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Mechanisms and Beneficial Applications of Resveratrol as Feed Additive in Animal and Poultry Nutrition: A Review

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ABSTRACT

The polyphenol resveratrol is an antioxidant nutrient, used to enhance growth performance through activation and modification of gut function and structure and to inhibit cancer initiation and promotion. The main application of resveratrol is in animal and poultry nutrition, in particular as a feed additive to reduce free radicals in a wide variety of animal species. Several studies carried out on diets supplemented with additives containing natural antioxidants as resveratrol demonstrated its capability to improve the productive performance, immune response and health of livestock besides reducing the risks of various animal diseases such as cancer and other degenerative diseases. Such activities could be attributed to its powerful antioxidant, immunomodulatory and anti-inflammatory effects by preventing free radicals from interacting with cellular DNA and its ability to alter the intestinal microbiota, increased digestibility and absorbance of nutrients. This review describes the modes of action, metabolism, the biological activities, natural sources and beneficial aspects/potential applications of resveratrol in animal and poultry nutrition, production and health.

Key words: Resveratrol, performance, oxidative status, health, animal, poultry

INTRODUCTION

Resveratrol (trans-3,5,4'-trihydroxystilbene) is a stilbenes, type of aromatic phytoalexin and natural phenol mainly presented in grapes, peanuts, berries, yucca (*Yucca shidigera*) and turmeric (*Curcuma longa*), also created naturally by many plants as a response to infection or injury which is induced by microbial pathogens such as fungi or bacteria (Fremont, 2000). Numerous studies (*in vitro* and *in vivo*) described different biological impacts and protective effects of resveratrol, including antioxidant, cardioprotective, anti-atherogenic, antiaging, anti-platelet aggregation, anticancer, antiinflammatory, Anti-diabetic, anti-tumor, immunomodulatory, health-promoting activities as well as chemopreventive and activities of metabolic rate (Pervaiz, 2001; Frojdo *et al*., 2007; De la Lastra and

Villegas, 2007; Kulkarni and Canto, 2014; Singh *et al*., 2014; Szkudelski and Szkudelska, 2014; Zordoky *et al*., 2014).

Resveratrol as a botanical polyphenolic compound is considered as an important monomeric bioactive compound that exhibits a strong antioxidant capacity to scavenge free radicals of oxygen and lipids (Rubiolo *et al*., 2008) and protect DNA from oxidative damage (Yan *et al*., 2012). Resveratrol inhibits the formation of glutathione disulfide and maintains glutathione in a reduced state, thereby inhibiting the cellular damage produced by free radical reactions (Hung *et al*., 2000) and also by reduction or prevention of the apolipoprotein B peroxidation accompanied with low density lipoprotein (Kubota *et al*., 2009; Shakibaei *et al*., 2009). Resveratrol or its derivatives also exhibit antimicrobial properties and prevent cancer cell proliferation (Yang *et al*., 2012). Liu *et al*. (2014) stated that the reduction of malonaldehyde and heat stress-induced ROS in chickens were achieved by resveratrol treatment.

Resveratrol as an anti-inflammatory agent is strongly linked with augmented pro-inflammatory mediators like, tumor necrosis factor-α, prostaglandin E_2, interferon-γ and interleukins 2, 6 and 12 (Sehirli *et al*., 2008). In animal studies, resveratrol has been shown to prevent ocular inflammation in endotoxin-induced glaucoma (Luna *et al*., 2009). Meanwhile, anticarcinogenic, immunostimulant and antiaging effects of resveratrol are related to phosphoinositide 3-kinase inhibitions which induce down regulation of insulin-like growth factor (Frojdo *et al*., 2007) and of nuclear factor κB activation and cyclooxygenase-2 and matrix metalloprotease-9 activities (Shakibaei *et al*., 2009). Animals exposed to heat stress often exhibit a weakened immune response and immune system, in general. Previous studies have shown that natural polyphenolic additives such as resveratrol could improve body immune response and scavenge free radicals in immune cells (Bub *et al*., 2003; Bayer *et al*., 2004). In view of a potent cytoprotective effect of resveratrol, cellular responses induced by resveratrol warrant further investigation.

Various feed additives and supplements are attaining importance nowadays in animal and poultry production as well as health care systems based on their wider beneficial applications as promoting growth and production, immune enhancing effects and safeguarding health (Mahima *et al*., 2012; Ashour *et al*., 2014; Dhama *et al*., 2013a, b, 2014; Farag *et al*., 2014; Rahal *et al*., 2014a, b; Tiwari *et al*., 2014). The present review describes the salient characteristics, mechanisms of action, metabolism, biological activities, natural sources, beneficial aspects and potential applications of resveratrol in animal and poultry nutrition, production and health which could be highly useful for researchers, pharmacists, veterinary professionals, pharmaceutical industries, livestock and poultry industry.

RESVERATROL SOURCES

Resveratrol is spread in some plants such as red grapes (*Vitis* spp.), grape products, raspberries, mulberries, grapevines, strawberry and Japanese knotweed roots (*Polygonum cuspidatum*) (Vuong *et al*., 2014), as well as peanuts (*Arachis* spp.), yucca (*Yucca shidigera*) and turmeric (*Curcuma longa*) (Sheu *et al*., 2013). Resveratrol is also found in *Gnetum cleistostachyum*, *Dracaena loureiri*, *Cassia* spp. and *Pterocarpus* spp. (Rimando *et al*., 2004; Yao *et al*., 2005). The amount of resveratrol in red wine is about 0.1-14.3 mg L^{-1} (Baur and Sinclair, 2006). Furthermore, resveratrol has been generated by chemical and biotechnological synthesis (Farina *et al*., 2006; Trantas *et al*., 2009).

CHEMICAL STRUCTURE

The chemical composition of resveratrol is 3, 5, 4'-trihydroxystilbene, derived from stilbenes. There are two geometric isomers of resveratrol: cis and trans. The isomers of resveratrol (cis and trans) can be either free or linked to glucose (Baxter, 2008).

The trans-form of resveratrol can undergo isomerization to the cis-form when exposed to ultraviolet irradiation, a process called photo-isomerization (Bernard *et al*., 2007). The structural formula of resveratrol is shown in Fig. 1.

PHYSICAL CHARACTERISTICS

Resveratrol as a natural antioxidant isolated from plants is a compound of highly lipophilic and hydrophilic properties; thus, it is assumed to be more effective than certain other antioxidants like Vitamin C and E (Murcia and Martinez-Tome, 2001). The Trans form of powder resveratrol is stable under high air humidity up to 75% and temperature about 40°C (Prokop *et al*., 2006). Cis-resveratrol form which is exposed to ultraviolet irradiation causes more photochemical reaction, gives a fluorescent molecule called resveratrone (Yang *et al*., 2012). Also, the trans-form of resveratrol is stabilized with the presence of transport proteins (Pantusa *et al*., 2014). http://en.wikipedia.org/wiki/Resveratrol-cite_note- pmid16579722-88.

MODES OF ACTION AND BIOLOGICAL ACTIVITIES

The positive effects of resveratrol as feed additives in animal or human diets on life extension are not exactly

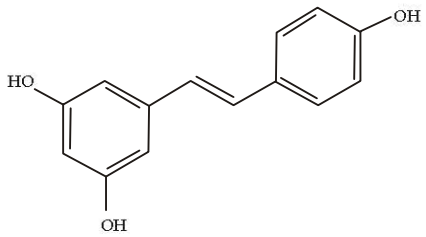

Fig. 1: Basic structural formula of resveratrol, resveratrol (3, 5, 4'-trihydroxy-trans-stilbene)

understood. But, these effects may be attributed to biochemical impacts of energy restriction (Timmers *et al*., 2012; Marchal *et al*., 2013). Some recent studies illustrated that resveratrol supplementation to diet increases the expression of Sirtuin1 and PGC-1α, this means that resveratrol supplementation improves Sirtuin1 activity as well as enhances the activity of the mitochondria and increases the linkage between Lamin A and Sirtuin 1 (Lagouge *et al*., 2006; Alcain and Villalba, 2009; Hubbard *et al*., 2013; Lakshminarasimhan *et al*., 2013).

Robb *et al*. (2008) observed that the activity of MnSOD (SOD_2) increases by 40 fold in cells treated with resveratrol compared to control group. Where, the SOD_2 decreases superoxide to hydrogen peroxide. SOD_2 is a defense mechanism against superoxide which in turn enhances the mitochondrial system to act normally and resist permeability transition and cell death in many diseases (Macmillan-Crow and Cruthirds, 2001). There are many beneficial activities of resveratrol including to inhibit or prevent pancreatic cancer and increase the body resistance to irradiation damage and infection and thereby, lifespan extension (Stojanovic *et al*., 2001; Cullen *et al*., 2003; Hu *et al*., 2007). Also, Khan *et al*. (2013) stated that the increase regulation of antioxidant enzyme like catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) but simple change in GSH-Px or CAT and their enzymatic activity in cancer cells results in the mitochondrial aggregation of hydrogen peroxide (H_2O_2), resulting in cancer cell apoptosis. This could explain the results from previous *in vitro* studies conducted on different kinds of cells and sub-cellular level which reported that resveratrol could counter act the effect of carcinogenicity throughout its different stages, since resveratrol could act as modulator for the transcription factor NF-κB (Leiro *et al*., 2005) as an inhibitor of many proliferative tumors (Aziz *et al*., 2006; Faber and Chiles, 2006; Riles *et al*., 2006; Sareen *et al*., 2006; Benitez *et al*., 2007).

On the other hand Marambaud *et al*. (2005) reported that resveratrol inhibited the abnormal functions of neuronal cell, preventing their death and this could clarify the role of resveratrol in inhibiting some dangerous diseases like Alzheimer's disease and Huntington's disease. There is another confirmatory study by Olson *et al*. (2005) which showed that resveratrol inhibits the activity of cardiac fibrosis and fibroblasts, thus prevent their progression. Moreover, Resveratrol statistically improves production of natural testosterone from being both a selective estrogen receptor modulator (Bhat *et al*., 2001) and an aromatase inhibitor (Wang *et al*., 2006).

Olas and Wachowicz (2005) assayed resveratrol activities in platelets and determined that the hydroxyl group was important in the inhibition of the production of ROS and malonaldehyde (MDA). Baxter (2008) found that the biological efficient of resveratrol for the prevention of free radicals or lipid peroxidation was 95% compared to the traditional antioxidants such as Vitamin E and C which were about 65 and 37%, respectively.

METABOLISM, BIOSYNTHESIS AND BIOAVAILABILITY

Resveratrol is presented in some plants; moreover these plants did not contain large amounts of resveratrol compound and it is created as a response to stress, indeed resveratrol belongs to phytoalexin that protect against injury or damage which is caused by exposure to ultraviolet irradiation (Dixon, 2001). Nakaune *et al*. (2002) showed that resveratrol is toxic to plant pathogens but there are certain parasites like fungi which overcome this toxicity, via the action of membrane proteins which transport the compound out of the cellular system. The biosynthesis of resveratrol occurred by stilbene synthase, via the repetitive decarboxylative condensation of a p-coumaroyl compound from p-coumaroyl-CoA with three C2-units from malonyl-CoA. Furthermore, reactions conjugate native resveratrol to sulfate or glucosyl compounds at the 3-sites of the bi-phenolic ring. Glycosylated piceid form is more resistant to oxidative degradation than resveratrol. Where, the biological activity of glycosylated resveratrol is maintained more soluble and stable thereby, is more speedily absorbed by the human and animal intestine (Regev-Shoshani *et al*., 2003). Sharan and Nagar (2013) showed that the body extensively metabolized resveratrol where gut, liver and lungs are the mainly positions of resveratrol metabolism. Wenzel and Somoza (2005) reported that around 75% of resveratrol is removed by urine and excreta out the body. Also, the resveratrol bioavailability is low or zero in almost time may be attributed to speed and extensive metabolism or its poor water solubility and the consequent compound of different metabolites such as resveratrol sulfates and resveratrol glucuronides (Augustin *et al*., 2013) but, encapsulated resveratrol provides a potential approach for improving the solubility of resveratrol, consequently, enhancing its bioavailability. On the same context, the oral resveratrol bioavailability is not related to dose or aqueous solubility (Das, 2011).

RESVERATROL IN ANIMAL AND POULTRY NUTRITION

A number of animal and poultry trails have been conducted previously to establish the dependency and functionality of resveratrol and supplementation of it in animal and poultry diets. Juan *et al*. (2002) reported that no negative effects occur on growth performance, feed utilization, water consumption, biochemical and hematological parameters or histopathological changes when tested at a very high dose (20 mg kg^{-1} through 20 day) of oral resveratrol supplementation to rats. Serum IgG concentration was improved in the diet supplemented with resveratrol and different plant extracts such as cinnamon, thyme and oregano compared to the control diet in mice and pigs (Namkung *et al*., 2004; Liu *et al*., 2005).

Hao *et al*. (2011) reported that resveratrol supplementation (5, 22.5 and 45 mg kg^{-1} diet) could decrease MDA

concentrations in liver of mice with high fat and high cholesterol diets. Also, the levels of GSH-Px, SOD were increased with resveratrol groups. Dal-Pan *et al.* (2010) observed that diet supplemented with resveratrol reduced body weight change by synchronous reducing energy consumption by 13% and increasing resting metabolic rate by 29%. The daily locomotor activity did not change by resveratrol supplementation by 200 mg kg^{-1} day^{-1}. Also, there are no observable effects of resveratrol supplementation on hormone plasma concentrations. Similar enhancements in FCR have been observed upon resveratrol supplementation (Paulo *et al.*, 2010) to pig diets. On the same context, Viveros *et al.* (2011) reported that broiler fed diets supplemented with polyphenol-rich grape products achieved the high levels of gut microbiota and the ratio of villus height to crypt depth at the jejunum of broiler, these results may have an effective influence on the biochemistry and physiology of the gastrointestinal tract.

Feed consumption, egg production and exterior and interior egg quality criteria as well as concentrations of vitamin A in serum and egg yolk were not statistically affected by dietary resveratrol supplementation (200 or 400 mg kg^{-1} diets) in quail layers except yolk width during period 4-16 weeks of age (Sahin *et al.*, 2010). Conversely, blood and yolk malondialdehyde concentrations and liver heat shock protein concentration were decreased with increasing resveratrol supplementation in layer quail diets from 200-400 mg kg^{-1} diet but the level of vitamin A in blood was augmented with resveratrol supplementation compared to the control diet.

Early studies conducted to enhance oxidative stability of meat and eggs by using natural or synthetic antioxidant or supplementation pure antioxidants to the poultry diets revealed an inverse relationship between the levels supplementation of antioxidant and lipid peroxidation in poultry meat, egg yolk and blood serum as well (Guo *et al.*, 2001; Sahin *et al.*, 2008) and reduction of blood and cholesterol contents in the egg yolk (Zhu *et al.*, 2008). Studies using resveratrol have suggested that it facilitates the inactivation and subsequent elimination of oxide precursors (Liu *et al.*, 2014) and mobilizes the expression of antioxidant-related proteins (Sgambato *et al.*, 2001), thus suggesting that it plays a protective role against oxidative stress.

Lopez-Velez *et al.* (2003) noted that resveratrol is an effective eliminator of superoxide, hydroxyl and metal-induced free radicals and enhances the activities of antioxidant enzymes (Young *et al.*, 2000), including SOD, GSH-Px, CAT, glutathione S-transferase and NADPH quinoneoxidoreductase as well as activates of erythroid-derived nuclear factor, a key transcription factor regulating the response of antioxidant (Rubiolo *et al.*, 2008). Similarly, previous studies indicated that supplemental dietary resveratrol reduced the MDA level and increased the activities of CAT, SOD and GSH-Px in the serum (Sahin *et al.*, 2010, 2012). Das (2011) found that resveratrol as a natural antioxidant scavenges reactive oxygen species and protects the organism from oxidative stress by improving the antioxidant capability to withstand thermal stress. Numerous studies have shown that resveratrol can attenuate cellular processes associated with high temperature (Das, 2011; Sahin *et al.*, 2012), UV radiation (Liu *et al.*, 2014), lipopolysaccharide (Sebai *et al.*, 2010) and ethanol-induced oxidative stress (Kasdallah-Grissa *et al.*, 2007).

Mice fed diets supplemented with resveratrol (7 mg kg^{-1} day^{-1}) for 12 months exhibited a larger follicle pool and number and quality of oocytes than those fed diet without resveratrol supplementation (Liu *et al.*, 2013). Also, Salzano *et al.* (2014) stated that resveratrol addition of bovine culture medium enhances the fertility rate, cell numbers, blastocyst development and embryo cryotolerance. Chickens fed diets supplemented with resveratrol (200, 400 or 600 mg kg^{-1} of diet) achieved a linear increase in feed consumption, body weight gain, GSH, GSH-Px, SOD and CAT activities in the serum as well as levels of insulin-like growth factor-1 and growth hormone compared with chickens fed diets without resveratrol during heat stress. Also, the growth index of immune organs (spleen, thymus and bursa of Fabricius) increased with increasing resveratrol supplementation levels. On the contrary, feed conversion ratio and serum MDA levels were decreased in the chickens fed resveratrol-supplemented diets (Liu *et al.*, 2014).

Sridhar *et al.* (2014) reported that birds fed resveratrol at both 0.5 and 1.0% levels with basal diet had lower body weight gain and feed intake during period 4-5 week of age. But, no variation was obtained in the feed conversion ratio in resveratrol supplementation group of broiler chicks. The inclusion of resveratrol in broiler diets helped in increasing the oxidative enzymes activities or enhanced antioxidant status of the birds as well as improved the total antioxidant capacity and protein in plasma. In resveratrol groups, the degree of the liver lesions was far less.

Resveratrol showed strong potential as antibiotic alternatives for reversing the adverse effects of weaning stress on growth performance, immunity, digestibility of nutrients and fecal microbial shedding of weaned piglets (Ahmed *et al.*, 2013), where FCR and serum IgG concentration were improved in the diet supplemented with 0.2% resveratrol compared to the control diet. But, TNF-α level was reduced in the supplemented groups compared to control. Poulsen *et al.* (2013) observed that resveratrol supplementation as anti-diabetic plays an important role to improve glucose metabolism and to prevent inflammation, metabolic abnormalities, cancer and nonalcoholic fatty liver disease. Further, Resveratrol supplementation to animal diet increased insulin secretion, glucose homeostasis, glycemic control and activity of SIRT1 and decreased insulin resistance and metabolic disorders compared to other diets did not contain resveratrol (Szkudelski and Szkudelska, 2014). Xu *et al.* (2013) found that resveratrol (3.85 μg mL^{-1}) supplementation decreases duck enteritis virus multiplication by 50%. This reduction in virus proliferation may be due to the inhibition of viral proliferation in the host cell.

Momchilova *et al.* (2014) showed that the saturated to unsaturated fatty acids ratio in the membrane phospholipids,

phosphatidylethanolamine and phosphatidylcholine was decreased with increasing resveratrol supplementation. Also, resveratrol addition to aged rat diet exhibited inhibition of phospholipids and free fatty acids synthesis. Additionally, the unsaturated fatty acids were increased with resveratrol inclusion in the control diet; this effect is an excellent target of oxidative attack. Moreover, the lipid peroxide and ROS levels were significantly lower but reduced glutathione (GSH) was almost unaffected in resveratrol-treated hepatocytes. Kucinska *et al.* (2014) observed that the activities of the anti-apoptotic proteins (caspase 3 and 9) were significantly increased with higher levels of resveratrol group compared to control diet, indicating the capability of resveratrol to reduce the factors responsible for cell death such as mitochondrial potential, oxidative stress and decrease of glutathione level as well as loss of both mRNA expression and activity of superoxide dismutase.

Zhang *et al.* (2014) found that chicks fed diets supplemented with resveratrol (200, 400 or 800 mg kg^{-1} of diet) achieved the highest values of body weight gain, IgM, thymus weight, cell proliferation index, antibody titers against avian influenza viruses H5 and H9 and Newcastle disease virus as well as growth hormone receptor gene mRNA expression and insulin-like growth factor-1 than those fed control diet during the experimental period (1-40 day of age). But, nuclear transcription factor-κB gene, tumor necrosis factor-α mRNA relative and interleukin-1β expression and apoptosis were linearly decreased with increasing resveratrol levels. On the same context, Yuan *et al.* (2012) observed that the immunity parameters (IgG, T cell-mediated and T helper cells) of aged male rats at 12 and 21 months of age were improved with increasing dietary intake of resveratrol. Liu *et al.* (2005) noted that resveratrol addition by 700 g t^{-1} diet augmented the density of bone mineral and decreased femur calcium loss linked to estrogen reduction. Tadolini *et al.* (2000) reported that resveratrol compound inhibited FeO-catalyzed lipid peroxidation mainly by eliminating lipid free radicals within the membrane cell and that it cannot alter the oxidation state of the ferric oxide in a way that would change the ratio of FeO to Fe O. Aburjai (2000) stated that both of rhaponticin and trans-resveratrol-3-O-β-D-glucopyranosid, perform antiplatelet activity while, the inhibitory effects of these compounds on platelet accumulation are lower compared to the action of resveratrol. Resveratrol has been found to down-regulate phase I genes of xenobiotic bio-transformation (CYP1A1, CYP2E1, CYP2C29) in female rats (Hebbar *et al.*, 2005).

There are many studies carried out on experimental animals, these studies demonstrated that resveratrol supplementation to diet of rats, mice and human plays an important role to protect heart cells or cardiovascular system from free radical-induced cell death or from damage which occur through obesity and chronic hypertension (Madhav *et al.*, 2009; Sadruddin and Arora, 2009; Ansari *et al.*, 2011; Santos *et al.*, 2011; Raederstorff *et al.*, 2013). Also, resveratrol supplementation improves the activation of sirtuins which in turn is a major contributor to prevent death of rat cardiac cells (Walle *et al.*, 2004).

CONCLUSION

The dietary resveratrol supplementation as a natural antioxidant or growth promoter has useful effects on feed utilization, immunity, oxidative status, egg quality criteria and productive performance. Additionally, useful effects of lowered serum MDA, lipid peroxidation have been observed in animal and poultry fed diets supplemented with resveratrol, indicating the positive effects and vital role of resveratrol dietary addition which could be attributed to its antioxidant and pharmacological effects and beneficial health impacts, such as anticancer, antiviral, antifungal, neuroprotective, antiaging and antiinflammatory. Exploration of the modes of action of resveratrol such as pharmacological, nutritional and biological activities are crucial for successful farm animal and poultry management that may provide further understanding of the health and performance parameters in agriculture species.

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