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EXPLORING THE POTENTIAL OF RESVERATROL AS FEED SUPPLEMENT IN AQUACULTURE – A REVIEW

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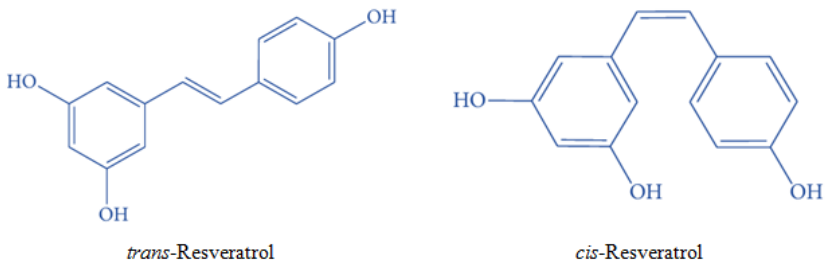
Abstract

Aquaculture serves a crucial role in meeting the global seafood demand. However, it grapples with issues associated with disease outbreaks, oxidative stress, and the imperative of fostering sustainable development. The supplementation of resveratrol in aquafeed has demonstrated the potential in addressing these issues. Resveratrol (RSV), a polyphenolic bioactive compound known for its antioxidant, anti-inflammatory, and neuroprotective properties, has garnered attention in recent research. Studies suggest resveratrol supplementation in feed, typically at the concentration of 0.5–1%, enhances growth performances, immune responses, resistance against disease, and stress tolerance in aquatic species. Despite its high metabolic rate and shorter half-life, the bioactive nature of resveratrol makes it a recommended phytochemical in aquafeed, highlighting its potential to improve overall aquaculture health and sustainability. This review is designed to give a comprehensive knowledge about the effects of resveratrol in fish, focusing on its antioxidant properties, influence on growth, impact on immune response, and benefits as a feed supplement.

Key words: resveratrol, feed additive, growth, antioxidant, reactive oxygen scavenger

List of abbreviations: ACAT2 – acetyl-CoA acyltransferase, ACH 50 – alternative complement pathway 50, AMPK – AMP activated protein kinase, CAT – catalase, CD – cluster of differentiation, CYP7A1 – cytochrome P450 family 7 subfamily A member 1, FABP – fatty acid binding protein, FCR – feed conversion ratio, FOXO – forkhead box O, GADD45 – growth arrest and DNA damage-inducible 45, GPX – glutathione peroxidase, GST – glutathione S-transferase, HEP – hepcidin, HMGCR – 3-hydroxy-3-methylglutaryl-CoA reductase, HO-1 – heme oxygenase-1, HSP70 – heat shock protein 70, Ig – immunoglobulin, IL – interleukin, KEGG – Kyoto Encyclopedia of Genes and Genomes, LDLR – low density lipoprotein receptor, LZM – lysozyme, MRPL – multidrug resistance-associated protein 2, MyD88 – myeloid differentiation primary response 88, NF-κB – nuclear factor kappa-light chain enhancer of activated B cell, NQO-1 – NAD(P)H quinone dehydrogenase 1, NRF2 – nuclear factor erythroid 2-related factor 2, PER – protein efficiency ratio, PPAR – peroxisome proliferator activated receptors, prx-6 – peroxiredoxin 6, RSV – resveratrol, SGR – specific growth rate, SIRT 1 – sirtuin 1, SOD – superoxide dismutase, TBA-RS – thiobarbituric acid reactive substance,

Resveratrol has been identified as a potential feed additive that attenuates oxidative stress created by a high-fat diet (Yan et al., 2017; Jia et al., 2019 a), as well as inflammation (Tan et al., 2019; Wu et al., 2023; Jia et al., 2019 b), immunological response (Naderi Farsani et al., 2021; Tan et al., 2019; Tian et al., 2021; Ye et al., 2023; Kowalska et al., 2017), antioxidative activity (Naderi Farsani et al., 2021; Tan et al., 2019; Tian et al., 2021; Chen et al., 2023; Liu et al., 2021; Menoyo et al., 2019; Yan et al., 2017; Jia et al., 2019 a), and enhanced growth performance (Naderi Farsani et al., 2021; Tan et al., 2019; Tian et al., 2021; Torno et al., 2018, Yan et al., 2017; Jia et al., 2019 a). Resveratrol compound originated from one chemical and a plant namely the res – from resorcinol and veratr – from the plant *Veratrum*. Additionally, the compound's name is "Res-veratr-ol" because of the hydroxyl group that is found at both its terminal ends (Gerszon et al., 2014; Catalgol et al., 2012). The resveratrol is extracted from many plant classes such as the Vitaceae, Cyperaceae, Gnetaceae, and Dipterocarpaceae (Gerszon et al., 2014; Catalgol et al., 2012). The rich sources of this compound are found in various berries (Kopeć et al., 2011).



trans-Resveratrol *cis*-Resveratrol

Figure 1. *Trans*- and *cis*- forms of resveratrol (Gambini et al., 2015)

The chemical formula of resveratrol is $C_{14}H_{12}O_3$, which has two forms viz *trans*- and *cis*- (Trela and Waterhouse, 1996) as shown in Figure 1. The stability of *trans* is more compared to that of the *cis* isomer. The introduction of the plant-based compound called resveratrol came as a solution for the oxidation caused by the free radicals (Colica et al., 2018). The plants synthesize this substance as a response to stress, mechanical damage, and injuries (Hsu et al., 2021). Resveratrol is widely used as an anticancer therapeutic (Grau et al., 2023) as it interferes in the different developmental stages of carcinoma and also inhibits or suppresses the ultimate and penultimate stages of cancer i.e., the metastasis and angiogenesis (Grau et al., 2023). Previously, the compound was utilized for its antioxidant properties and its prophylactic effects on cancer cell development cells. But in modern times its cytotoxic properties depend on the administered dosage (Bishayee, 2009).

The preventive action of resveratrol in lipid peroxidation accounts for the amplification of the NrF2 pathway (Jia et al., 2019 a, b). Ge et al. (2023) and Jia et al. (2019 a) have reported that lipid metabolism is augmented by the resveratrol in the liver. The MDA content, T-SOD, CAT, and prx-6 are the enzymatic indices of the anti-oxidant capacity of the tissue (liver, muscle). The increased SOD and prx-6 are the criteria for the antioxidant property of the resveratrol (Tan et al., 2019; Wu et al., 2023; Chen et al., 2023; Tian et al., 2021; Ge et al., 2023). Decreased plasma C3 and IgM show that the resveratrol subdues the inflammatory response caused due to TNF-α, lipopolysaccharide-treated macrophages, IL-1β, and IL-8 (Tan et al., 2019, Wu et al., 2023). The impact of resveratrol on growth and growth-related gene expression is attributed to the growth factor, increased SGR and PER, and elevation of the SIRT1 gene, Cu/Zn-SOD, CAT, and glutathione peroxidase (GPX) activity. In addition, the caspase-8 and TNF-α mRNA expression down-regulation is also treated by resveratrol supplementation. The addition of resveratrol sequesters essential fatty acids (EPA and DHA) in the tissues and accelerates the Δ6-desaturase activity in the liver (Torno et al., 2017, 2018; Menoyo et al., 2019). Tian et al. (2021) suggested that the optimal amount of incorporation of resveratrol in the diet ranges from 75 to 125 mg/kg in *Channa argus* fish. Resveratrol has been identified as a distinctive polyphenolic compound that exhibits unique biological effects in fish. Therefore, the present review aims to comprehensively elucidate the role of resveratrol in the antioxidant function, immunomodulation, and growth performance enhancement of fish.

Structure of resveratrol

The advances in the improvement of biological activities of the subject compound are brought about by the addition or formation of the new phenolic rings and it serves as the typical approach in modulative pharmacology (Grau et al., 2023). The cyclic counterparts or their analogue modulative changes rigidify the compound and confer its special characteristic properties. In addition, they provide the methods for clear biological profiling of the pharmacophore groups present in the structure (Grau et al., 2023). Specifically, the *cis* and *trans* variants of resveratrol are available. Comparing the *trans* or E form to that of the *cis* or Z form reveals that the *trans* or E form is more stable. The conversion of the *trans* form to the *cis* form is catalysed by the ultra-violet spectral rays (Trela and Waterhouse, 1996; Vian et al., 2005). They are soluble in inorganic substances like ethanol, dimethyl sulfoxide, and fats as well (Grau et al., 2023). They are insoluble in other solvents like water (Grau et al., 2023). The crystalline form of the resveratrol can be kept for up to 3 months under stipulated conditions prescribed in the works of literature (Jensen et al., 2010). Given in the Figure 2 are the different derivatives of resveratrol.

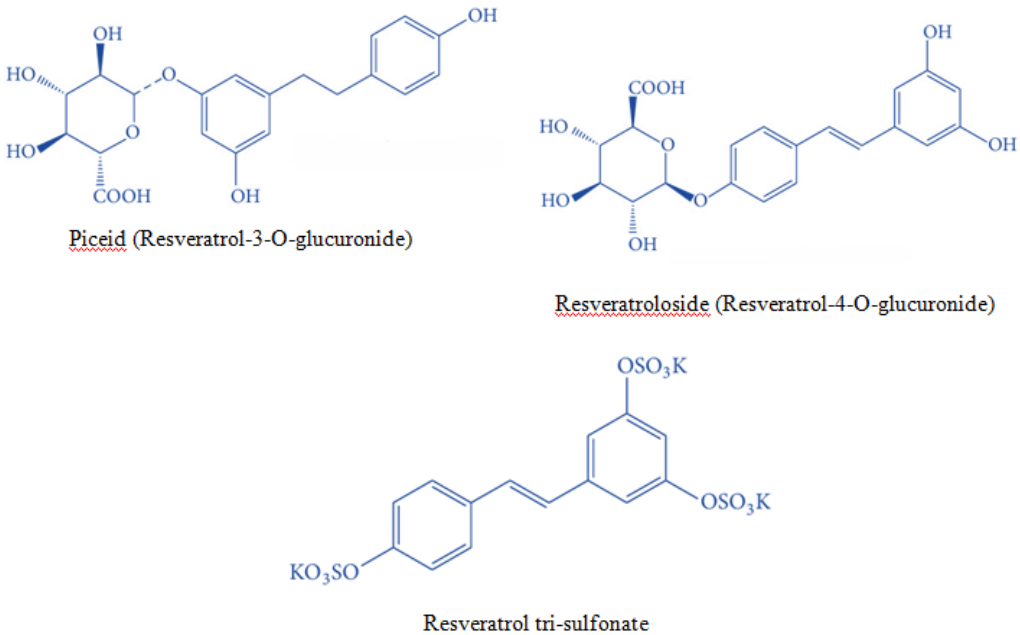


Figure 2. Derivatives of resveratrol (Gambini et al., 2015)

Synthesis of resveratrol

When glucose is metabolized, 4-coumaroyl-CoA is produced, which is then converted into malonyl CoA with the assistance of a specific enzyme called stilbene synthase. This compound is the precursor in producing the trans-resveratrol (Hsu et al., 2021). The transformation of glucose to *trans* form resveratrol is detailed in Figure 3.

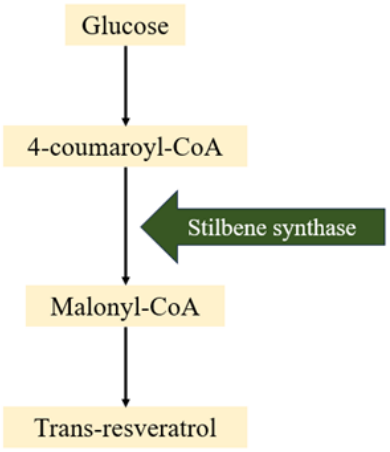


Figure 3. Synthesis of resveratrol (Hsu et al., 2021)

Antioxidant mechanism of resveratrol

Generally, plant derived polyphenolic compounds are known for their antioxidant activity, primarily through controlling cell damage due to excessive production of reactive oxygen species (ROS) (Abdel-Daim et al., 2019; Moustafa et al., 2020; Ahmadifar et al., 2021 a). Among many polyphenolic compounds, resveratrol is an effective scavenger of both reactive oxygen (ROS) and nitrogen (RNS) species. It is the secondary metabolite as a by-product of the reaction of the ROS or RNS and biomolecules (Gerszon et al., 2014; Cordova-Gomez et al., 2013). The specific chemical structure of resveratrol, which includes three hydroxyl groups in the 3rd, 4th and 5th positions, the polyphenolic rings, and double bonds, contributes significantly to its antioxidant activity (Cao et al., 2003; Iuga et al., 2012). However, resveratrol loses its antioxidant capacity when its hydroxyl groups are removed and replaced by the methoxy group (-OCH3) (Gerszon et al., 2014). This indicates that the antioxidant efficacy of resveratrol is strongly dependent on its intact chemical structure. On the other hand, polyphenols, such as quinone/quinone methide intermediates can switch between antioxidant and pro-oxidant roles based on their oxidation state (Shahidi and Ambigaipalan, 2015). Phenolic compounds may exhibit pro-oxidant characteristics under certain conditions such as in the presence of redox-active transition metals and high pH (Nimse and Pal, 2015). The pro-oxidant properties of phenolic compounds arise from the formation of unstable redox complexes with metal cations (Hodnick et al., 1988). These radicals can interact with oxygen, producing a radical form of O_2, and may also form ternary compounds with copper, flavonoids, and DNA (Hodnick et al., 1988). Certain dietary phenolics act as pro-oxidants in systems containing redox-active metals, directly generating ROS and altering the redox environment (León-González et al., 2015).

The antioxidant properties of resveratrol are additionally linked with the activation of enzymes essential for clearing out reactive oxygen species and modulating signalling pathway (PI3K/AKT and GSK-3-catenin) to enhance antioxidant activity (Gerszon et al., 2014; Fukui et al., 2010). Enzymes such as catalase, heme-oxygenase, glutathione peroxidase, and superoxide dismutase (SOD) are activated by resveratrol (Kavas et al., 2013; Robb et al., 2008). Catalase and mitochondrial superoxide dismutase (SOD2) enzymes assist in the antioxidant activities of resveratrol (Spanier et al., 2009). According to investigations, the PI3K/AKT as well as GSK-3-catenin signalling channels are modulated by resveratrol to activate the enzyme mitochondrial superoxide dismutase (SOD2) (Fukui et al., 2010). Along with catalase and dismutase, resveratrol also elevates heme oxygenase-1 expression (HO-1). This effect has been observed in cell types such as macrophages, neurons (HT22, PC12, C60-astrocytes line), and human aortic cells of smooth muscle (Chen et al., 2005; Juan et al., 2005; Quincozes-Santos and Gottfried, 2011). Conversely, polyphenols like flavanols, isoflavones, flavones, flavanones, anthraquinones, diarylheptanoids, anthocyanins, coumarins, aryl alkanones, chalcones, phenolic acids, proanthocyanidins, simple phenols, and stilbenes have been reported to activate the *Nrf2* (nuclear factor erythroid 2-related factor 2) which subsequently regulates the activities of several antioxidant enzymes (Kumar and Pandey, 2013; Ahmadifar et al., 2021 a). However, their effects can vary significantly based on the compound and context. Resveratrol has a positive impact on mitochondrial function by activating the SOD2 as mentioned above, whereas some flavonoids may cause mitochondrial toxicity through collapsing the cell membrane and forming pro-oxidant phenoxyl radicals inside it (Galati and O'Brien, 2004).

Resveratrol also activates the bio-catalyst enzymes that help in maintaining the redox balance inside the cell (Gerszon et al., 2014; Kavas et al., 2013; Kincaid and Bossy-Wetzel, 2013). It reduces the activity of xanthine oxidase (Delmas et al., 2005), a primary source of superoxide anion (Spanier et al., 2009; Ryan et al., 2010), and cyclooxygenase 1 (COX 1) (Gerszon et al., 2014), enzymes which are responsible for producing reactive oxygen species (Gerszon et al., 2014; Delmas et al., 2005). The significant decline in COX 1 activity by resveratrol further inhibits the formation of prostaglandin (PGE2) and 8-iso-prostaglandin F2 (8-iso-PGF2), both of which are associated with the generation of free radicals (Gerszon et al., 2014).

Bioavailability of resveratrol

The constrained bioavailability of resveratrol is one characteristic that could reduce its therapeutic value. Lower bioavailability is due to multiple factors, which include sparingly water-soluble, poor stability under conditions with severe environmental stress, and lack of the capacity to reach the target site for its intended benefit (Augustin et al., 2013). The encapsulation strategy of medication delivery is used as a result to improve the solubility in water, bioavailability, and ability to regulate the release in the gastrointestinal tract (Augustin et al., 2013).

Although its mobility in tissues is fairly restricted, resveratrol has been shown to have a powerful effect on physiology and beneficial effect on cells in *in vitro* studies (Gambini et al., 2015). Resveratrol can be delivered effectively and with increased bioavailability employing an array of techniques, including nanoparticle delivery systems, microencapsulation, and protein coatings such as zein. They were discovered to be stable at 4°C for up to three months (Augustin et al., 2013). When resveratrol is administered to stressed cells in tissue culture, this strategy of encasing it works better (Kristl et al., 2009). The presence of protein protects resveratrol from isomerization from *trans* to *cis* form as a second approach (Zhang et al., 2012 a, b; Liang et al., 2008). When resveratrol binds to a protein at the tryptophan-containing region, there may occasionally be a change in the protein's structure (Zhang et al., 2012 a). The third method uses cyclodextrin complexes that have been coupled with resveratrol. When resveratrol and cyclodextrin interact, an inclusion complex is created, which traps resveratrol in the inner hydrophobic layer (Lopez-Nicolás et al., 2006).

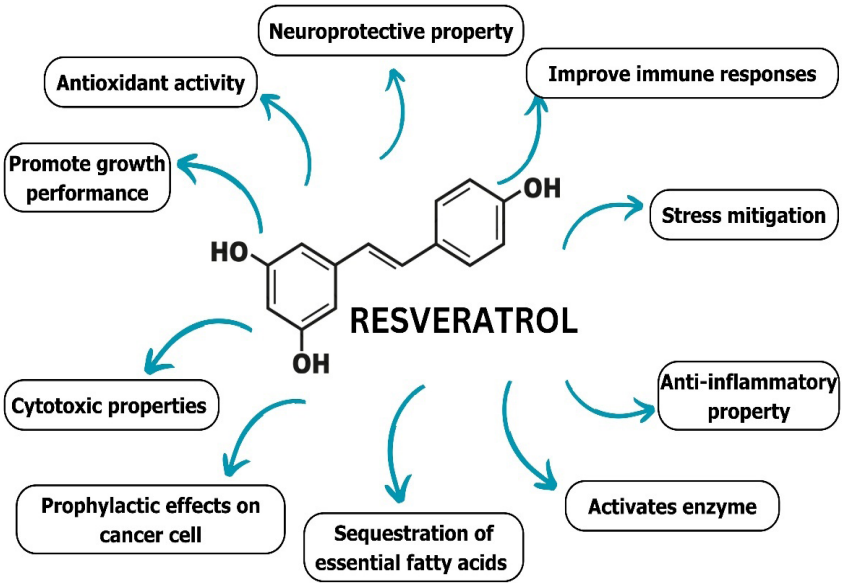


Figure 4. Actions of resveratrol

Table 1. Physiological effects of dietary resveratrol in fish

Species	Dosage	Physiological effects	References
1	2	3	4
Turbot (*Scophthalmus maximus*)	600 mg/kg	↑ The activity of SOD, GPX, and prx-6 ↑ The expression of cytokine transforming growth factor (β) ↓ The expression of TNF-α, IL-1, and IL-8	Tan et al. (2019)
Gibel carp (*Carassius gibelio*)	160 mg/kg	Activated Nrf2 and SIRT1 ↑ The activity of SOD and GPX ↓ The level of plasma C3 and IgM ↑ The phosphorylation of AMPK ↔ Structure and damage of hepatic mitochondria	Wu et al. (2023)
Marine mussel (*Mytilus coruscus*)	20μM	↑ The antioxidant activity ↓ The production of MDA Amplification of the mRNAs for the gene expression of AMPK, FOXO, GADD45, and SIRT1	Chen et al. (2023)
Pacific white leg shrimp (*Litopenaeus vannamei*)	0, 40, 80, 120, and 180 ppm	↓ The production of MDA ↑ The activity of GPX and CAT enzymes ↑ The total antioxidant capacity ↑ Ammonia-stress 80 ppm and 120 ppm	Liu et al. (2021)

Table 1 – contd.

1	2	3	4
Tilapia (*Oreochromis niloticus*)	0, 0.1, 0.3, and 0.6 g/kg diet	↓ The peroxidation of lipid ↑ The expression of HO-1, NQO-1, GST, and Nrf2 signalling pathway ↓ The expression of TLR2-Myd88-NF-B signalling pathway	Jia et al. (2019 b)
Zebrafish (*Danio rerio*)	5 µM	↑ The survival rate ↓ The ratio of green/red in the membrane potential of the mitochondria	Giordo et al. (2020)
Rainbow trout *(Oncorhynchus mykiss)*	400 ppm, 800 ppm, 400 ppm Res + 0.5 g/kg Pro, and 800 ppm Res + 1 g/kg Pro	↑ The survival rate, final weight, weight development, and FCR ↑ SGR and PER ↑ Total leucocyte count, monocyte and neutrophil percentages, serum complement, lysozyme, and bactericidal activity ↑ The resistance to the *Y. ruckeri* ↑ The activity of GPX, CAT, and SOD	Naderi Farsani et al. (2021)
Snakehead *(Channa argus)*	75–125 mg/kg	↑ SGR ↑ The activity of SOD, CAT, and GST	Tian et al. (2021)
Wuchang bream (*Megalobrama amblycephala*)	0.04% and 0.08%	↑ The activity of SOD, CAT, and GPX ↑ The transcription of Cu/Zn-SOD ↑ The expression of LDLR ↓ The expression of HMCGR and ACAT2 ↑ The expression of CYP7A1 ↓ The expression of MRP2 and OATP	Ge et al. (2023)
Rainbow trout (*Oncorhynchus mykiss*)	0.3% (*w*/*w*)	↑ 6-desaturase protein and fatty acid content in the liver tissue ↑ The level of DHA, EPA and total PUFA	Torno et al. (2017)
Atlantic salmon (*Salmo salar*)	1.5 g/kg	↑ The fraction of C18:3n-3 and C18:2n-6 ↔ Modifications in the lipid homeostasis genes	Menoyo et al. (2019)
Broodstock medaka (*Oryzias latipes*)	20, 40, and 80 µg/g BW/day	↑ The intracellular phagocytosis and metabolic activity ↑ Display of proliferative lymphocyte activity ↑ The percentage of macrophages ↑ The quality of the ovaries and sperm ↓ The embryo survival rate	Kowalska et al. (2017)
Blunt snout bream (*Megalobrama amblycephala*)	0.04%, 0.36%, and 1.08%	↓ SGR ↓ The activity of SOD and CAT in plasma ↑ The plasma concentration of complement 3 and the hepatic expression levels of HSP70 (heat shock proteins) and TNF-α	Yan et al. (2017)
Blunt snout bream (*Megalobrama amblycephala*)	Resveratrol (0, 0.5% and 1.0%), quercetin (0.4% and 0.8%).	↑ The expressions of the mRNAs for SIRT1, Cu/Zn-SOD, CAT, and GPX ↓ The expression of Caspase-8 and TNF-α ↑ The hepatocyte survival, antioxidant protection, lipid metabolism, and immunology ↓ The growth performance	Jia et al. (2019 a)
Tilapia (*Oreochromis niloticus*)	0.025 g/kg	↑ The intestinal goblet cells and hepatic hemosiderin ↑ The reinforcement of Herpes simplex virus-related KEGG pathways, the calcium signalling route, cell adhesion molecules, apoptosis, PPAR and MAPK pathways ↑ The PPAR pathways ↑ The expression of FABP6 gene in the gut	Ye et al. (2023)

↑ – increase, ↓ – decrease, ↔ – no change, ACAT2 – acetyl-CoA acyltransferase, AMPK – AMP activated protein kinase, CAT – catalase, CYP7A1 – cytochrome P450 family 7 subfamily A member 1, FABP – fatty acid binding protein, FCR – feed conversion ratio, FOXO – forkhead box O, GADD45 – growth arrest and DNA damage-inducible 45, GPX – glutathione peroxidase, GST – glutathione S-transferase, HMGCR – 3-hydroxy-3-methylglutaryl-CoA reductase, HO-1 – heme oxygenase-1, HSP70 – heat shock protein 70, IgM – immunoglobulin M, IL – interleukin, KEGG – Kyoto Encyclopedia of Genes and Genomes, LDLR – low density lipoprotein receptor, MRPL – multidrug resistance-associated protein 2, MyD88 – myeloid differentiation primary response 88, NF-κB – nuclear factor kappa-light chain enhancer of activated B cell, NQO-1 – NAD(P)H quinone dehydrogenase 1, Nrf2 – nuclear factor erythroid 2-related factor 2, OATP – organic anionic transporting, PER – protein efficiency ratio, PPAR – peroxisome proliferator activated receptors, prx-6 – peroxiredoxin 6, SGR – specific growth rate, SIRT 1 – sirtuin 1, SOD – superoxide dismutase, TLR 2 – toll-like receptor 2, TNF-α – tumour necrosis factor-alpha.

Functions of resveratrol

Antioxidant role

Oxidative stress triggers the creation of reactive oxygen species (ROS), leading to an imbalance in physiological equilibrium. These powerful and extremely reactive ROS are produced by the endoplasmic reticulum and mitochondria during respiratory metabolism. The enzymatic and non-enzymatic groups make up the two components of the antioxidant system. Enzymatic groups encompass GPX, SOD, CAT, and glutathione reductase, whereas non-enzymatic groups comprise GSH, ascorbic acid, carotenoids, α-tocopherol, and total thi-

ols. As polyphenol, resveratrol is particularly attractive due to its enhanced support for the antioxidant system, achieved either by neutralizing ROS directly or by indirectly upregulating cellular defence genes and pathways. Several studies have reported that resveratrol alleviates and avoids oxidative conditions associated with stress including hyperglycemia (Xu et al., 2012), tissue damage (Chen et al., 2015, 2021), Parkinson's disease (Kung et al., 2021), and toxic substances like ethanol (Kasdallah-Grissa et al., 2007) and hydrogen peroxide (Kao et al., 2010). Truong et al. (2018) found that resveratrol is capable of effectively scavenging a variety of oxidants, including superoxide anion, nitrogen oxygen, hydrogen peroxide, singlet oxygen, hydroxyl radicals, and peroxynitrite. This is attributed to the compound phenolic rings, conjugated double bond, and potential for electron delocalization. By boosting the activity of antioxidant enzymes including GPX, CAT, and SOD, it has also been claimed to raise the effectiveness of the antioxidant defence system against oxidative stress (Kasdallah-Grissa et al., 2007; Kitada et al., 2011; Liu et al., 2013). Resveratrol capacity to scavenge free radicals was caused by hydrogen atom transfer and successive proton loss electron transfer (Truong et al., 2018). Similar effects have been observed with other polyphenols, including chlorogenic acid, quercetin, caffeic acid, tannins, and p-coumaric acid. These compounds have been reported for their role in mitigating oxidative stress and enhancing antioxidant defence through boosting the antioxidant enzyme activities in various fish species (Ahmadifar et al., 2019, 2021 a, b, 2022 a; Safari et al., 2020; Ghafarifarsani et al., 2023; Armobin et al., 2023).

According to reports, the antioxidant defence system endogenous transcriptional factor nuclear factor-erythroid 2 (NRF2) plays a significant role in the transcriptional control of genes associated with the antioxidant system. NRF2, for instance, reduces liver damage brought on by oxidative damage as reported in tilapia (Jia et al., 2019 b). Only mild oxidative stress was found to render NRF2 active, whereas excessive oxidative stress caused NRF2 to be downregulated. In phase II, decreased NRF2 also caused the antioxidant/detoxifying enzymes HO-1, HQO-1, and GST to be downregulated (Kaspar et al., 2009). In the aforementioned study, tilapia's NRF2 expression was increased by 0.3–0.6 g/kg of resveratrol (Jia et al., 2019 b). In phase II, dietary factors also increased the expression of antioxidant enzymes as heme oxygenase 1 (HO-1), NAD(P)H quinone dehydrogenase 1(HQO-1), and glutathione S-transferase (GST) was upregulated in phase II by dietary resveratrol. Dietary supplementation of resveratrol activates the NRF2 signalling pathway by which it elicits the antioxidant activity not only scavenging ROS and also upregulating the detoxifying/antioxidant enzymes such as heme oxygenase 1, HQO-1, and GST. The resveratrol involvement in the NRF2 signalling pathway in NRK-52E cells and astrocytes, which decreases the oxidative stress generated by hydrogen peroxide in the liver, was made clear in previous investigations, which provided support for the aforementioned assertion. Similar pathways are likely involved with the other polyphenols, although the specific activation of NRF2 pathway was not detailed in the comparative studies. Nevertheless, the enhancement of antioxidant enzymes such as GPX, SOD, and CAT indicates the common underlying mechanism (Ahmadifar et al., 2019, 2021 a, b, 2022; Safari et al., 2020; Ghafarifarsani et al., 2023; Armobin et al., 2023). Table 1 lists and illustrates several beneficial benefits of supplementing resveratrol in diverse fish species. The activation or modulation of NRF2 in epithelial cells, HepG2 cells, endothelial cells, intestinal epithelial cells, and PC12 cells was also described in prior research to result in reduced oxidative stress in *in vitro* models. Rats and mice were shown to exhibit comparable effects.

Growth performance

Development or accretion of muscles and atrophy are governed by the net equilibrium between protein synthesis and degradation (Mente et al., 2011). Aquaculture production primary goal is net protein synthesis, with muscle development garnering special attention. By increasing protein accretion and decreasing protein breakdown, this can be accomplished. The regulation of protein synthesis in the muscle, which is utilized as a measure of the increased rate of protein synthesis, is controlled by the activation of mTOR (mechanistic target of rapamycin) (Hemmings and Restuccia, 2012). In the muscle, there are lysosomal and non-lysosomal mechanisms for protein breakdown (Bonaldo and Sandri, 2013). In the non-lysosomal pathway, ubiquitin protein is tagged to the unnecessary/damaged protein, and the proteome complex (Bonaldo and Sandri, 2013) will recognize and result in the breakdown of the protein. Whereas in the lysosomal pathway, lysosomes receive materials to be degraded by phagocytosis, endocytosis, and autophagy (muscle protein turnover) (Rice-Evans and Burdon, 1993).

Reactive oxygen species are produced by phagocytosis and specific enzymes, such as oxidases, which cause the degradation of protein by oxidation and lipids by peroxidation (Latruffe and Rifler, 2013). Generally, ROS are produced in the mitochondria of most cells where dioxygen is reduced to one electron to form a superoxide anion (Nyström, 2005). When the antioxidant defence system cannot bear the excess level of ROS, oxidative stress occurs, leading to the formation of free radicals. This process is unavoidable due to the nature of respiration. For example, oxidative stress causes irreversible protein carbonylation, indicating protein damage by ROS (Kairisalo et al., 2011). It has been found that protein carbonylation has been linked to decreased protein synthesis and reduced growth. The mechanism behind protein degradation involves the exposure of the unfolded proteins to ubiquitin tagging, leading to degradation by the proteasome complex. Supporting this, dietary supplementation of resveratrol as polyphenolic compound significantly decreased the process of carbonylation which

indicates the reduced protein oxidation induced by ROS in the white epaxial muscle tissue of juvenile southern flounder (Wilson et al., 2015). The mechanistic effect of resveratrol is in agreement or similar with the immunomodulatory (increasing Ig, ACH50, and lysozyme activity) and antioxidant properties (increasing SOD, CAT, and GPX and decreasing ROS) of *Artemisia annua* leaf extract, which have been attributed to the polyphenolic compound present in it, resulting in increased growth performances of common carp (Sarhadi et al., 2020). In addition, Ahmadifar et al. (2022 b) reported that supplementation of cornelian cherry (*Cornus mas* L.) fruit extract, rich in polyphenolic bioactive substances, enhanced the growth performance of common carp through increasing the expression of antioxidant enzymes (CAT, glutathione reductase, glutathione S-transferase, and SOD) and through enhancing the immune responses (lysozyme activity, total Ig, total protein, CC-chemokine and IL-10).

In contrast, it has been found that chlorogenic acid, quercetin, tannins, and other polyphenols may directly impact growth performance through improving growth parameters (FCR, SGR, and weight gain), digestive enzyme activity, gut microbiota, intestinal morphology (colon crypt size, villi, etc.), and synthesis of DNA, RNA, and proteins, as well as by upregulating the growth hormone (IGF1), thus providing a comprehensive improvement in fish growth performance (Ahmadifar et al., 2019, 2021 a, b, 2022; Safari et al., 2020; Ghafarifarsani et al., 2023; Armobin et al., 2023).

Based on research reports, resveratrol antioxidant activities involve capturing and removing ROS (Xia et al., 2011; Giovannini and Masella, 2012; Gao et al., 2012). Additionally, it has been noted to alter cell signalling pathways and boost the antioxidant activity of mitochondrial enzymes. When the above protein degradation is influenced by antioxidants, much research has been conducted with antioxidants including vitamins E, C, and D, astaxanthin, etc. which results in enhanced growth (Lee and Dabrowski, 2004). Vitamin E supplementation in the diet decreased the value of thiobarbituric acid-reactive substance (TBA-RS), a biochemical indicator of lipid peroxidation (Lee and Dabrowski, 2004). Similarly, dietary vitamin C enhanced the growth of various species including seabass, yellow perch (Wang et al., 2003), and parrot fish (Valenzano et al., 2006). In relation to the previous investigations, resveratrol antioxidant properties might be employed as a beneficial feed supplement to increase protein synthesis by lowering the degradation of proteins. Wilson et al. (2015) found that dietary resveratrol had no difference in the marker of lysosomal protein degradation (LC3), though non-lysosomal marker (ubiquitin) was significantly reduced. The preceding study findings showed that lowering ubiquitinoylation significantly increased growth in resveratrol-fed fish while having no effect on LC-3. There was little information in the study on fish species dietary resveratrol supplements. In addition to the growth-promoting effects, dietary resveratrol enhanced the lifespan of short-lived (9 weeks) killifish (Valenzano et al., 2006). More insights on experiments performed on the growth performances of different fishes are depicted in Table 1.

Immunomodulatory effects

Immunity is greatly influenced by the profound beneficial effects of the nutritional status of the animal. Dietary supplementation with functional foods or feed additives would be an effective way to increase the immune status. Resveratrol is a polyphenolic bioactive substance that has been discovered to be highly effective at protecting against neurodegenerative diseases and immune system enhancement (Anal et al., 2023). Chen et al. (2014) reported that resveratrol has immunomodulatory actions that prevent thrombocytes and monocytes from producing and secreting the pro-inflammatory mediator (PGE2) from arachidonic acid. Immune suppression was another reason for liver damage caused by oxidative stress. The downregulation of LZM, HEP, and complement 3 mRNA levels induced by hydrogen peroxide in the plasma of Atlantic salmon (Chalmers et al., 2018) and the liver of tilapia (Jia et al., 2019 b) serves a critical role in shielding the host from oxidative stress and microbial expression lowers the activity of immunological markers. The activity of LZM, HEP, and C3 was increased in treated fish, according to the study on the immunomodulatory effects of resveratrol (Ognik et al., 2016). The activation of neutrophils (phagocytes) results in the generation of ROS, and this elevated amount of ROS both produces oxidative stress and, during respiratory burst activity, destroys pathogens. The incubation of resveratrol is found to have a scavenging role in ROS and thus reduce the amount of ROS in fish leukocytes in order to protect the internal organs (Castro et al., 2008). Similar to this, dietary resveratrol decreased the generation of ROS brought on by phorbol 12-myristate 13-acetate, shortly called as PMA in fish leukocytes (Castro et al., 2008). The outcome of a study demonstrated that resveratrol has a beneficial impact on phagocyte and lymphocyte activity (Kowalska et al., 2017). Additionally, it was shown that supplementing with resveratrol at a level of 80 grams per gram of body weight improved the immune system in medaka fish (Kowalska et al., 2017). With an array of molecular targets, resveratrol is known to operate as a regulatory body in suppressive functions of $CD25^+$ and $CD4^+$ in both immune systems. By preventing spleen cells from proliferating and reducing the production of IFNγ (interferon-gamma), IL-2 (interleukin 2), TNF-α (tumour necrosis factor α), and IL-12 (interleukin 12), it also plays a significant part in immunomodulation (Anal et al., 2023). Table 1 portrays the immunomodulatory functions and prophylactic effects of resveratrol. In rodents, dietary resveratrol promoted macrophages, natural killer cells (NK), and T-cells (Sorrenti et al., 2022). Resveratrol exhibits unique immunomodulatory characteristics compared to other polyphenolic compounds. It reduces a broad range of pro-inflammatory cytokines

and impacts various immune cells, such as macrophages, neutrophils, NK cells, and T-cells, showcasing a more comprehensive role in immunomodulation. In contrast, several authors have reported that other polyphenols, including quercetin, caffeic acid, chlorogenic acid, ferulic acid, and p-coumaric acid, typically enhance the specific immune parameters or the antioxidant defense system rather than broad control over the immune system of fish (Ahmadifar et al., 2019, 2021 a, b, 2022 a; Safari et al., 2020; Ghafarifarsani et al., 2023; Armobin et al., 2023).

As a polyphenolic compound, resveratrol has been widely studied for its role in intestinal immunity. It has been reported that resveratrol has positive impacts on the intestinal immune response by downregulating the expression of TNF-α, IL-1β, IL-10, and IL-8 and upregulating anti-inflammatory cytokines, including IFN-γ and TGF-β (Zheng et al., 2017; Tan et al., 2019). The mechanistic action of resveratrol on intestinal health was found to be similar to that of prebiotics, where it decreases the production of pro-inflammatory cytokines IL-6 and IL-1β, and increases the expression of anti-inflammatory cytokines (Nawaz et al., 2018).

Disease prevention

Due to intensive progression of aquaculture, there is a need to maintain the balance between the production and disease resistance and the health status of fish (Ashley, 2007; Kowalska et al., 2017). The immunosuppressive effects of physical stress led to decreased resistance and heightened susceptibility to disease (Kowalska et al., 2017). Certain feed additives, along with the high-quality nutrients, are found to improve the immune response of the host. Resveratrol is reported to have immunomodulatory function (Flippin et al., 2007; Kowalska et al., 2017). It functions by enhancing the production of highly active prostaglandins via cyclooxygenase enzymes (COX) from arachidonic acid, which plays a crucial role in fish immunity (Rowley et al., 1995; Hata and Breyer, 2004; Furne et al., 2013; Chen et al., 2014). Besides probiotics, prebiotics, antibiotics, and vaccines, it has been identified that resveratrol could be used as a virulence factor to combat various diseases (Kari et al., 2024).

Hemolysin is a toxin produced by pathogenic bacteria from the *Vibrio* genus, which is responsible for various diseases (Soto-Rodriguez et al., 2010). This toxin can lyse red blood cells by either forming a protein pore on their surface or by activating the phospholipase enzyme (Rowe et al., 1994). *Vibrio harveyi* is a common pathogenic bacterium known to produce hemolysin and is responsible for increased mortality rate in most aquaculture species (Lee et al., 2009; Kari et al., 2024). Notably, resveratrol mitigated the toxicity of *Vibrio harveyi* hemolysin (VHH) in *Takifugu rubripes* by inhibiting VHH-induced hemolysis and downregulating the transcription level of the virulence factor (Zhao et al., 2020). Furthermore, resveratrol exhibited therapeutic effects on tissue lesions caused by *V. harveyi* infection, improving the condition of affected organs such as the kidney and liver (Zhao et al., 2020). Another study found that dietary resveratrol enhances lysozyme activity and downregulates the mRNA expression of hepatic heat shock proteins HSP90 and HSP70, as well as tumour necrosis factor alpha (TNF-α), to protect snout bream against *Aeromonas hydrophila* infection (Yan et al., 2017).

Synergistic effects of resveratrol and β-glucan

The synergistic effects of resveratrol and β-glucan in various biological systems, including antioxidant activity (Vetvicka and Vetvickova, 2014), immune response, and growth performances, are quite fascinating. Their combined effects offer promising avenues for therapeutic and nutritional interventions, although specific outcomes can vary depending on the dosage, duration of treatment, and species of interest. β-glucan possesses antioxidant properties through enhancing the antioxidant enzyme activities and related genes (Khanjani et al., 2022). β-glucan, as complex polysaccharides have indirectly activated immune mechanisms, such as phagocytes, lysozyme secretion, immunoglobulin M, complement C3, interferons, and cytokines (IL-6 and IL-1) by binding to the glucan receptor on the surface of macrophages and other white blood cells (NK cells and neutrophils) (Sakai, 1999; Gantner et al., 2003; Herre et al., 2004; Dalmo and Bøgwald, 2008; Meena et al., 2013; Sahoo et al., 2005; Khanjani et al., 2022). Many researchers have investigated the effect of β-glucan alone or in combination with other functional additive on growth performance and survival rate in fish. It has been found that β-glucan can enhance growth and survival possibly through improved immunity, digestive function and colonic fermentation by probiotic bacteria (Itami et al., 1989; Abdel-Tawaab et al., 2008; Lam and Cheung, 2013; Khanjani et al., 2022). Hence, there is a promising opportunity for future research into the synergistic effects of resveratrol and β-glucan, which enhance antioxidant activity, immune responses, and growth performances through complementary mechanisms in fish.

Conclusion

Resveratrol is a potential candidate for feed supplementation to improve lipid oxidation, accumulation and prevention of lipid peroxidation, and oxidative stress caused by high-fat diets in fish. The use of resveratrol as a feed additive has the potential to revolutionize the aquaculture and fish feed industry in a sustainable direction. It can improve growth performance, strengthen immune systems, and improve fish welfare by increasing antioxidant levels.

Declaration of competing interest

The authors affirm that they have no known financial or interpersonal conflicts that may have seemed to have influenced the research presented in this publication.

Data availability statement

This manuscript contains data that supports the findings of the study available within manuscript.

Author contributions

Kavitha Malarvizhi: writing original draft and literature collection, Kalaiselvan Pandi: help in the collection of literature and draft writing, and Amit Ranjan: conceptualization, review, editing, and supervision.

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