Chapter 1

Evaluation of Resveratrol Supplementation on Laboratory Animals, Cats, Pigs, Horses, Dogs, Cattle, and Birds

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Additional information is available at the end of the chapter

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Abstract

This chapter evaluated resveratrol supplementation on laboratory animals, cats, pigs, horses, dogs, cattle and birds. Resveratrol (3, 5, 4′-trihydroxystilbene) is a stilbenoid, a derivate of stilbene. It is found in some plants such as red grape, grape products, cocoa, peanuts, raspberries, mulberries, strawberry and Japanese knotweed roots. The most important dietary source of resveratrol is red wine, and it is often assumed to be an important factor in the French Paradox, a term used to describe the observation that the French population has a very low incidence of cardiovascular disease, despite a diet high in saturated fats. Research has shown some therapeutic effects of resveratrol ranging from antioxidant, anti-inflammatory, cardioprotective, antiatherogenic, antiaging, anti-platelet aggregation, anticancer, antidiabetic, antitumor, and immunomodulatory activities. In laboratory animals, benefits of resveratrol comprise antitumor effects while in cats it has shown to improve hepatic function. In pigs, the antibiotic and antiviral effects of resveratrol have been illustrated. The anti-inflammatory and antioxidative properties of resveratrol in horses and cattle were also reviewed. The supplement was shown to be useful as an antibiotic and an aid in improving alertness in dogs. Resveratrol also showed to increase growth performance in birds. It is therefore concluded that use of resveratrol is a potent aid in improving animal production and health.

Keywords: animals, anti-inflammatory, antioxidant, benefits, resveratrol

1. Introduction

Resveratrol (3, 5, 4′-trihydroxystilbene) is a stilbenoid, a derivate of stilbene. It exists as two geometric isomers: *cis*-(*Z*) and *trans*-(*E*) [1] (**Figure 1**). The *Tran*- and *cis*-resveratrol can be either free or bound to glucose [2].

Resveratrol is a natural polyphenol nonflavonoid compound present in strongly pigmented vegetables and fruits. It is found in more than 70 species of plants such as grapes (*Vitis vinifera*), cranberry (*Vaccinium macrocarpon*), peanut (*Arachis hypogaea*), cocoa, raspberries, mulberries, grapevines, strawberry and Japanese knotweed roots (*Polygonum cuspidatum*) [3] which has the highest concentration of resveratrol (**Figure 2**). Resveratrol is also present in yucca (*Yucca schidigera*) and turmeric (*Curcuma longa*) [4]. The most important dietary source of resveratrol is red wine, and it is often claimed to be an important factor in the French Paradox, a term coined to describe the observation that the French population has a very low incidence of cardiovascular disease, despite a diet high in saturated fats [5]. A new bioconversion system is known to produce resveratrol in the blastospore of *Tremella fuciformis* [6]. *Tremella fuciformis* is a known edible macrofungus that has medicinal value and is widely cultivated in China. Resveratrol has also been produced from tyrosine in metabolically engineered *Saccharomyces cerevisiae* [7].

Resveratrol was first used as a traditional Chinese and Japanese medicine for treatment of human inflammatory, allergic, hypertensive, and lipid diseases [9].

Current research into resveratrol benefits shows that resveratrol has amazing antiaging properties at the cellular level [10, 11]. This effect may be attributed to biochemical impacts of energy restriction [12, 13]. Caloric restriction is an effective means of preventing chronic disease and ultimately increasing lifespan [14]. SIRT1, an NAD + −dependent deacetylase, was identified as one of the molecules through which calorie restriction extends lifespan or delays age-related diseases [15]. This has led to breakthroughs in geriatric and antiaging medicine. Resveratrol is recognized to increases the expression of Sirtuin1 and Peroxisome proliferator-activated receptor co-activator 1 alpha (PGC-1α). Sirtuin1 is a protein encoded by the SIRT1 gene [16] which implies (Silent mating type information regulation 2 homolog 1). SIRT1 is an enzyme that occurs in living organisms and is known to regulate cellular aging, apoptosis and resistance to stress [17]. Sirtuin 1 also aids mitochondria to metabolize glucose more efficiently [14]. The result is increased energy output from cellular metabolic reactions. PGC-1α as well slows the aging process and prevents a number of chronic diseases [18].

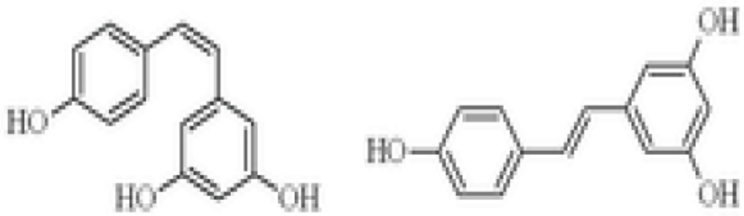

Figure 1. Chemical structures of *cis*-(Z)-resveratrol and *trans*-resveratrol (E)-resveratrol [1].

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Figure 2. Japanese knotweed, a well-known rich source for resveratrol [8].

Khan et al. [19] and Sahin et al. [20], stated that resveratrol increases regulation of antioxidant enzyme like catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px). This result in reduction of oxidative stress and attenuation of inflammation, and these mechanisms may account for many of its health benefits. The antioxidant activity of resveratrol may also inhibit oxidation of low-density lipoproteins (LDL), and therefore, decrease endothelial damage associated with cardiovascular disease [21, 22].

Results of cellular and animal studies have indicated that resveratrol inhibits a nuclear cofactor (NF-kappa B) involved in the gene expression of numerous inflammatory compounds, including cyclooxygenases (COX-2), lipoxygenases, peroxidases, nitrous oxide synthases and cytokines such as tumor necrosis factor alpha (TNFα) [23]. Resveratrol has also been shown to suppress apoptosis and inflammatory signaling via its actions on the NF-kappa B pathway in human chondrocytes [24]. It is therefore, important that resveratrol be investigated further for the prophylactic treatment of osteoarthritis in humans and companion animals. Resveratrol regulates neuronal inflammation in various disease models and protects the brain against ischemic injury [25]. This finding supports important benefits of resveratrol in modulation of the excitotoxic cascade postischemia, which are similar with anti-inflammatory effects observed in various pathological models.

Ghanim et al. [26] found that 6 weeks of supplementation with 200 mg of *Polygonum cuspidatum* extract containing 40 mg of resveratrol did not alter fasting plasma concentrations of cholesterol (total, LDL, and HDL), triglycerides, or leptin compared with placebo in 20 healthy individuals. However, mononuclear cells from the resveratrol group demonstrated suppressed nuclear factor kappa B (NFκB) binding, decreased ROS generation, and TNF-α and Interlukin-6. Additionally, plasma TNFα and C-reactive protein (CRP) were significantly reduced. These findings reveal that resveratrol's actions on the cellular level can indeed influence plasma biomarker measurements associated with inflammation and risk for various diseases.

One of the key cardioprotective mechanisms of resveratrol stems from its ability to upregulate endothelial nitric oxide synthase (eNOS), which ultimately increases nitric oxide (NO) mediated vasodilation and increases blood flow [27]. Additionally, human platelets exposed to physiologically attainable concentrations of resveratrol have been shown to increase eNOS activation, leading to greater NO production and decreased platelet activation [28].

Studies have shown that resveratrol has antidiabetic effects [29, 30]. Poulsen et al. [31] observed that resveratrol supplementation as antidiabetic played an important role in improving glucose metabolism and preventing inflammation, metabolic abnormalities, cancer and nonalcoholic fatty liver disease. Furthermore, resveratrol decreased insulin resistance and metabolic disorders, compared to other diets that did not contain resveratrol [32].

Resveratrol or its derivatives also prevent cancer cell proliferation [33]. This is possible because Resveratrol can inhibit the activity of one type of enzyme, matrix metalloproteinase [34] which aids proliferation of cancerous cells as well as angiogenesis which enhances invasive tumors [35, 36].

Das [37] found that resveratrol helps in reduction of thermal stress. Numerous studies have shown that resveratrol can attenuate cellular processes such as protein damage associated with high temperature [20, 37] and UV radiation [38].

Recent advances of resveratrol have shown that it could be used for treatment and prevention of HIV/AIDS, and it has been shown to synergistically enhance the anti-HIV-1 activity [39].

The effects of resveratrol on cellular factors mediating liver damage and regeneration in acute carbon tetrachloride (CCl_4) liver injuries have been investigated [40]. The result showed that resveratrol therapy can be beneficial for acute toxic liver injury.

Resveratrol bioavailability is low or zero and this may be attributed to speed and extensive metabolism or its poor water solubility [41] and the consequent compound of different metabolites such as resveratrol sulfates and resveratrol glucuronides [42]. Encapsulated resveratrol provides a potential approach for improving the solubility of resveratrol, consequently, enhancing its bioavailability. Against this background, the oral resveratrol bioavailability is not related to dose or aqueous solubility [35, 43]. While 70% of orally administered resveratrol is absorbed, its oral bioavailability is approximately 0.5% due to extensive hepatic glucuronidation and sulfation [44]. Microencapsulation of resveratrol product helps to reduce rapid metabolization and excretion of resveratrol when administered to horses [45]. Resveratrol conjugated gold nanoparticles is effectively used as delivery vehicles [46]. Bio-directed synthesis of metal nanoparticles is gaining importance due their biocompatibility, low toxicity and eco-friendly characteristics.

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2. Studies of resveratrol in animals

2.1. Laboratory animals

Studies demonstrated that resveratrol supplementation in diet of rats and mice played an important role in protecting heart cells or cardiovascular system from free radical-induced cell death or from damage which occurs through obesity and chronic hypertension [47].

Resveratrol has shown much promise in treating cancer in laboratory animals [48, 49]. A recent study demonstrated resveratrol to decrease liver tumors, while increasing lymphoma and possibly solid tumors. This is consistent with the concern that resveratrol can have pro-oxidant effects, especially in the presence of copper, which is elevated in certain tumors, and that this may exacerbate the effects of cancer [50].

A study on rodent models showed that, oral administration, topical application, and injection of resveratrol inhibited the development of chemically-induced cancer at many sites, including gastrointestinal tract, liver, skin, breast, prostate, and lung [51, 52]. The anticancer effects of resveratrol in rodent models involved the reduction of cell proliferation, the induction of apoptosis, and the inhibition of angiogenesis, tumor growth, and metastasis [53]. Resveratrol has shown promise on skin cancers when used on the body surface of mice [54] and effective against esophageal cancer when ingested orally in rats [55].

The benefits of resveratrol for memory and prevention of neurodegenerative diseases has been documented in laboratory animals [56]. The potential benefits of resveratrol were linked to an increase in the production of a peptide called insulin-like growth factor-I (IGF-I), which is reported to promote the growth of blood vessels and neurons in the hippocampus [57].

Laboratory models have also shown that resveratrol reduces oxidative stress in skeletal muscles during exercise [58] and disuse [59] and suppresses aging-associated decrements in physical performance [60] but does not attenuate sarcopenia [61].

A study revealed that resveratrol does not extend life-span in healthy mice or in a model of premature aging [62] but may delay or attenuate many age-related changes and prevent early mortality in obese animals [63].

An investigation on the effects of resveratrol on the insulin signaling pathway in the liver of obese mice showed that resveratrol restored the phosphorylation levels of proteins involved in the insulin signaling pathway, which were decreased by a high fat diet [64]. Further studies indicated that consumption of red wine containing 20 milligrams of resveratrol per liter improved cognitive function in mice. Japanese researchers, Harada et al. [57] postulated that the average concentration of resveratrol in red wine is 4.7 mg/L.

Resveratrol has been shown to restore spermatogenesis in cryptorchid mice [65]. Mice fed diets supplemented with resveratrol (7 mg/kg/day) for 12 months exhibited a larger follicle pool and number and quality of oocytes than those fed diet without resveratrol [66].

Studies by Hichem et al. [67], on ameliorative effects of resveratrol on lipopolysaccharide (LPS)-induced oxidative stress in rat liver showed that the supplement counteracted LPS-induced lipoperoxidation and depletion of SOD and catalase but slightly reduced that of GPx.

Previous work on suppressive effects of resveratrol on leucocyte count has also been reported in rats [68]. This may be due to the anti-inflammatory property of resveratrol.

2.2. Resveratrol effects in cats

A team of researchers studied the mechanisms of action of resveratrol using a cat model. They induced hepatotoxicity in the experimental cat using arsenic trioxide (As_2O_3). Their findings showed that pretreatment with resveratrol reversed changes in As_2O_3-induced morphological and liver parameters and resulted in a significant improvement in hepatic function. Resveratrol administration also improved the activities of antioxidant enzymes and attenuated As_2O_3-induced increases in reactive oxygen species and malondialdehyde production [69].

2.3. Studies of resveratrol in pigs

Resveratrol showed strong potential as antibiotic alternatives for reversing the adverse effects of weaning stress on growth performance, immunity and digestibility of nutrients and fecal microbial shedding of weaned piglets [70].

Previous work on suppressive effects of resveratrol on leucocyte count has been reported in pigs [71]. This indicates the anti-inflammatory effects of resveratrol.

Will Block [72], reported the inhibitory effect of *Polygonum cuspidatum* and its active components, resveratrol and emodin. They were found to preferentially inhibit the replication of H1N1 swine flu virus.

An *in-vitro* dose-dependent antiviral effect of resveratrol and oxyresveratrol (extracted from mulberry twigs) showed the antiviral activities of these compounds on African swine fever virus (ASFV). Oxyresveratrol differs from resveratrol because it has an extra hydroxyl group, which enhances its antioxidant activity. The antiviral effect of these two compounds achieved a 98–100% reduction in viral titers of ASFV. The compounds allowed early protein synthesis but inhibited viral DNA replication, late viral protein synthesis and factory formation. Resveratrol and oxyresveratrol were therefore postulated to be potential tools for the treatment or prevention of ASFV infection [73].

Fu et al. [74] suggested that resveratrol dry suspension (RDS) could be considered as an adjuvant to enhance immune responses to vaccines and dietary additives for animals to boost humoral and cellular immunity. In their study on immune function in piglets fed different doses of RDS for 2 weeks, they observed significant effects on the development, maturation, proliferation, and transformation of T lymphocytes. The result also showed upregulation and the release of interferon gamma (IFN-γ), downregulation of the release of TNF-α and high resistance to improve total superoxide dismutase (T-SOD) activity. Vaccination of the piglets against classical swine fever virus and foot-and-mouth disease virus as well produced significantly increase in antibody titers after supplementation of RDS.

Cui et al. [75] studied pretreatment with resveratrol dry suspension via basal diet on diarrhea induced rotavirus (RV) infection in piglets for 3 weeks. They observed a decrease in diarrhea, reduction on TNF-α production and elevated IFN-γ level. These results indicated that resveratrol could be used to control RV infection.

A 7 week study to determine effects of red wine and vodka on swine showed that the subjects that were given wine or vodka had significantly increased blood flow to the heart, although the red wine had the larger cardiovascular benefit [76].

2.4. Resveratrol studies in horses

Studies have evaluated the effects of resveratrol in horses [77, 78]. Report by Kohnen et al. [77] showed the inhibitory effect of resveratrol on equine neutrophil myeloperoxidase, while resveratrol treatment (1 g/d) in 20 old horses for 4 weeks decreased equine inflammatory cytokine production both *in vitro* and *in vivo* [45]. The compound has significant potential as a therapeutic agent in the management of acute and chronic inflammatory conditions in horses [45]. Trainers and horse owners have observed an improvement in health, comfort and performance in horses receiving resveratrol therapy. Refs. [79, 80] reported that resveratrol reduces gene expression of inflammatory mediators to allow horses move comfortably during aging, training and competition.

Daily resveratrol administration improves energy metabolism through its effects on mitochondria, the body's cellular power house [45].

Studies by Ememe et al. [82], showed a significant reduction in values of creatine kinase and glucose in the horses administered resveratrol and hyaluronic acid (equithrive joint®) (**Figure 3**) supplement. Elevated levels of these substances have been associated with a reduction in metabolic efficiency in aging animals. Hence, administration of equithrive joint® may help to reduce the harmful effects of these biochemical parameters during aging in horses. Also a study on horses exhibiting hind-limb lameness and poor performance was carried out with equithrive joint®. The researchers injected each horse's lower jock joints with triamcinolone before supplementing with equithrive joint® for 4 months [83]. The result showed higher percentage of riders who reported better performance of their horses. Ememe et al. [84] also reported that administration of equithrive joint to aged and lame horses decreased the serum MDA concentration and modulated the serum content of GPx, catalase, and SOD. The results suggested a potential protective effect of equithrive joint against oxidative stress and aging in

Figure 3. Equithrive®: a horse supplement, containing resveratrol and hyaluronic acid [81].

horses. Siard et al. [85] suggested that polyphenol supplementation such as resveratrol could decrease the amount of nonsteroidal anti-inflammatory drugs given to older horses, thereby reducing the side effects of such drugs.

2.5. Studies in dogs

Japanese Knotweed is the best source of resveratrol for dogs. An is an unproved evidence regarding the use of Japanese knotweed and lyme disease in dogs. Herbalist Stephen Buhner recommends Japanese knotweed in his book, Healing Lyme. He suggested that it is the only herbal treatment that blocks the bacterial phyla, spirochetes, which lead to Lyme disease and other infections like *Bartonella* [86].

Ref. [87] produced Resvantage Canine® (**Figure 4**) which contains resveratrol blended together with a unique combination of nutrients. It is alleged that the supplement maintains longevity by providing powerful support for pet's health needs (**Figure 5**).

A small dosage of resveratrol in the range of five to seven milligrams per 30 pounds of body weight daily has been reported to increase energy levels and alertness in dogs [86].

A research conducted on five known natural chemopreventive agents namely, resveratrol, ellagic acid, curcumin, genistein and quercetin over a period of 3 weeks indicated that the supplementation significantly decreased H_2O_2-inducible DNA damage [88].

2.6. Studies in cattle

The meat of cows that drank a liter of homemade local wine was found to have a wonderful texture and impressive aroma and flavor. Researchers at Thompson Rivers University in British Columbia are studying the effects of wine on cows. The study is to demonstrate the

Figure 4. Resvantage Canine®: a resveratrol supplement used to improve health needs of dogs.

Figure 5. An alert and healthy dog on resveratrol supplementation [86].

effects of wine diet on cow's methane production and possible health benefits of resveratrol in wine [89]. Salzano et al. [90] showed that resveratrol addition to bovine culture medium enhanced the fertility rate, cell numbers, blastocyst development and embryo cryotolerance.

A study on pretreatment of cultured bovine mammary epithelial cells (MAC-T) with resveratrol prevented decrease in cell viability and resulted in lower intracellular reactive oxygen species (ROS) accumulation after H_2O_2 exposure. The study showed that resveratrol could potentially be used as a therapeutic medicine against oxidative stress in lactating animals [91].

2.7. Effects of resveratrol in birds

In a recent study, 42-day-old female blackboned chickens were exposed to heat stress at 37 ± 2°C for 15 days after dietary supplementation of resveratrol at 0, 200, 400, or 600 mg/kg. The performance, immune organ growth index, serum parameters, and expression levels of heat shock protein in the bursa of Fabricius, thymus, and spleen were observed after supplementation. The result showed that administration of resveratrol improved growth performance and reduced oxidative stress biomarkers in the chickens by increasing serum growth hormone concentrations and modulating the expression of heat shock genes in organs of the immune system [38]. Sridhar et al. [92] advised on the use of resveratrol as a feed additive to control aflatoxicosis in poultry farms. In the new study at the National Institute of Animal Nutrition and Physiology in Bangalore, India, 0.5% or 1% resveratrol was administered for 42 days to broilers on aflatoxin-induced toxicity. It was observed that activities of the oxidative enzymes were increased and plasma total antioxidant capacity and total protein improved [93]. They also observed that the severity and degree of the liver lesions were decreased in supplemented birds (**Figure 6**).

Figure 6. Resveratrol administered as a feed additive to control aflatoxicosis in broilers [92].

Xu et al. [94] observed that resveratrol (3.85 μg mL^{-1}) supplementation decreased duck enteritis virus multiplication by 50%. This may be due to the inhibition of viral proliferation in the host cell.

Sahin et al. [95] studied the Effects of dietary resveratrol supplementation on egg production and antioxidant status in quail (*Coturnix coturnix japonica*). They found out that addition of resveratrol at 400 mg/kg into quail diets improved the antioxidant status of birds and eggs.

Supplementation of dried grape pomace to 96 molted 80-week-old *Bovans* laying hens led to the reduction in plasma and egg yolk MDA, and serum glucose levels by 4 and 6% [96]. It was opined that grape pomace supplementation has the potential to extend shelf life. Grape pomace is produced as a by-product during the production of molasses, grape juice, vinegar, dried fruit pulp and wine [97]. The polyphenol content of the grape pomace and seed include some flavonoids such as catechin, epicatechin, procyanidin, and antocyanidin; some phenolic acids such as gallic and ellagic acid, and some stilbenes such as resveratrol and piseid [98].

Supplementation with resveratrol (200, 400 or 800 mg kg^{-1} of diet) to chicks produced 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. It also enhanced growth hormone receptor gene mRNA expression and insulin-like growth factor-1 than those fed control diet during the study period [99].

3. Conclusion

This review illustrated the useful effects of supplementation of resveratrol in animals. The benefits highlighted consist of protective effects on cardiovascular system, treatment of various cancers, prevention of neurodegenerative diseases, suppression of age related decrements in physical performance and improvement in cognitive functions. Others included suppressive effects on inflammatory factors, therapeutic medicine against oxidative stress, antibiotic alternative, decrease in viral replication and enhancement of immune responses. In view of the many benefits of resveratrol supplementation in animals, it may be considered as an aid to maintain longevity and increase in production in animals.

4. Recommendation

It is recommended that resveratrol should be included as a feed additive for dogs, cats, horses, pigs and cattle to improve immunity, reduce risk of various diseases and enhance productive performance.

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