doi: 10.30495/MEDHERB.2021.687324

Journal of Medicinal Herbs

journal homepage:**www.jhd.iaushk.ac.ir**

Effects of Echinacea on fish growth and health: A review

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ARTICLE INFO

Type: *Review Article*
Topic: *Medicinal Plants*
Received *September15th 2021*
Accepted *December 29th 2021*

Key words:
- ✓ *Echinacea*
- ✓ *Fish*
- ✓ *Herbal medicine*
- ✓ *Immunostimulation*

ABSTRACT

Background & Aim: Fish, having a vast role in providing sufficient protein for most humans across the globe, requires strict standards and quality assurance. Disease prevalence in fish farms has been an obstacle considered by many farmers. Various synthetic therapeutics such as antibiotics and chemical substances exist vastly in the market and are constantly used for disease prevention. Nevertheless, chemicals come along with a set of drawbacks putting both fish and human health in danger.
Experimental: In this study, we discussed and reviewed the chemical composition as well as the benefits of Echinacea as a natural growth promoter and an immunostimulant in aquaculture. We reviewed 31 different studies conducted on a variety of fish. Biological activities, following the administration of different levels of Echinacea, were discussed as well.
Results: A variety of functions had been reported for Echinacea species. These properties were classified into growth increase, disease resistance, antioxidant and immunostimulating effects, along with the promotion of blood biochemical parameters.
Recommended applications/ industries: Based on the reviewed literature, Echinacea could improve growth and immunity in cultured fish. Using natural compounds instead of chemicals could substantially help create sustainable aquaculture.

1. Introduction

The world population is continually increasing at incredible speeds. The United Nations predicts the world population to reach 9.7 billion people within the next 30 years (Abdelkhalek *et al*., 2015). With the increase of the human population, the requirement for sustainable food has become eminent. Amongst the various food sources, aquaculture is considered to play a determinant role in providing healthy food. According to the Food and Agriculture Organization of the United Nations, Seafood currently accounts for 3.3 billion people's dietary intake in which fish construct 20 percent of their average per capita animal protein consumption (Alinezhad, 2019). The demand for dietary aquaculture has increased significantly in the past 20 years. A 5-fold increase indicates the need for greater production and demand of the aquaculture industry. This demand for food from marine and inland waters recorded 114.5 million tons of aquaculture in 2018. It is estimated that this number will project to 200 million tons by 2030 (FAO, 2020).

Producing aquaculture in large quantities opens the doors to various risk factors, including disease. A broad spectrum of pathogenic agents, including bacteria, viruses, and other infectious agents, are present and found everywhere. Numerous countermeasures have been accounted for, including vaccines, antibiotics, and other biochemical substances which inhibit pathogen-organism interactions (Alishahi *et al.*, 2012;Raissy *et al.*, 2015; Akbary *et al.*, 2016; Yu, 2020; Kamalii, 2018;Yang, 2020). However, strict limitations are present to implement anti-pathogenic measures. Vaccinating fish requires extensive labour and is occasionally nonpractical in cases of mutation. On the other hand, antibiotic use can cause pathogenic resistance leading to mutations and ultimately neutralizing the effects of the therapeutics (Aly and Mohamed, 2010). Not to mention, the toxicity that occurs in such methodology represents a major environmental and biological hazard. Having acknowledged such, the primary solutions that farmers seek are antibiotics and chemical substances. In recent findings, it has been estimated that approximately 10 259 tons of antibiotics were consumed for aquaculture. This number is expected to increase to 13 600 tons by 2030 (Alinezhad, 2019). Thus, immediate anti-pathogenic approaches increase risk and can cause a series of undesirable hazards. Therefore, new approaches are needed to promote aquaculture while considering environmental conditions.

Several substances are known to increase immune response amongst fish and lead to a stronger and more efficient defense system against pathogens. These immunostimulant products include bacterial cell wall fragments, ß-1,3 glucans of yeast and mycelial fungi, peptides, and medicinal herbs (Aly *et al.*, 2016). Echinacea, a genus from the herbaceous flowering plant, has been reported in many studies to have immunostimulant effects in fish species (Aly and Mohamed, 2010; Aly *et al.*, 2016). It has three species, including *E. purpurea*, *E. angustifolia*, and *E. pallida* found in parts of the United States, Canada, and Europe, especially in Germany (Barrett, 2003). The attempts to use Echinacea as an immunostimulant were first seen in 1913 on Guinee pigs, where researchers observed an increase in phagocytosis of the tuberculosis bacteria (Barrett, 2003). Other studies on rats and birds have also signified similar results (Bauer and Wagner, 1993; Boshra *et al.*, 2006). Also, the effects of this herb in aquatic animals, including a variety of fish, have shown promising results (Rahman *et al.*, 2018).

Physiological mechanisms of Echinacea include growth increase, immunomodulatory effects such as the increase in phagocytosis, polymorphonuclear (PMN), leukocyte population and natural killer (NK) cells, variation in T- and B-cell leukocytes, and carbon clearance (Barrett, 2003; Oniszczuk *et al.*, 2019). Supplying the diet of fish with this potent substance is proved to increase the fish's health status, survival, and quality of life. Therefore, not only would this be beneficial to farmers and the aquaculture industry, but in fact would make for a higher quality food product for consumers. This review elucidates physical and chemical properties as well as the practical applications of Echinacea in aquaculture.

2. Herbology

Echinacea purpurea, which belongs to the Asteraceae family, is also known as purple coneflower. This perineal herb is native to North America; however, it can be observed worldwide. *E. purpurea* has been used amongst the native people of North America as a therapeutic for infections, trauma, inflammation, and fever. Most of the plants' immunostimulatory substances exist in the root (El-Sayed *et al.*, 2014). The plant's roots consist of two branches, the main branch and the secondary branch, each varying in diameter. The Echinacea leaf holds a variety of chemical substances, including flavonoids such as Luteolin, Kaempferol, Quercetin (El-Sayed *et al.*, 2014).

Throughout history, Echinicea has been sought for a variety of therapeutic reasons, including antitoxin, infections such as syphilis, and many more (Hobbs 1994; Mills and Bone 2000). Echinicea was once introduced as a therapeutic for viral and bacterial infections, furunculosis (nodules within theskin that constantly reoccur), boils, and abscesses (British Herbal Medicine Association 1990; Bradley 1992; Tyler 1993; Williamson 2003). Nasopharyngeal catarrh, pyorrhoea (periodontitis),and tonsillitis were other examples of Echinicea being vigorously used as an assistive treatment infection similar to influenza and reoccurring urinary and respiratory tract infections. On the other hand, Echinicea was used superficially to healcuts and wounds to the skin. (British Herbal Medicine Association, 2003). The constant growth of studies and research on Echinacea is considerable. An increase of scientific publications regarding Echinacea has been seen by Bibliometric studies on a year-by-year basis (Yu, 2004).

3. Mechanism of action

Polysaccharides, glycoproteins, alkamides, and cichoric acid are considered active ingredients in Echinicea (Fig. 1). Numerous biological activities have been attributed to a derivative of the plant called Cichoric acid B-lymphocyte and macrophage proliferation, TNF-, and interleukin one have been seen to be stimulated by arabinogalactan containing glycoproteins and chichoric acid inanimal and in vitro studies (Bodinet and Beuscher, 1991; Parnham, 1996).

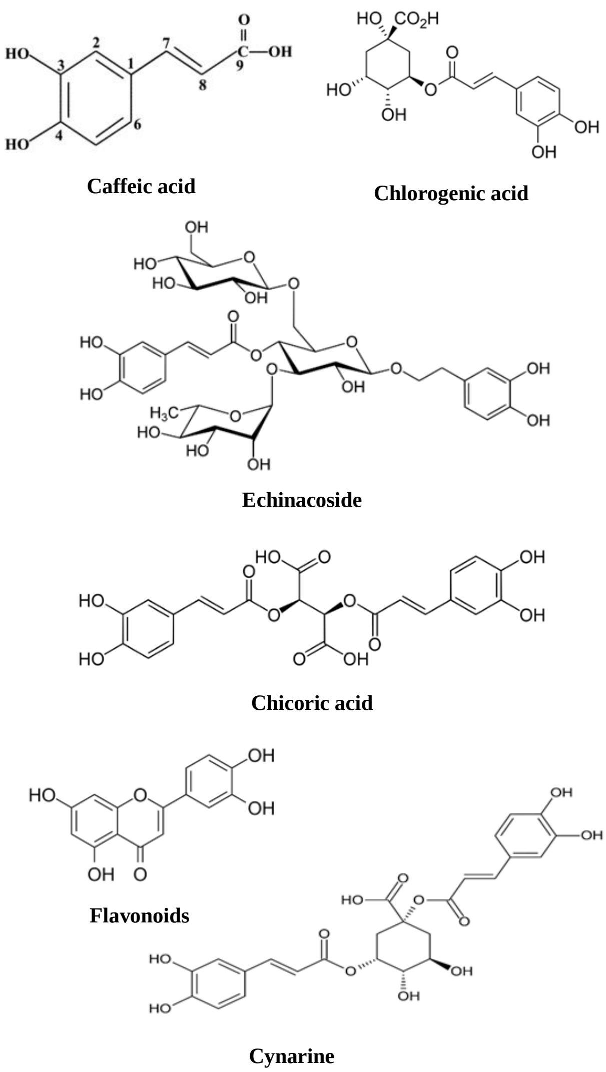

Fig. 1. Active ingredients present in Echinacea.

Antiviral and fungal measures have been reported by categories of Phenolic compounds and alkamides (Binns *et al*., 2002a; Merali *et al*., 2003). Manayi *et al.* (2015) pointed out that alkamides, ketoalkenes, caffeic acid derivatives, polysaccharides, and glycoproteins exist as chemical compositions in the plant's herbs and roots. These compounds were thought to be the cause for noted immunostimulatory and anti-inflammatory activities (Barnes *et al*., 2005). Moreover, alkamides have been seen to affect type 2 Cannabinoid receptors (CB2) and are considered as a possible function of their immunostimulatory characteristics (Raduner *et al*., 2006; Woelkart and Bauer, 2007; Chicca *et al*., 2009). Their molecular mechanism can cause theenhancement of cyclic adenosine monophosphate (cAMP), p38 mitogen-activated protein kinases (p38/MAPK), c-Jun N-terminal kinase (JNK) signaling, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and even activate the transcription factor 2/cAMP responsive element-binding protein 1 (ATF-2/CREB-1) in primary human macrophages and monocytes. (Gertsch *et al*., 2004). Other studies indicated that N-alkamides from tinctures of roots and herbs stimulate synergistic activity on CB2 and eventually cause immunomodulatory effects alongside the super stimulation of interleukin-10 (IL-10) as well as the inhibition of tumor necrosis factor (TNF-α) in vitro (Chicca *et al*., 2009).

The ability to inhibit cyclooxygenase enzymes (COX-1 and COX-2) and 5-lipoxygenase (F-LO) was also observed in N-alkamides, inhibiting anti-inflammatory activity and NK cells (Muller-Jakic *et al*., 1994). Primary immune response mediators, as well as antiviral activity, were likely caused by the mentioned. TNF-α, interferon gamma (IFNγ), or IL-2 secretion by splenocytes, however, was not affected by alkamide, polysaccharide and cichoric acid dosage. (Goel *et al*., 2002). The NO response is also known to be stimulated by *E. purpurea* in peritoneal exudate cells (PEC) to LPS much more (2x-4x) when compared to control (Patel *et al*., 2008). Furthermore, alkamides can diffuse through Caco-2 monolayers which is not influenced by the company of other constituents (Matthias *et al*., 2004). Also, by using liquid chromatography-tandem mass spectrometry (LC-MS/MS), alkamides were characterized in the bloodstream after oral administration (Dietz *et al*., 2001; Goey *et al*., 2012). Basu *et al.* (2002) reported that administrating alkylamides at 12 mg/kg body weight increased the index of phagocytosis and phagocytic activity of alveolar macrophages quite significantly. The alveolar macrophages extracted from this category of rats similarly produced more TNF-a and nitric oxide after in vitro stimulation with LPS; alveolar macrophages secreted a greater amount of TNF-a and nitric oxide extracted from rat when compared to the control or any other active component. Splenocyte secretion of TNF-a, IFN-g and IL-2 was not affected. Thus, it can be depictedthat an active part of *E. pupurea*is it's alkylamides.

The polysaccharides have been seen to stimulate macrophage activity and numerous functions related to cytokine production (Bauer, 1998; Rininger *et al*., 2000; Goel *et al*., 2002; Randolph *et al*., 2003). The polysaccharides extracted from *E. purpurea* can be used to terminate bacteria such as staphylococci. A high molecular weight purified polysaccharide such as Arabinogalactan from plant cell cultures of *E. purpurea* has potent to activate macrophage cytotoxicity functions in contrary to tumor cells and microorganisms.

Anti-inflammatory mechanisms have been allocated to caffeic acid derivatives, including caftaric acid, chlorogenic acid and echinacoside. Echinicea, when applied to the skin, affects the crucial role of wound healing. The free radical generation systems had also seen effects caused by the antioxidant properties of Caffeic acid derivatives.

4. Growth promotion

Weight gain was observed in nearly all studies that included oral intake of *E. purpurea*. Gabor et al. (2012), Alishahi *et al.* (2012) and Aly *et al.* (2010) observed weight gain as well as significant improvement in growth performance (Table 1). An upsurge of food consumption, due to an increased appetite, such as in the study of Gabor *et al.* (2012) on *Cyprinus carpio* is causal in increasing the weight and growth rates of the studied fish. Kasiri *et al.* (2011) have illustrated a significant bodyweight gain in angelfish, *Pterophyllum scalare*. They reported that consuming *E. purpurea* improved feed conversion ratio, as detected before by Maass *et al.* (2005) and Saleh *et al.*(2008). In another study, *Poecilia reticulata* was fed with 30 g/kg of *E. purpurea*, which caused the best result in SGR and body gain weight (Guz *et al*., 2011). Similarly, final weight gain and SGR were increased in *O. mykiss* (Oskoii *et al*., 2012). However, the highest effect was revealed in the fish that received 0.5 g/kg of *E. purpurea*. Bodyweight gain and growth rate were elevated in *C. carpio*, based on an experiment carried out by Gabor *et al.* (2012). Likewise, Aly *et al.* (2008) have signified body weight gain and specific growth rate (SGR) in *O. niloticus*. It is believed that *E. purpurea* can enhance the digestive system's functions. Also, metabolism is assumed to be elevated, leading to higher food consumption and ultimately to a higher growth rate (Nazerian *et al*., 2014).

4. Immunomodulatory effects

An increase in the levels of immunoglobulin, lysozyme, complement, as well as leukocyte population, and T-cell proliferation has been reported in a variety of studies on fish (Haller *et al*., 2013). However, the immunological response of Echinacea on fish species varies from fish to fish. The plant's immunostimulatory activity is a sum of three main mechanisms: Phagocytosis activation, stimulation of fibroblasts and the augmentation of respiratory activity, which ultimately leads to an enhancement of leukocyte mobility (WHO, 1999). Cytokine production increase has been observed in certain studies. These cytokines includeTNF-α, IL-1, IL-6, and IL-10 by macrophages (Burger *et al*., 1997). On the other hand, an augmentation in the stimulation of lymphocyte function and proliferation has been suggested in diseased and normal human mononuclear cells in vitro (See *et al.* 1997).

In a study conducted by Mesalhy *et al.* (2007), *O. niloticus* were orally fed 0.25 ppt *E. purpurea* with one-month intervals. The observation was the increased number of leukocytes, signifying stimulatory effects of Echinacea on the fish's immune system. Similarly, Aly *et al.* (2008) studied the same species, administrating 1.0 ppt of *E. purpurea* orally. Analogous results were recorded as increased leukocytes were observed, consequently raising the fish's survival rate when exposed to pathogens. Leukocyte raise was also recorded amongst various fish species, including *O. mykiss*. Oskoii *et al.* (2012) reported a similar augmentation in leukocytes after administering 0.25, 0.5, 1, and 2 g.kg^{-1}/8 weeks *E. Purpurea*. In another study, a significant increase in leukocyte count was observed in *Mugil Cephalus*, leading to a decrease in overall mortality rates (Kakooliki *et al*., 2017).

Neutrophils are a vital part of the immune system and act against diverse pathogens. They are highly motile and can conduct chemotaxis via amoeboid movement. Neutrophil assays in studies that observed the effects of

Echinacea on fish signified augmentation of immune cells. As seen in a study by Alagawany *et al.* (2010) on the *O. niloticus*, aside from the raised neutrophils, lysosomal activity was observed to have a positive change (Alagawany *et al*., 2010). The lysosomal increase also was reported in *Oncorhynchus mykiss* by Pourgholam *et al.* (2013) and Sharif Rohani *et al.* (2016). Alishahi *et al.* (2012) similarly observed a rise in lysozyme in *Ctenopharyngodon idella*. This increase in lysosomal enzymes was also observed in *Oreochromis niloticus* (Khalil and Elhady, 2015). Similar reports were found for other fish species, including *Aciperserbaerii*, *Husohuso*, and *Oncorhynchus mykiss* (Khajepour and Javadian, 2020, Nazerian *et al*., 2016). C3 proteins are amongst the most important and abundant proteins in the complementary system. They have immunomodulatory effects and aid in destroying and tearing pathogens apart (John *et al*., 2007). Measuring C3 levels allows for a better and more complete understanding of the complementary system. Pourgholam *et al.* (2013), in a study on *O. mykiss* fish, observed a rise in Complement C3 protein leading to an increased immunostimulatory effect. Nazerian *et al.* (2014) administered *E. Purpurea* with a dosage of 0.5% for 60 days in *H.huso* fish. Blood assay signified an increase in hematological parameters and serum alternative complement (Nazerian *et al*, 2016). Similar results were reported by Alishahi *et al.* (2017) and Khajepour and Javadian (2020).

5. Disease resistance

Bacterial resistance has been studied in several studies after supplying the fish's diet with *E. purprea*. (Aly and Mohamed, 2010, Pourgholam *et al*., 2013, Abdelkhalek *et al*., 2015). Echinacea has been reported to prevent mortality in several fish species when challenged with a wide variety of bacterial species. The supplementation of fish diet with Echinacea has reduced mortality against *Aeromonas hydrophila*, *Aeromonas bestiarum*, *Aeromonas sobria*, *Pseudomonas fluorescens*, *Streptococcus iniae*, *Yersinia ruckeri*, *Flavobacterium columnare*, *Photobacterium damselae* (Mesalhy *et al*., 2007, Aly *et al*., 2008, Guz *et al*., 2011, Pourgholam *et al*., 2013, Imani *et al*., 2014, Khalil and ElHady, 2015, Guz *et al*., 2014, kakoolaki *et al*., 2017). The impact of *E. purpurea* on the survival of *O. niloticus* when challenged with *P. fluorescens* has been reported (Aly and Mohamed, 2010; Aly *et al*., 2008). Gabor *et al.* (2012) also investigated the impact of consuming *E. purpurea* in *C. carpio*, resulting in a high survival rate. In an experiment on *Poecilia reticulate*, which lasted for 67 days, Guz *et al.* (2011) showed the resistance of the fish fed Echinacea against *A. besiarum*. They reported that the mortalities varied from 5.8% to 9.2%. Similarly, according to Imani *et al.* (2014), mortality was decreased in rainbow trout fed Echinacea than in the control when confronted with *Y. ruckeri*.

Considering the reports, Echinacea implies its immunomodulatory effects successfully and prevented several disease-related deaths (Guz *et al*., 2011, Gabor *et al*., 2012, Imani *et al*., 2014). It also has been influential on the efficacy of bacterial vaccines in aquaculture. In a study conducted by Guz et al. (2014), the immune response against *F. columnare* vaccine in *Danio rerio* fish was observed, indicating increased bacterial resistance. In this investigation, scientists began feeding the selected fish three weeks prior to bath immunization using different levels of *E. purpurea*. Twenty-eight days after vaccination, the fish were infected with *F. columnare*. It is concluded that the survival rate was the highest in group 4 (36.0%), which were fed with 30g/kg dietary *E. purpurea*.

6. Antioxidant activity

Aerobic biochemical pathways imply the production of excess oxidation in Intracellular fluid as well as tissue components. The accumulation of oxidized biochemical by-products can cause a variety of pathologies, including cancer. (Rafael Radi, 2018). As indicated intable 1, 3 of the 31 studies measured oxygen radical assays (Mesalhy *et al*., 2007; Pourgholam *et al*., 2013; Sharif Rohani *et al*., 2016). Fish including *O. niloticus* and *O. mykiss* both signified an increase in oxygen-free radicals. This observation can point to an increased risk for a number of pathologies within the fish and contradicts the positive effects of Echinacea. Mesalhy *et al.* (2007) showed that *Echinacea* stimulates phagocytosis – both in vitro and in vivo in *O. niloticus*, which leads to the enhancement of producing oxygen radicals.

Table 1. Effect of Echinacea on fish performance**.**

No.	Supplement form*	Echinacea	Fish species	Biological activities	Reference
1.	Powder/0.25 ppt/1, 2, 3 months	*Echinacea* sp.	*Oreochromis niloticus*	↑Total leukocyte count, hematocrit value, production of oxygen radicals, resistance against *Aeromonas hydrophila*	Mesalhy *et al*., 2007
2.	Extract/1 ppt/90 days (Summer phase)	*Echinacea purpurea*	*Oreochromis niloticus*	↑Weight gain, survival rate, hematocrit values, total fish biomass, resistance against *Pseudomonas* sp. ↓mortality	John *et al*., 2007
	Extract/0.25 ppt/6 months (Winter phase)			↑Final weight and weight gain, survival, resistance against *Pseudomonas* sp. ↓mortality	
3.	Extract/0.25 ppt/6 months	*Echinacea purpurea*	*Oreochromis niloticus*	↑Weight gain, growth rate, hematocrit values, lysozyme activities, leukocyte count, survival rate, resistance against *Pseudomonas fluorescens*	Aly *et al*., 2008
4.	Powder/1.0 ppt with *Allium sativum* /1, 2, and 3 months	*Echinacea purpurea*	*Oreochromis niloticus*	↑Leukocyte count, hematocrit values, survival rate, body weight gain, resistance against *Aeromonas hydrophila*	Aly and Mohamed, 2010
5.	Extract/1.5% with *Allium sativum*, and probiotic/150 days	*Echinacea purpurea*	*Oreochromis niloticus*	↑Survival	Aly *et al*., 2010
6.	Powder/ 5, 10, 20, 30, and 60 g kg^{-1}/67 days	*Echinacea purpurea*	*Poeciliareticulata*	↑ Weight gain, Resistance against *Aeromonas bestiarum*	Guz *et al*., 2011
7.	Ethanolic extract/0.25 ppt/3 months	*Echinacea purpurea*	*Pteropyllumscalare*	↑Weight gain and growth performance, larva survival, reproductive parameters, survival of yolk-sac absorption	Kasiri *et al*., 2011
8.	Extract/ 0.25, 0.5, 1, and 2 g kg^{-1}/8 weeks	*Echinacea purpurea*	*Oncorhynchus mykiss*	↑Final weight, leukocyte count, total protein, albumin, and globulin 0.25 and 0.5 g: growth and biochemical and hematological indices ↓FCR	Oskoii *et al*., 2012
9.	Powder/0.5% with *Origanum vulgare* /93 days	*Echinacea* sp.	*Cyprinus carpio*	↑Growth and consumption rate, body weight gain, survival rate, resistance against *Aeromonas hydrophila* ↓FCR	Gabor *et al*., 2012
10.	Powder/0.5% with *Origanum vulgare* /95 days	*Echinacea* sp.	*Oncorhynchus mykiss*	↑Weight gain and growth rate, survival rate ↓FCR value	Gabor *et al*., 2012
11.	Extract/0.5%/6 weeks	*Echinacea purpurea*	*Cyprinus carpio*	↑Leukocyte count, growth and body weight gain, immunostimulatory effects, survival rate, resistance against *Aeromonas hydrophila* ↓Mortality	Alishahi *et al*., 2012
12.	Hydroalcoholic extract/0.5%/6 weeks	*Echinacea purpurea*	*Barbus barbulus*	↑Growth rate and SGR, immunostimulatory effects, FCR, resistance against *Aeromonas hydrophila* ↓Mortality	Alishahi *et al*., 2013
13.	Extract/0.5, 1, 1.5 g kg^{-1}/60 days	*Echinacea purpurea*	*Oncorhynchus mykiss*	↑Complement C3, lysozyme, oxygen free radicals, leukocyte count, resistance against *Streptococcus iniae*	Pourgholam *et al*., 2013
14.	Extract/0.5 and 1% with *Allium sativum*/30 days	*Echinacea purpurea*	*Oncorhynchus mykiss*	↑Leukocyte count, resistance, hematocrit values, ↓ resistance against *Yersinia ruckeri*	Imani *et al*., 2014
15.	Extract/with *Panas ginseng*, and oxytetracycline/ (0.75 g kg^{-1})/4 and 8 weeks	*Echinacea purpurea*	*Oreochromis niloticus*	↑Weight gain and growth, FCR, Condition Factor (CF), SGR. total leukocyte count and immunostimulatory effects, lysozyme, serum bactericidal activity against *Aeromonas hydrophila*	El-Sayed *et al*., 2014
16.	Powder/0.5 g kg^{-1}/60 days	*Echinacea* sp.	*Husohuso*	↑Body weight gain and growth, FCR, SGR, Condition Factor (CF)	Nazerian *et al*., 2014

17.	Powder/5, 10, 20, and 30 g kg^{-1}/21 days	*Echinacea purpurea*	*Danio rerio*	↑Response to *Flavobacterium columnare* vaccines and survival rate	Guz *et al*., 2014
18.	Extract/ 500 mg kg^{-1}) with Vitamin C/28 days	*Echinacea purpurea*	*Oreochromis niloticus*	↑Hematological indices, serum lysozymes and resistance against *Aeromonas sobria*, total leukocyte count, total protein and globulins, survival rate	Khalil and ElHady, 2015
19.	Extract/4 g kg^{-1}/5 months	*Echinacea purpurea*	*Oreochromis niloticus*	↑Growth performance, survival rate, resistance against *Pseudomonas fluorescens* and *Aeromonas hydrophila* ↓ FCR, Adverse effect of high stocking density	Abdelkhalek *et al*., 2015
20.	Hydroalcoholic extract/ 0.5 and 1% with *Allium sativum*/30 days	*Echinacea purpurea*	*Oncorhynchus mykiss*	↑Immunostimulatory effects and resistance	Ghiasi and Meshkini, 2016
21.	Extract/4 ppt/5 months	*Echinacea purpurea*	*Oreochromis niloticus*	↑Resistance against *Aeromonas hydrophila* ↓Mortality	Aly *et al*., 2016
22.	Methanolic extract/50, 100, and 200 mg kg^{-1}/60 days	*Echinacea purpurea*	*Mugilcephalus*	↑Final weight, daily growth ratio, hematological parameters, and protein efficiency ratio, RBC, WBC, Hb, and hematocrit ↓FCR	Akbary *et al*., 2016
23.	Ethanolic extract/0.5, 1, and 1.5 g kg^{-1}/60 days	*Echinacea purpurea*	*Oncorhynchus mykiss*	↑Immunity responses and resistance against *Streptococcus iniae*, hematological parameters, lysozyme concentration and oxygen free radicals ↓The amount of glucose, serum total protein, and albumin	Sharif Rohani *et al*., 2016
24.	Powder/0.5% with *Allium sativum*/60 days	*Echinacea purpurea*	*Husohuso*	↑Growth performance, serum alternative complement, lysozyme, respiratory burst activity, and hematological parameters	Nazerian *et al*., 2016
25.	Methanolic extract/50, 100, and 200 mg kg^{-1}/8 weeks	*Echinacea purpurea*	*Mugilcephalus*	↑Final weight, food intake, daily growth rate, hematological parameters, total leukocyte count, resistance against *Photobacterium damselae* ↓Mortality	Kakooliki *et al*., 2017
26.	Hydroalcoholic extract (0.5% oral and 400 mg kg^{-1} I.P)/40 days	*Echinacea purpurea*	*Ctenopharyngodon idella*	Oral and I.P: ↑Lysozyme, resistance against *Aeromonas hydrophila*, complement activity, and nitro blue tetrazolium reduction I.P: ↑total leukocyte count ↓Mortality and losses	Alishahi *et al*., 2017
27.	Extract/0.5, 1, and 2 g kg^{-1}/60 days	*Echinacea purpurea*	*Acipenserruthenus*	↑Lysozyme and immunoglobulin M, ↓Growth performance	Salati *et al*., 2017
28.	Dry extract/ 500 mg kg^{-1}) with Vitamin C /28 days	*Echinacea purpurea*	*Oreochromis niloticus*	↑Intestinal mucosal epithelium, number of goblet cells, heights of villi, and immune response	Abdel Rahman *et al*., 2018
29.	Essential oil/ 1% / 21 days	*Echinacea angustifolia*	*Oncorhynchus mykiss*	↑serum lysozyme level and phagocytic germs	Fadeifard *et al*., 2018
30.	Methanolic extract/50, 100, and 200 mg kg^{-1}/60 days	*Echinacea purpurea*	*Mugilcephalus*	↑Final weight, food intake, daily growth rate, and efficiency of protein, lysozyme activity, biochemical and hematological indices ↓Mortality after challenge with *Photobacteriumdamselae*	Akbari and Kakoolaki, 2019
31.	Powder/with *Achillea millefolium* and *Mentha piperita*/60 days	*Echinacea purpurea*	*Cyprinus carpio*	↑Growth, hematological and immunological indices	Alinezhad, 2019
32.	Hydroalcoholic extract/0.5%, 1%, and 1.5%/8 weeks	*Echinacea purpurea*	*Acipenserbaerii*	↑Final weight, specific growth rate, and condition factor, feed conservation ratio, hematological indices, WBC and RBC count, hematocrit, lysozyme, complement, and respiratory burst levels	Khajepour and Javadian, 2020

Equally, Pourgholam *et al.* (2013) revealed that oxygen free radicals have considerably increased after feeding *O. mykiss*with *E. purpurea*. Similarly, Sharif Rohani *et al.* (2016) proved the increase in oxygen free radicals and lysozyme concentration in *O. mykiss* fed with 1.5 g/kg of *E. purpurea*, which were notably higher in comparison with the other groups.

Considering the reports, Echinacea implies its immunomodulatory effects successfully and prevented several disease-related deaths (Guz *et al*., 2011, Gabor *et al*., 2012, Imani *et al*., 2014).

It also has been influential on the efficacy of bacterial vaccines in aquaculture. In a study conducted by Guz *et al.* (2014), the immune response against *F. columnare* vaccine in *Danio rerio* fish was observed, indicating increased bacterial resistance. In this investigation, scientists began feeding the selected fish three weeks prior to bath immunizationusing different levels of *E. purpurea*. Twenty-eight days after vaccination, the fish were infected with *F. columnare*. It is concluded that the survival rate was the highest in group 4 (36.0%), which were fed with 30 g/kg dietary *E. purpurea*.

7. Antioxidant activity

Aerobic biochemical pathways imply the production of excess oxidation in Intracellular fluid as well as tissue components. The accumulation of oxidized biochemical by-products can cause a variety of pathologies, including cancer. (Rafael Radi, 2018). As indicated intable 1, 3 of the 31 studies measured oxygen radical assays (Mesalhy *et al*., 2007; Pourgholam *et al*., 2013; Sharif Rohani *et al*., 2016). Fish including *O. niloticus* and *O. mykiss* both signified an increase in oxygen-free radicals. This observation can point to an increased risk for a number of pathologies within the fish and contradicts the positive effects of Echinacea. Mesalhy *et al.* (2007) showed that *Echinacea* stimulates phagocytosis – both in vitro and in vivo in *O. niloticus*, which leads to the enhancement of producing oxygen radicals. Equally, Pourgholam *et al.* (2013) revealed that oxygen free radicals have considerably increased after feeding *O. mykiss*with *E. purpurea*. Similarly, Sharif Rohani *et al.* (2016) proved the increase in oxygen free radicals and lysozyme concentration in *O. mykiss* fed with 1.5 g $^{kg-1}$ of *E. purpurea*, which were notably higher in comparison with the other groups.

8. Hemato-biochemical indices

Hematocrit value was another variable assessed in related studies. Khajepour and Javadian (2020) studied *Acipenser baerii* fish, adding 0.5%, 1% and 1.5% of *E. purprea* to their diet for 8 weeks. Observation included augmentation of RBC and WBC count, consequently raising the Hematocrit values. A similar study signified an increased RBC count by 10 g/kg' ultimately increasing hematocrit values (Akbary *et al*., 2012).

In another study, fish were fed with Echinacea in two phases of summer and winter (Mesalhy *et al*., 2007). This caused an augmentation in the hematocrit values of *O. niloticus* compared with the control group. Therefore, it indicates the safety of the medicinal product. Following the previous study, John *et al.* (2007) performed an experiment on *O. niloticus* using Echinacea. However, a significant increase in the hematocrit value was detected by the end of the first phase (summer phase). Similarly, Aly *et al.* (2008) reported a notable augmentation in hematocrit value. In another related study, Aly and Mohamed (2010) illustrated a significant hematocrit increase along with neutrophil adherence in *O. niloticus* in Echinacea supplemented groups. It is noted that based on the higher lymphocytic count, the total leukocyte count has been elevated. Due to the mentioned facts, the mortalities were highly decreased as a result of Echinacea consumption.

WBC levels were seen to increase in an investigation on *O. mykiss* once the fish were fed Echinicae, with the concentration of 0.5% , whilst it was reduced after that. (Oskoii *et al*., 2012). Elevated RBC count was seen; however, HB and Hematocrit values had seen no significant change, withthe concentration of 0.25% Echinacea. Comparison with the control group signified a slight augmentation in albumin/globulin value. On the other hand, total protein, albumin, and globulin level increased. Also, Khalil and Elhady, (2015) demonstrated an enhancement in hematological parameters, such as RBC and WBC count, hematocrit, and hemoglobin value in *O. niloticus*. They also noted that Echinacea and Vitamin C consumption led to a healthy enhancement in the fish. Also, Nazerian *et al.* (2016) signified Echinacea to increase Hemoglobin concentration, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration in *H. huso*.

A study revealed no significant alteration in total protein, albumin, and glucose levels (Sharif Rohani *et al*., 2016). Kakoolaki *et al.* (2017) carried out an experiment on *M. Cephalus*, which indicated a significant enhancement in the groups fed with 100 and 200 mg/kg of Echinacea. Nonetheless, the alteration was unidentifiable when 50 mg/kg of Echinacea was fed. The maximum level of total protein, albumin, and globulin was seenwhen 200 mg/kg of Echinacea was used.

9. Conclusion

Aquaculture, consisting of various organisms, is constantly exposed to pathogens such as viruses, parasites, fungi and bacteria. Fish constitute a large portion of aquaculture, and due to its direct effect on the human diet, quality assurance and health protocols are of utmost importance. Increasing production rates of fish to sustain the increase in world population increases the pathogenic risks that fish are exposed to. Currently, antibiotics and other synthetic measures are used to control and prevent infectious diseases. However, as discussed, occurrences such as mutations, factors such as labour and or impracticality are drawbacks accompanied by these methods. According to the literature, fish performance in terms of leukocytes, neutrophils, WBC, and antioxidant activity were all seen to increase significantly in fish that received Echinacea. Also, several studies depicted positive effects when growth parameters such as SGR were analyzed and measured, emphasizing the beneficial impact echinacea has on enhancing cultured fish life and consumer health.

10. References

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