edwardsiella tarda

The Edwardsiella (family Enterobacteriacae) was initially recognized as a new genus of the Enterobacteriaceae in the mid-1960s, and characterized 37 isolates recovered from open wounds, blood, urine and faeces of humans and animals (Ewing et al., 1965).

E. tarda has mainly been considered a warm-water, opportunistic fish pathogen. Environmental variables such as high temperature, poor water quality and high organic content contribute to the harshness of infections (Woo & Capriano, 2017). *E. tarda* has also been reported from intensively reared rainbow trout in the Czech Republic (Rehulka et al., 2012). Diseased fish were anorexic and lethargic, having internal hyperaemia and petechial haemorrhages on the liver, with chronic lymphocytic portal hepatitis, focal necrosis, steatosis, dilation of the blood sinuses and activation of sinusoidal cells (Woo & Cipriano, 2017).

Baba et al. (2016b) investigated the effects of citrus lemon peel essential oil on the antioxidant activity and disease resistance (*E. tarda*) of tilapia. The highest RPS value (54.20%) was detected in the group with 0.5% citrus lemon peel essential oil added.

In another study, the effects of the addition of olive leaf ethanolic extract on *C. carpio* feeds on some blood parameters of fish, immune related genes and disease resistance (*E. tarda*) were investigated (Zemheri-Navruz et al., 2019). It was determined that the group with 1% olive leaf extract added had the highest RPS (43.75%). Similarly, the highest survival rate of carp infected with *E. tarda* was found in groups with dill (1 g/kg) and garden cress (2 g/kg) feed additive (Bilen et al., 2018).

Plesiomonas shigelloides, Mycobacterium salmoniphilum and Spironucleus salmonis

Blackberry syrup (Yilmaz 2019c), Rosa canina powder (Duman & Sahan, 2018) and *Artemisia campestris* ethanolic extract (Diler et al., 2018b) were incorporated to fish diets and identified to increase protection against *Plesiomonas shigelloides*, *Mycobacterium salmoniphilum* and *Spironucleus salmonis*, respectively (Table 8). Duman and Sahan (2018) found the highest RPS value as 47.61% in the group with 15% *Rosa canina* powder addition. Diler et al. (2018b) determined the highest RPS value as 87.50% in the 1 g/kg *A. campestris* (L) ethanol extract incorporation group, which determined the *in vivo* antiparasitic activity of *Artemisia campestris* (L) plant ethanol extract on Spironucleosis (Hexamitiasis) infections seen in rainbow trout.

Conclusion and Perspectives

Until recent years, antibiotics have been used as a feed additive that encouraged development in fish feed quality, and the use of antibiotics as a substance that promotes development has been banned in EU countries including Turkey. Many products considered as alternatives to antibiotics have been investigated. Result from intensive research challenges provide strong and reliable evidences that medicinal plants, herbal extracts, phytochemicals, plant secondary metabolites, immunostimulants, probiotics etc., are available in place of antibiotics in the fish diets. The positive effects of these additives especially killing pathogenic microorganisms stands in their strong ability of developing in the digestive organs, inhibiting the development of toxins in feed, increasing the activity of digestive enzymes, strengthening the immune system and, as a result, improving the growth performance and disease resistance of fish.

The exponential increase of the aquaculture industry is undeniable. As a result of the growing pressure from intensive production, environmental load from biogenic wastes such as organic waste and inorganic nutrients is likely to increase remarkably in the near future. Hence, using alternative feed additives with higher nutrient utilization efficiency might help to reduce waste load into the environment that in terms may support best aquaculture practice in long run.

As a result of this review, important information has been presented regarding the use of medicinal and aromatic plants as fish feed additives. Fish feed producers may encounter difficulties in accessing to medicinal or aromatic plants. In Turkey, there is a wide variety of medicinal and aromatic plants, a good source of feed additives with significantly strong antimicrobial and antioxidant effects. Approximately 6% of the world's medicinal and aromatic plants are naturally grown in Turkey and the production of 72 different kinds of medicinal and aromatic plants such as thyme, rosemary, garlic, sumac, ginger, turmeric, mint, etc is supported by the Turkish Agriculture and Rural Development Support Institution.

In the light of this information, feed companies are encouraged to benefit from medicinal and aromatic plants, which are abundant in Turkey, easily accessible at affordable prices, and whose effectiveness on fish health and welfare has been proven by intensive scientific studies.

Ethical Statement

No ethical statement required.

Funding Information

No funding required.

Table 1. The role of beneficial feed ingredients supplemented to fish feed in Turkey at laboratory and field levels

Additives	Fish species	Initial body weight	Stocking density (kg/m³)	Doses and supplementation duration	Results	References
Extracts, powders, organic acids						
Viscum album, *Urtica dioica* and *Zingiber officinale* (aqueous extract)	*O. mykiss*	41 g	0.82	0.1 and 1%, 3 weeks	NSIRs ↑	Dugenci et al. (2003)
Thymus vulgaris, *Rosmarinus officinalis* and *Trigonella foenum graecum L.* (powders)	*D. labrax*	20.43±0.03 g	2.48	1%, 45 days	HS ↑	Yilmaz et al. (2013a)
	D. labrax	20.4±0.1 g	2.47	1%, 45 days	NSIRs ↑ and HS ↑	Yilmaz et al. (2016)
Tribulus terrestris (extract)	*O. niloticus*	2.61±0.35 g	6.26	200, 400, 600 mg/kg, 88 days	HS ↑ and NSIRs ↑	Gultepe et al. (2014)
Pimenta dioica (powder)	*O. mossambicus*	20.05±0.10 g	4.51	5, 10, 15, 20 g/kg, 60 days	NSIRs ↑, HS ↑ and ASS ↓	Yilmaz et al. (2015a)
	O. mossambicus	16.05±0. 08 g	3.61	5, 10, 15, 20 g/kg, 60 days	HS ↑ and NSIRs ↑	Gullu et al. (2016)
Carvacrol	*O. mykiss*	10.79±0.57	0.44	1, 3, 5 g/kg, 60 days	HS ↑ and NSIRs ↑	Yilmaz et al. (2015b)
Artemisia vulgaris (powder and ethanolic extract)	*O. mykiss*	21 g	1.10	Powder: 0.1, 0.5, 1, 2% Extract: 250, 1000 mg/kg, 90 days	AS ↑	Diler et al. (2017a)
Black cumin (methanolic extract)	*O. mykiss*	15.02±0.01 g	1.00	0.1 and 0.5 g/kg, 30 days	NSIRs ↑	Altunoglu et al. (2017)
Tilia tomentosa (methanolic extract)	*C. carpio*	4.35 ± 0.16 g	no information available	0.01, 0.05, 0.1%, 45 days	NSIRs ↑	Almabrok et al. (2018)
Chenopodium album (methanolic extract)	*C. carpio*	2.4±0.1 g	0.87	0.5, 0.1, 1 g/kg, 45 days	NSIRs ↑	Amhamed et al. (2018)
Propolis (ethanolic extract)	*O. mossambicus*	15.43±0.16 g	6.17	2 and 4 g/kg, 60 days	NSIRs ↑	Acar (2018a)
Cherry laurel (*Laurocerasus officinalis* Roem.) leaf extract	*O. mykiss*	6.05±0.03 g	0.045	1, 5, 10, 15 g/kg, 52 days	SR ↑, AS↑	Akyüz et al. (2018)
root powder	*O. mykiss*	108.7±17.0 g	no information available	0.0, 0.5, 1.0, 2.5, 5.0, 10.0 and 20.0 g/kg	HS ↑, NSIRs ↑	Savaşer et al. (2019)
Cinnamic acid	*O. mykiss*	17.49±0.08 g	3.74	250, 500, 750, 1500 mg/kg, 60 days	AGER ↑, AS ↑, HS↑	Yilmaz et al. (2019a)
Artemisia campestris and *A. absinthium* (ethanolic extracts)	*O. mykiss*	1.5-2 g	0.86	1, 2, 3 g/kg, 21 days	IM ↑	Diler & Gormez (2019)
Fig and rosemary extract	*O. mykiss*	12.47±0.15	0.34	0.5, 1, 2 g/kg, 60 days	HS ↑	Yilmaz & Er (2019)
Melissa officinalis (extract)	*O. mykiss*	12.04±0.71 g	0.35	0.1, 0.5, 1 g/kg, 75 days	HS ↑, NSIRs ↑	Bilen et al. (2020a)
Crocus cancellatus subsp. mazziaricus (Herbert) Mathew extract	*D. labrax*	130±3.5 gr	No information available	0.5 mg/fish, 2 mg/fish	NSIRs ↑	Öntaş et al. (2020)
Fruits and Plants Syrups						
Carob syrup	*O. mossambicus*	30.70±1.58 g	6.57	0.625, 1.25, 2.5, 5%, 60 days	HS ↑ and NSIRs ↑	Yilmaz et al. (2018b)
Carob syrup	*O. niloticus*	3.68±0.092 g	0.78	0.625, 1.25, 2.5, 5%, 60 days	NSIRs ↑, HS ↑, IRGER ↑, AGER ↑ and AMS ↑	Yilmaz (2020)
Fruit pigments						
Anthocyanin	*O. niloticus*	8.24±0.64 g	1.76	20, 40, 80, 160 mg/kg, 60 days	IRGER ↑, AGER ↑, AS ↑, NSIRs ↑ and AMS ↓	Yilmaz (2019d)
Essential oils and plant oils						
Rosmarinus officinalis	*O. mykiss*	10.14±0.06 g	0.72	0.025, 0.05 and 0.1%, 60 days	NSIRs ↑	Kıvrak & Didinen (2017)
Lavandula stoechas (oil)	*C. carpio*	10.88±0.90 g	2.33	5 and 10 g/kg, 60 days	HS ↑	Yilmaz (2019b)
Juniper berry (oil)	*C. carpio*	3.07±0.15 g	2.30	5 and 10 mL/kg, 60 days	HS ↑	Kesbic (2019a)
Cinnamon (oil)	*O. mykiss*	10.68±0.35 g	1.60	1, 2, 4, 10 mL/kg, 60 days	HS ↑	Kesbic (2019b)
Hot pepper (oil)	*O. mykiss*	~7 g	no information available	1, 2, 4, 6‰, 60 days	HS ↑	Parrino et al. (2019)
Hypericum perforatum (oil)	*C. carpio*	3.07±0.02 g	2.30	5 and 10 g/kg, 60 days	HS ↑	Acar (2018b)
Vitis vinifera seed (oil)	*O. mykiss* (fry)	30 g	1.2	250, 500, 1000 mg/kg, 60 days	HS ↑, AS ↑ and SR ↑	Arslan et al. (2018)
Green tea (*Camellia sinensis*) oil	*O. mykiss*	76.25±2.75 g	no information available	0.25, 0.5, 1.0 %, 42 days	NSIRs ↑	Altınterim al.(2018)
Allium sativum Limne, *Allium tuncelianum Kollman* oils	*O. mykiss*	39.0±1.64 g	9.75	2%	NSIRs↑, NBT ↓	Altınterim & Aksu (2019)

Table 1 *Continued*

Additives	**Fish species**	**Initial body weight**	**Stocking density (kg/m³)**	**Doses and supplementation duration**	**Results**	**References**
Bergamot peel oil	*D. labrax*	5.10±0.05 g	2.04	0.5, 1, 2%, 60 days	NSIRs ↑	Acar et al. (2019)
	O.niloticus	2.57±0.06 g	2.45	0.5, 1, 2%, 8 weeks	NSIRs ↑ and HS ↑	Kesbic et al. (2020a)
Monterey cypress Leaf essential oil	*C.carpio*	7.86±0.15 g	1.96	0.5, 0.75, 1%, 60 days	HS ↑	Kesbic et al. (2020b)
Mushrooms						
Lentinula edodes (water extract)	*O. mykiss*	56.2±6.6 g	11.94	1 and 2%, 6 weeks	Reduce lipid in liver	Ulukoy et al. (2016)
Yeast autolysates						
Saccharomyces cerevisiae	*O. mykiss*	35 g	0.7	0.1 and 0.2%, 8 weeks	NSIRs ↑ and HS ↑	Guven & Yalcın (2017)
β-glucans						
MacroGard	*O. mykiss*	54 g	1.59	0.1 and 1%, 3 weeks	NSIRs ↑	Dugenci & Candan (2001)
β-1,3/1,6 glucan	*O.niloticus*	25.61±0.03 g	0.3	0.1 and 0.5%, 2 weeks	NSIRs ↑	Sahan & Duman (2010)
Levamisole						
	O. mykiss	99.4 and 216.0g	6.27 and 13.64	5 mg/kg fish (intraperitonally), 14 days	NSIRs ↑	Ispir & Dorucu (2005)

AGER=antioxidant gene expression responses; AMS=ammonia stress; AS=antioxidant status; ASS=acidic stress; HS=health status; IM=modulation of intestinal morphology; IRGER=immune related gene expression responses; NSIRs=non-specific immune responses; SR=survival rate

Table 2. Studies addressing beneficial uses of fish feed additives against *Aeromonas* spp.

Additives	**Fish species**	**Initial body weight**	**Stocking density (kg/m³)**	**Doses and supplementation duration**	**Results**	**References**
Extracts, powders, organic acids, compounds						
Camellia sinensis (seed powder)	*O. mykiss*	10±0.12g	4	10%, 10 days	DR to *A. hydrophila*	Er and Kayıs (2015)
Capparis spinosa (methanolic extract)	*O. mykiss*	12.04±0.71 g	0.80	0.1 and 0.5 g/kg, 30 days	IRGER ↑, NSIRs ↑ and DR to *A. hydrophila*	Bilen et al. (2016a)
Avena sativa (water extract)	*C. carpio*	9.91±1.52 g	3.56	5, 10, 20 g/kg, 60 days	NSIRs ↑ and DR to *A. hydrophila*	Baba et al. (2016a)
Pleurotus ostreatus (methanolic extract)	*O. mykiss*	10.28±0.1 g	1.03	0.1 and 0.5 g/kg, 30 days	NSIRs ↑ and DR to *A. hydrophila*	Bilen et al. (2016b)
Zingiber officinale powder	*O. niloticus*	25.61±0.03 g	0.12	0.1, 0.5, 1%, 90 days	HS ↑, AS ↑ and DR to *A.hydrophila*	Sahan et al. (2016)
Anethum graveolens and *Lepidium sativum* (methanolic extract)	*C. carpio*	3.46±0.1 g	1.76	1 and 2 g/kg, 45 days	NSIRs ↑, and DR to *A. hydrophila*	Bilen et al. (2018)
Caffeic acid	*O. niloticus*	17.49±0.08 g	3.74	1, 5, 10 g/kg, 60 days	NSIRs ↑, IRGER ↑, AGER ↑, AS ↑, HS ↑ and DR to *A. veronii*	Yilmaz (2019a)
Curcumin (powder)	*O. mykiss*	31.29±1.17 g	1.44	1, 2, 4%, 8 weeks	HS ↑, NSIRs ↑, AS ↑ and DR to *Aeromonas salmonicida* subsp. *achromogenes*	Yonar et al. (2019)
L-alliin and Oleuropein	*O. mykiss*	12.6±0.91 g	2.57	10 mg/kg, 60 days	HS ↑ and DR to *A.salmonicida*	Yilmaz et al. (2020a)
Malva sylvestris (Methanolic extract)	*O. mykiss*	54.97±0.03 g	3.66	0.1 and 0.5 g/kg, 30 days	NSIRs ↑, IRGER ↑, DR to *A. hydrophila*	Bilen et al. (2020b)
Fruits and Plants Syrups						
Black mulberry syrup	*O. niloticus*	9.74±0.9 g	2.08	0.75, 1.5, 2.0, 3.0%, 60 days	NSIRs ↑, HS ↑, IRGER ↑, and DR to *A. veronii*	Yilmaz et al. (2020c)

AGER=antioxidant gene expression responses; AS=antioxidant status; DR=disease resistance; HS=health status; IRGER=immune related gene expression responses; NSIRs=non-specific immune responses

Table 3. Studies addressing beneficial uses of fish feed additives against *Streptococcus spp.*

Additives	Fish species	Initial body weight	Stocking density (kg/m³)	Doses and supplementation duration	Results	References
Extracts, powders						
Cuminum cyminum	*O. mossambicus*	0.56±0.02 g	0.015	0.5, 1, 1.5, 2%, 75 days	DR to *S. iniae*	Yilmaz et al. (2012)
	O. mossambicus (fry)	0.012±0.001 g	0.02	0.5, 1, 1.5, 2%, 45 days	DR to *S. iniae*	Yilmaz et al. (2013c)
Thymus vulgaris, *Rosmarinus officinalis* and *Trigonella foenum graecum L.* (powders)	*O. mossambicus* (fry)	0.012±0.001 g	0.02	1%, 45 days	DR to *S. iniae*	Yilmaz et al. (2013b)
Tribulus terrestris (extract)	*O. mossambicus* (fry)	0.0120 g	0.02	200, 400, 600, 500 mg/kg, 45 days	PRHD ↓ and DR to *S. iniae*	Yilmaz et al. (2014)
Pimenta dioica (powder)	*O. mossambicus* (fry)	0.012 g	0.02	5, 10, 15, 20 g/kg, 50 days	DR to *S. iniae*	Yilmaz and Ergun (2014)
Essential oils						
Sweet orange peel	*O. mossambicus*	0.91±0.03 g	0.56	0.1, 0.3, 0.5%, 90 days	NSIRs ↑ and DR to *S. iniae*	Acar et al. (2015)

DR=disease resistance; NSIRs=non-specific immune responses; PRHD=pathogen related histological damage

Table 4. Studies addressing beneficial uses of fish feed additives against *Vibrio anguillarium*

Additives	Fish species	Initial body weight	Stocking density (kg/m³)	Doses and supplementation duration	Results	References
Extracts, powders, essential oil						
Cotinus coggygria leaf powder	*C. carpio*	4.14±0.08 g	1.81	0.5, 1, 1.5 g/kg 4 weeks	NSIRs ↑ and DR to *V. anguillarum*	Bilen et al. (2013)
Artemisia vulgaris (powder and ethanolic extract)	*O. mykiss*	20.48±0.19 g and 20.81±0,04 g	0.35 and 0.36	Powder: 0.1, 0.5, 1, 2% Extract: 250, 1000 mg/kg, 45 days	NSIRs ↑ and DR to *V. anguillarum*	Diler et al. (2018a)
Vaccinium myrtillus, Glycyrrhize glabra, Echinacea angustifolia and *Salvia officinalis*	*O. mykiss*	15±2 g	1.28	0.1 and 1%, 45 days	NSIRs ↑ and DR to *V. anguillarum*	Terzioglu and Diler (2016)
Cotinus coggygria and *Malva sylvestris* (methanolic extract)	*S. aurata* and *D. labrax*	19.92±0.40 g and 18.66±0.86 g	1.10 and 1.03	500, 1000 mg/kg, 60 days	NSIRs ↑ and DR to *V. anguillarum*	Bilen et al. (2019)
Origanum vulgare L. essential oil	*O. mykiss*	26 g	0.45	0.125, 1.5, 2.5, 3.0 ml/kg, 90 days	DR to *V. anguillarum*	Diler et al. (2017c)

DR=disease resistance; NSIRs=non-specific immune responses;

Table 5. Studies addressing beneficial uses of fish feed additives against *Yersinia ruckeri*

Additives	Fish species	Initial body weight	Stocking density (kg/m^3)	Doses and supplementation duration	Results	References
Extracts, powders, oils						
Thyme and Fennel oils	*O. mykiss*	84±1.02 g	5.6	10 mL/100 g, 1 week	HS ↑ after *Y. ruckeri* infection	Gulec et al. (2013)
Rosa canina powder	*O. mykiss*	50 to 60 g	2.5 to 3	10, 20, 30%, 50 days	HS ↑, AS ↑, NSIRs ↑ and DR to *Y.ruckeri*	Sahan et al. (2017)
Pomegranate seed (oil)	*O. mykiss*	6.79±0.02 g	2.71	0.5, 1, 2%, 60 days	HS ↑ and DR to *Y. ruckeri*	Acar et al. (2018)
Olive leaf (ethanolic extract)	*O. mykiss*	51.22±3.04 g	5.48	0.1, 0.25, 0.5, 1%, 60 days	IRGER ↑, NSIRs ↑, HS ↑ and DR to *Y. ruckeri*	Baba et al. (2018)
Cinnamic acid	*O. mykiss*	17.01±0.05 g	3.64	250, 500, 750, 1500 mg/kg, 60 days	NSIRs ↑, IRGER ↑, HS ↑ and DR to *Y. ruckeri*	Yilmaz and Ergun (2018)
Orange peel essential oil	*O. mykiss*	4.48±0.03 g	2.46	0.5, 1, 3 mL/kg, 90 days	NSIRs ↑, HS ↑, DR to *Y. ruckeri*	Gultepe, (2020)

AS=antioxidant status; DR=disease resistance; HS=health status; IRGER=immune related gene expression responses; NSIRs=non-specific immune responses

Table 6. Studies addressing beneficial uses of fish feed additives against *Lactococcus garvieae*

Additives	Fish species	Initial body weight	Stocking density (kg/m^3)	Doses and supplementation duration	Results	References
Plant oils, essential oils						
Argan oil	*O. mykiss*	18.31±0.10 g	6.59	0.5, 1, 2%, 45 days	NSIRs ↑ and DR to *L. garvieae*	Baba et al. (2017)
Olive pomace oil	*O. mykiss*	12.10±0.13 g	2.59	4, 8, 12%, 60 days	HS ↑ and DR to *L. garvieae.*	Yilmaz et al. (2020b)
Origanum onites essential oil	*O. mykiss*	26.05±0.15 g	5.21	0.125, 1.5, 2.5, 3 mL/kg, 90 days	DR to *L. garvieae*	Diler et al. (2017b)
Mushrooms						
Lentinula edodes (water extract)	*O. mykiss*	20 g	0.6	1 and 2%, 6 weeks	NSIRs ↑ and DR to *L. garvieae*	Baba et al. (2015)

DR=disease resistance; HS=health status; NSIRs=non-specific immune responses

Table 7. Studies addressing beneficial uses of fish feed additives against *Edwardsiella tarda*

Additives	Fish species	Initial body weight	Stocking density (kg/m³)	Doses and supplementation duration	Results	References
Extracts						
Anethum graveolens and *Lepidium sativum* (methanolic extract)	*C. carpio*	3.46±0.1 g	1.76	1 and 2 g/kg, 45 days	NSIRs ↑, and DR to *E. tarda*	Bilen et al. (2018)
Olive leaf (ethanolic extract)	*C. carpio*	15.90±0.93 g	0.318	0.1, 0.25, 0.5, 1%, 60 days	IRGER ↑, NSIRs ↑, HS ↑ and DR to *E. tarda*	Zemheri-Navruz et al. (2019)
Essential oils						
Citrus limon peel	*O. mossambicus*	12.87±0.18 g	6.43	0.5, 0.75, 1%, 60 days	NSIRs ↑, HS ↑ and DR to *E. tarda*	Baba et al. (2016b)

DR=disease resistance; HS=health status; IRGER=immune related gene expression responses; NSIRs=non-specific immune responses

Table 8. Studies addressing beneficial uses of fish feed additives against *Plesiomonas shigelloides, Mycobacterium salmoniphilum and Spironucleus salmonis*

Additives	Fish species	Initial body weight	Stocking density (kg/m³)	Doses and supplementation duration	Results	References
Powders, Extracts						
Rosa canina powder	*A.gueldenstaedtii*	307.8±11.4-g	1.53	5, 10, 15%, 35 days	NSIRs ↑ and DR to *M. salmoniphilum*	Duman and Sahan (2018)
Artemisia campestris (ethanolic extract)	*O. mykiss*	1.5-2.0 g	0.18	1.0, 1.5, 2.0, 2.5, 3.0 g/kg, 7 and 21 days	DR to *S. salmonis*	Diler et al. (2018b)
Fruits and Plants Syrups						
Blackberry syrup	*O. niloticus*	26.75±2.67 g	5.73	7.5, 15, 30 g/kg, 90 days	NSIRs ↑, IRGER ↑, AGER ↑, AS ↑ and DR to *P. shigelloides*	Yilmaz (2019c)

AGER=antioxidant gene expression responses; AS=antioxidant status; DR=disease resistance; IRGER=immune related gene expression responses; NSIRs=non-specific immune responses

Author Contribution

Authors shared equally in this work. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors declare that they have no conflict interest.

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