

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



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

Mary U. Ememe, Anthony K.B. Sackey and Joseph O. Ayo

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.79104>

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 increase the expression of Sirtuin1 and Peroxisome proliferator-activated receptor co-activator 1 alpha (PGC-1 α). 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-1 α as well slows the aging process and prevents a number of chronic diseases [18].

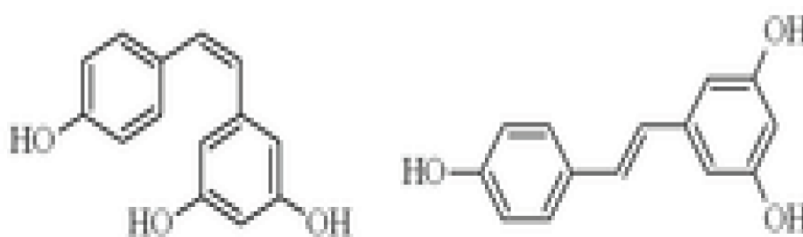


Figure 1. Chemical structures of *cis*-(Z)-resveratrol and *trans*-resveratrol (E)-resveratrol [1].



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 co-factor (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 (TNF α) [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 (NF κ B) binding, decreased ROS generation, and TNF- α and Interleukin-6. Additionally, plasma TNF α 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 (CCl₄) 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.

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 ($\text{IFN-}\gamma$), downregulation of the release of $\text{TNF-}\alpha$ 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 $\text{TNF-}\alpha$ production and elevated $\text{IFN-}\gamma$ 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 triamcortolone 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 H₂O₂-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.

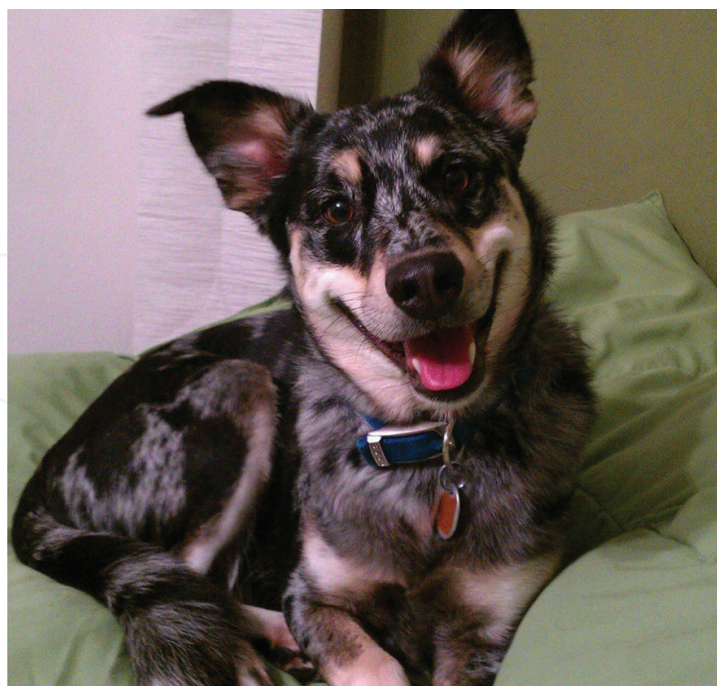


Figure 5. An alert and healthy dog on resveratrol supplementation [86].

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 $37 \pm 2^\circ C$ 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 ($3.85 \mu\text{g mL}^{-1}$) 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 piceid [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.

Author details

Mary U. Ememe^{1*}, Anthony K.B. Sackey² and Joseph O. Ayo³

*Address all correspondence to: maryeneme@yahoo.com

1 Department of Veterinary Medicine, College of Veterinary Medicine, Michael Okpara University of Agriculture, Umudike, Nigeria

2 Department of Veterinary Medicine, Faculty of Veterinary Medicine, Ahmadu Bello University, Zaria, Nigeria

3 Department of Veterinary Physiology, Faculty of Veterinary Medicine, Ahmadu Bello University, Zaria, Nigeria

References

- [1] Camont L, Cottart CH, Rhayem Y, Nivet-Antoine V, Djelidi R, Collin F, Beaudoux JL, Bonnefont-Rousselot D, Nivet-Antoine CR, Collin D, Bonnefont-Rousselot B. Simple spectrophotometric assessment of the trans/cis-resveratrol ratio in aqueous solutions. *Analytica Chimica Acta*. 2009;**634**(1):121-128
- [2] Mattivi F, Reniero F, Korhammer S. Isolation characterization and evolution in red wine vinification of resveratrol monomers. *Journal of Agricultural and Food Chemistry*. 1995;**43**(7):1820-1830
- [3] Vuong TV, Franco C, Zhang W. Treatment strategies for high resveratrol induction in *Vitis vinifera* L. cell suspension culture. *Biotechnology Reports*. 2014;**1**:15-21
- [4] Sheu SJ, Liu NC, Ou CC, Bee YS, Chen SC, Lin HC, Chan JY. Resveratrol stimulates mitochondrial bioenergetics to protect retinal pigment epithelial cells from oxidative damage. *Investigative Ophthalmology & Visual Science*. 2013;**54**:6426-6438

- [5] Liu BL, Zhang X, Zhang W, Zhen HN. New enlightenment of French Paradox: Resveratrol's potential for cancer chemoprevention and anti-cancer therapy. *Cancer Biology & Therapy*. 2007;**6**:1833-1836
- [6] Kang L, Li Q, Lin J, Guo L. Biosynthesis of resveratrol in blastospore of the macrofungus *Tremella fuciformis*. *Molecular Biotechnology*. 2015;**57**(7):675-684
- [7] Shin SY, Jung SM, Kim MD, Han NS, Seo JH. Production of resveratrol from tyrosine in metabolically engineered *Saccharomyces cerevisiae*. *Enzyme and Microbial Technology*. 2012;**51**(4):211-216
- [8] MDA (Minnesota Department of Agriculture). Leaves and stem of Japanese knotweed. mda.info@state.mn.us 2018. [Accessed: 2018-6-14].
- [9] Smoliga JM, Sage CE, Campen MJ. A healthier approach to clinical trials evaluating resveratrol for primary prevention of age related diseases in healthy populations. 2013. *Ageing*;5(7):495-506
- [10] Giovannelli L, Pitozzi V, Jacomelli M, Mulinacci N, Laurenzana A, Dolara P, Mocali A. Protective effects of resveratrol against senescence-associated changes in cultured human fibroblasts. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*. 2011;**66**:9-18
- [11] Kitada M, Kume S, Takeda-Watanabe A, Kanasaki K, Koya D. Sirtuins and renal diseases: Relationship with aging and diabetic nephropathy. *Clinical Science*. 2013;**124**(3):153-164
- [12] Timmers S, Auwerx J, Schrauwen P. The journey of resveratrol from yeast to human. *Ageing*. 2012;**4**:146-158
- [13] Marchal J, Pifferi F, Aujard F. Resveratrol in mammals: Effects on ageing biomarkers, age-related diseases and life span. *Annals of the New York Academy of Sciences*. 2013;**1290**:67-73
- [14] Baur JA, Sinclair DA. Therapeutic potential of resveratrol: The *in vivo* evidence. *Nature Reviews. Drug Discovery*. 2006;**5**(6):493-506
- [15] Guarente L. Sirtuins, aging and medicine. *The New England Journal of Medicine*. 2011;**364**:2235-2244
- [16] Frye RA. Characterization of five human cDNA with homology to the yeast. SIRS gene: Sir2-like protein (Sirtuins) metabolize NAD and may have protein ADP-ribosyltransferase activity. *Biochemical and Biophysical Research Communications*. 1999;**260**(1):273-279
- [17] Sinclair DA, Guarente L. Unlocking the secrets of longevity genes. *Scientific American*. 2006;**294**(3):48-51 54-57
- [18] Lakshminarasimhan M, Rauh D, Schutkowski M, Steegborn C. Sirt1 activation by resveratrol is substrate sequence-selective. *Ageing*. 2013;**5**:151-154

- [19] Khan MA, Chen HC, Wan XX, Tania M, Xu AH, Chen FZ, Zhang DZ. Regulatory effects of resveratrol on antioxidant enzymes: A mechanism of growth inhibition and apoptosis induction in cancer cells. *Molecular Cell*. 2013;**35**:219-225
- [20] Sahin K, Orhan C, Akdemir F, Tuzcu M, Iben C, Sahin N. Resveratrol protects quail hepatocytes against heat stress: Modulation of the Nrf2 transcription factor and heat shock proteins. *Journal of Animal Physiology and Animal Nutrition*. 2012;**96**:66-74
- [21] Frankel EN, Waterhouse AL, Kinsella JE. Inhibition of human LDL oxidation by resveratrol. *Lancet*. 1993;**341**:1103-1104
- [22] Nigdikar SV, Williams NR, Griffin BA, Howard AN. Consumption of red wine polyphenols reduces the susceptibility of low-density lipoproteins to oxidation *in vivo*. *The American Journal of Clinical Nutrition*. 1998;**68**:258-265
- [23] de la Lastra CA, Villegas I. Resveratrol as an anti-inflammatory and anti-ageing agent: Mechanisms and clinical implications. *Molecular Nutrition & Food Research*. 2005;**49**:405-430
- [24] Im HJ, Li X, Chen D, Yan D, Kim J, Ellman MB, Stein GS, Cole B, Kc R, Cs-Szabo G, van Wijnen AJ. Biological effects of the plant-derived polyphenol resveratrol in human articular cartilage and chondrosarcoma cells. *Journal of Cellular Physiology*. 2012;**227**(10):3488-3497
- [25] Girbovan C, Plamondon H. Resveratrol downregulates type-1 glutamate transporter expression and microglia activation in the hippocampus following cerebral ischemia reperfusion in rats. *Brain Research*. 2015;**1608**:203-214
- [26] Ghanim H1, Sia CL, Abuaysheh S, Korzeniewski K, Patnaik P, Marumganti A, Chaudhuri A, Dandona P. An antiinflammatory and reactive oxygen species suppressive effect of an extract of *Polygonum cuspidatum* containing resveratrol. *The Journal of Clinical Endocrinology and Metabolism*. 2010;**95**(9):E1-E8
- [27] Wallerath T, Deckert G, Ternes T, Anderson H, Li H, Witte K, Förstermann U. Resveratrol, a polyphenolic phytoalexin present in red wine, enhances expression and activity of endothelial nitric oxide synthase. *Circulation*. 2002;**106**:1652-1658
- [28] Gresele P, Pignatelli P, Guglielmini G, Carnevale R, Mezzasoma AM, Ghiselli A, Momi S, Violi F. Resveratrol, at concentrations attainable with moderate wine consumption, stimulates human platelet nitric oxide production. *The Journal of Nutrition*. 2008;**138**:1602-1608
- [29] Bhatt JK, Thomas S, Nanjan MJ. Resveratrol supplementation improves glycemic control in type 2 diabetes mellitus. *Nutrition Research*. 2012;**32**(7):537-541
- [30] Hausenblas HA, Schoulda JA, Smoliga JM, Schoulda S. Resveratrol treatment as an adjunct to pharmacological management in type 2 diabetes mellitus-systematic review and meta-analysis. *Molecular Nutrition & Food Research*. 2014;**59**(1):147-159

- [31] Poulsen MM, Jorgensen JO, Jessen N, Richelsen B, Pedersen SB. Resveratrol in metabolic health: An overview of the current evidence and perspectives. *Annals of the New York Academy of Sciences*. 2013;**1290**:74-82
- [32] Szkudelski T, Szkudelska K. Resveratrol and diabetes: From animal to human studies. *Biochimica et Biophysica Acta-Molecular Basis of Disease*. 2015;**1852**(6):1145-1154
- [33] Yang I, Kim E, Kang J, Han H, Sul S, Park SB, Kim SK, Kim K, Han S, Park K. Photochemical generation of a new, highly fluorescent compound from non-fluorescent resveratrol. *Chemical Communications*. 2012;**48**(32):3839-3841
- [34] Yu H, Pan C, Zhao S, Wang Z, Zhang H, Wu W. Resveratrol inhibits tumor necrosis factor- α -mediated matrix metalloproteinase-9 expression and invasion of human hepatocellular carcinoma cells. *Biomedicine & Pharmacotherapy*. 2008;**62**(6):366-372
- [35] Chen Y, Tseng SH. Review. Pro- and anti-angiogenesis effects of resveratrol. *In Vivo*. 2007;**21**(2):365-370
- [36] Kanavi MR, Darjatmoko S, Wang S, Azari AA, Farnoodian M, Kenealey JD, van Ginkel PR, Albert DM, Sheibani N, Polans AS. The sustained delivery of resveratrol or a defined grape powder inhibits new blood vessel formation in a mouse model of choroidal neovascularization. *Molecules*. 2014;**19**(11):17578-17603
- [37] Das A. Heat stress-induced hepatotoxicity and its prevention by resveratrol in rats. *Toxicology Mechanisms and Methods*. 2011;**21**:393-399
- [38] Liu LL, He JH, Xie HB, Yang YS, Li JC, Zou Y. Resveratrol induces antioxidant and heat shock protein mRNA expression in response to heat stress in black-boned chickens. *Poultry Science*. 2014;**93**:54-62
- [39] Singh G, Pai RS. Recent advances of resveratrol in nanostructured based delivery systems and in the management of HIV/AIDS. *Journal of Controlled Release*. 2014;**194**:178-188
- [40] Chan CC, Lee KC, Huang YH, Chou CK, Lin HC, Lee FY. Regulation by resveratrol of the cellular factors mediating liver damage and regeneration after acute toxic liver injury. *Journal of Gastroenterology and Hepatology*. 2014;**29**(3):603-613
- [41] Santos AC, Veiga F, Ribeiro AJ, Veiga R. New delivery systems to improve the bioavailability of resveratrol. *Expert Opinion on Drug Delivery*. 2011;**8**(8):973-990
- [42] Augustin MA, Sanguansri L, Lockett T. Nano- and micro-encapsulated systems for enhancing the delivery of resveratrol. *Annals of the New York Academy of Sciences*. 2013;**1290**:107-112
- [43] Smoliga JM, Baur JA, Hausenblas HA. Resveratrol and health—A comprehensive review of human clinical trials. *Molecular Nutrition & Food Research*. 2011;**55**(8):1129-1141
- [44] Walle T, Hsieh F, DeLegge MH, Oatis JE, Walle UK, Hsieh D, Oatis Jr W. High absorption but very low bioavailability of oral resveratrol in humans. *Drug Metabolism and Disposition*. 2004;**32**(12):1377-1182

- [45] Lawless P. Two New Research Projects Study on Resveratrol's Effect on EMS. Lexington, Kentucky: Biological Prospects/Equithrive; 2010 [Accessed: 2013-9-30]
- [46] Kumar CG, Poornachandra Y, Mamidyala SK. Green synthesis of bacterial gold nanoparticles conjugated to resveratrol as delivery vehicles. *Colloids and Surfaces. B, Bio-interfaces*. 2014;**123**:311-317
- [47] Raederstorff D, Kunz I, Schwager J. Resveratrol, from experimental data to nutritional evidence: The emergence of a new food ingredient. *Annals of the New York Academy of Sciences*. 2013;**1290**:136-141
- [48] Gupta SC, Kannappan R, Reuter S, Kim JH, Aggarwal BB. Chemosensitization of tumours by resveratrol. *Annals of the New York Academy of Sciences*. 2011;**1215**:150-160
- [49] Shukla Y, Singh R. Resveratrol and cellular mechanisms of cancer prevention. *Annals of the New York Academy of Sciences*. 2011;**1215**:1-8
- [50] Burkitt MJ, Duncan J. Effects of trans-resveratrol on copper-dependent hydroxyl-radical formation and DNA damage: Evidence for hydroxyl—Radical scavenging and a novel glutathione sparing mechanism of action. *Archives of Biochemistry and Biophysics*. 2000;**15**(381(2)):253-263
- [51] Bishayee A. Cancer prevention and treatment with resveratrol: From rodent studies to clinical trials. *Cancer Prevention Research (Philadelphia, PA)*. 2009;**2**(5):409-418
- [52] Bishayee A, Darvesh AS, Politis T, McGory R. Resveratrol and liver disease: From bench to bedside and community. *Liver International*. 2010;**30**(8):1103-1114
- [53] Tome-Carneiro J, Larrosa M, Gonzalez-Sarrias A, Tomas-Barberan FA, Garcia-Conesa MT, Espin JC. Resveratrol and clinical trials: The crossroad from in vitro studies to human evidence. *Current Pharmaceutical Design*. 2013;**19**(34):6064-6093
- [54] Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CWW, Fong HHS, Farnsworth NR, Kinghorn AD, Mehta RG, Moon RC, Pezzuto JM. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science*. 1997;**275**:218-220
- [55] Li ZG, Hong T, Shimada Y, Komoto I, Kawabe A, Ding Y, Kaganoi J, Hashimoto Y, Imamura M. Suppression of N-nitrosomethylbenzylamine (NMBA) induced oesophageal tumorigenesis in F344 rats by resveratrol. *Carcinogenesis*. 2002;**23**(9):1531-1536
- [56] Chiavaroli A, Brunetti L, Orlando G, Recinella L, Ferrante C, Leone S. Resveratrol inhibits isoprostane production in young and aged rat brain. *Journal of Biological Regulators and Homeostatic Agents*. 2010;**24**:441-446
- [57] Harada N, Zhao J, Kurihara H, Nakagata N, Okajima K. Resveratrol improves cognitive function in mice by increasing production of insulin-like growth factor-I in the hippocampus. *The Journal of Nutritional Biochemistry*. 2011;**22**(12):1150-1159
- [58] Ryan MJ, Jackson JR, Hao Y, Williamson CL, Dabkowski ER, Hollander JM, Alway SE. Suppression of oxidative stress by resveratrol after isometric contractions in

- gastrocnemius muscles of aged mice. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*. 2010;**65**:815-831
- [59] Jackson JR, Ryan MJ, Hao Y, Alway SE. Mediation of endogenous antioxidant enzymes and apoptotic signaling by resveratrol following muscle disuse in the gastrocnemius muscles of young and old rats. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*. 2010;**299**:R1572-R1581
- [60] Murase T, Haramizu S, Ota N, Hase T. Suppression of the aging-associated decline in physical performance by a combination of resveratrol intake and habitual exercise in senescence-accelerated mice. *Biogerontology*. 2009;**10**:423-434
- [61] Jackson JR, Ryan MJ, Alway SE. Long-term supplementation with resveratrol alleviates oxidative stress but does not attenuate sarcopenia in aged mice. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*. 2011;**66**(7):751-764
- [62] Labbé A, Garand C, Cogger VC, Paquet ER, Desbiens M, Le Couteur DG, Lebel M. Resveratrol improves insulin resistance hyperglycemia and hepatosteatosis but not hypertriglyceridemia, inflammation, and life span in a mouse model for Werner syndrome. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*. 2011;**66**:264-278
- [63] Miller RA, Harrison DE, Astle CM, Baur JA, Boyd AR, de Cabo R, Fernandez E, Flurkey K, Javors MA, Nelson JF, Orihuela CJ, Pletcher S, Sharp ZD, Sinclair D, Starnes JW, Wilkinson JE, Nadon NL, Strong R. Rapamycin, but not resveratrol or simvastatin, extends life span of genetically heterogeneous mice. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*. 2011;**66**:191-201
- [64] Hong HJ, Kang W, Kim DG, Lee DH, Lee Y, Han C. Effects of resveratrol on the insulin signaling pathway of obese mice. *Journal of Veterinary Science*. 2014;**15**(2):179-185
- [65] Li E, Guo Y, Wang G, Chen F, Li Q. Effect of resveratrol on restoring spermatogenesis in experimental cryptorchid mice and analysis of related differentially expressed proteins. *Cell Biology International*. 2015;**39**(6):733-740
- [66] Liu S, Ren J, Xia Q, Wu X, Han G, Ren H, Yan D, Wang G, Gu G, Li J. Preliminary case-control study to evaluate diagnostic values of C-reactive protein and erythrocyte sedimentation rate in differentiating active Crohn's disease from intestinal lymphoma, intestinal tuberculosis and Behcet's syndrome. *The American Journal of the Medical Sciences*. 2013;**346**(6):467-472
- [67] Hichem SB, Mamane S, Mohamed TY, Ezzedine A, Néziha GB, Mossadok BA. Resveratrol, a red wine polyphenol, attenuates lipopolysaccharide-induced oxidative stress in rat liver. *Ecotoxicology and Environmental Safety*. 2010;**73**(5):1078-1108
- [68] Hişmioğullari SE, Hişmioğullari AA, Yavuz MT, Yavuz O, Yaman I, Seyrek K, Hayirli A, Rahman K. The protective effect of resveratrol in experimentally induced non-sterile clean wound inflammation in rats. *Kafkas Üniversitesi Veteriner Fakültesi Dergisi*. 2013;**19**(Suppl. A):1-5

- [69] Zhang Z, Gao L, Cheng YJ, Jiang J, Chen Y, Jiang H, Yu H, Shan A, Cheng B. Resveratrol, a natural antioxidant, has a protective effect on liver injury induced by inorganic arsenic exposure. *BioMed Research International*. 2014;**2014**:Article ID 617202, 7 pp
- [70] Ahmed ST, Hossain ME, Kim GM, Hwang JA, Ji H, Yang CJ. Effects of resveratrol and essential oils on growth performance, immunity, digestibility and fecal microbial shedding in challenged piglets. *Asian-Australasian Journal of Animal Sciences*. 2013;**26**(5):683-690
- [71] Holešovská Z, Volný T, Kotrbáček V, Doubek J. Influence of ethanol solution of resveratrol on leukocyte count and phagocytic activity in piglets. *Bulletin of the Veterinary Institute in Pulawy*. 2009;**53**:449-453
- [72] Block W. Resveratrol fights influenza virus ... by inhibiting the swine flu virus's ability to replicate. 2015. <http://www.life-enhancement.com> [Accessed: 2018-4-5]
- [73] Galindo I, Hernáez B, Berná J, Fenoll J, Cenis JL, Escribano JM, Alonso C. Comparative inhibitory activity of the stilbenes resveratrol and oxyresveratrol on African swine fever virus replication. *Antiviral Research*. 2011;**91**:57-63
- [74] Fu Q, Cui Q, Yang Y, Zhao X, Song X, Wang G, Bai L, Chen S, Tian Y, Zou Y, Li L, Yue G, Jia R, Yin Z. Effects of resveratrol dry suspension on immune function of piglets. *Evidence-Based Complementary and Alternative Medicine*. 2018;**2018**:Article ID 5952707, 10 pp
- [75] Cui Q, Fu Q, Zhao Z, Song X, Yu J, Yang Y, Sun K, Bai L, Tian Y, Chen S. Protective effects and immunomodulation on piglets infected with rotavirus following resveratrol supplementation. *PLoS One*. 2018;**13**(2):e0192692
- [76] Chu LM, Lassalette AD, Robich MP, Liu Y, Burgess T, Laham RJ, Sweeney JD, Shen TL, Sellke FW. Effects of red wine and vodka on collateral-dependent perfusion and cardiovascular function in hypercholesterolemic swine. *Circulation*. 2012;**126**(11 Suppl 1): S65-S72
- [77] Kohnen S, Franck T, Van Antwerpen P, Boudjeltia KZ, Mouithys-Mickalad A, Deby C, Moguilevsky N, Deby-Dupont G, Lamy M, Serteyn D. Resveratrol inhibits the activity of equine neutrophil myeloperoxidase by a direct interaction with the enzyme. *Journal of Agricultural and Food Chemistry*. 2007;**55**:8080-8087
- [78] Zambito JL. Effects of resveratrol supplementation on glycemic response and oxidant status in moderately exercised mature quarter horse geldings [master's thesis]. Morgantown: West Virginia Univ.; 2011. <http://www.proquest.com> [Accessed: 2014-9-8]
- [79] Handler N. Equithrive-pioneering resveratrol therapy. In: *Sport Horse*. 2011 <http://www.sporthorsez.com> [Accessed: 2013-9-20]
- [80] Rowen R. Resveratrol. *Advanced Bionutritionals*, Norcross Georgia. United States; 2013 <http://www.advancedbionutritional.com/> [Accessed: 2014-9-15]
- [81] Equithrive biological prospects. 2018. <http://equithrive.com/> [Accessed: 2018-4-5]

- [82] Ememe MU, Abdullahi US, AKB S, Ayo JO, Mshelia WP, Edeh RE. Effects of a joint supplement whose main components are resveratrol and hyaluronic acid on some biochemical parameters in aged lame horses. *Journal of Equine Science*. 2016;**27**(1):19-22
- [83] Watt AE, Dabareiner R, Marsh C, Carter GK, Cummings KJ. A randomized, controlled trial of the effects of resveratrol administration in performance horses with lameness localized to the distal tarsal joints. *Journal of the American Veterinary Medical Association*. 2016;**249**(6):650-659
- [84] Ememe MU, Mshelia WP, Ayo JO. Ameliorative effects of resveratrol on oxidative stress biomarkers in horses. *Journal of Equine Veterinary Science*. 2015;**35**:518-523
- [85] Siard MH, McMurry KE, Adams AA. Effects of polyphenols including curcuminoids, resveratrol, quercetin, pterostilbene, and hydroxypterostilbene on lymphocyte pro-inflammatory cytokine production of senior horses in vitro. *Veterinary Immunology and Immunopathology*. 2016;**173**:50-59
- [86] Your Old dog. Safely using Japanese knotweed for dog. 2017. <http://youolddog.com> [Accessed: 2018-4-5].
- [87] Onlynaturalpet. Resvantage. 2018. <https://www.onlynaturalpet.com/products/Resvantage-Resveratrol/406000.aspx> [Accessed: 2018-4-5]
- [88] Timeless life. Study provides evidence that supplements may help prevent cancer in your dog. 2018. <http://www.timelesslifemag.com/> [Accessed: 2018-4-5]
- [89] Eber H. Drunk cows, better beef? 2010. <http://theweek.com/articles/492359/drun-cows-better-beef> [Accessed: 2018-4-5]
- [90] Salzano A, Albero G, Zullo G, Neglia G, Abdel-Wahab A, Bifulco G, Zicarelli L, Gasparrini B. Effect of resveratrol supplementation during culture on the quality and cryotolerance of bovine *in vitro* produced embryos. *Animal Reproduction Science*. 2014;**151**:91-96
- [91] Xiaolu J, Wang K, Liu H, Hu F, Zhao F, Liu J. Protection of bovine mammary epithelial cells from hydrogen peroxide-induced oxidative cell damage by resveratrol. *Oxidative Medicine and Cellular Longevity*. 2016:2016;Article ID 2572175, 15 pp
- [92] Sridhar M, Suganthi RU, Thammiaha V. Effect of dietary resveratrol in ameliorating aflatoxin B1-induced changes in broiler birds. *Journal of Animal Physiology and Animal Nutrition*. 2015;**99**(6):1094-1104
- [93] Stephen D. We advise use of resveratrol as a feed additive to control aflatoxicosis in poultry farms. *Researchers*. 2014. <https://www.feednavigator.com> Accessed: 2018-4-5.
- [94] Xu J, Yin Z, Li L, Cheng A, Jia R, Song X, Lu H, Dai S, Lv C, Liang X, He C, Zhao L, Su G, Ye G, Shi F. Inhibitory effect of resveratrol against duck enteritis virus in vitro. *PLoS One*. 2013;**8**:6 Article ID e65213
- [95] Sahin K, Akdemir F, Orhan C, Tuzcu M, Hayirli A, Sahin N. Effects of dietary resveratrol supplementation on egg production and antioxidant status. *Poultry Science*. 2010;**89**(I 6): 1190-1198

- [96] Güçlü BK K, Baytok E, Şentürk M. Effects of grape pomace supplementation to laying hen diet on performance, egg quality, egg lipid peroxidation and some biochemical parameters. *Journal of Applied Animal Research*. 2015;**44**(1):303-310
- [97] Nerantzis ET, Tataridis P. Integrated enology – Utilization of winery by-products into high added value products. *e-Journal of Science (e-JST)*. 2006 http://e-jst.teiath.gr/issue_3_2006/Nerantzis_3.pdf [Accessed: 2018-4-5]
- [98] Jayaprakasha GK, Selvi T, Sakaria KK. Antibacterial and antioxidant activities of grape (*Vitis vinifera*) seed extracts. *Food Research International*. 2003;**36**:117-122
- [99] Zhang CY, Tian YD, Yan FB, Kang ST, Han RL, Sun GR, Zhang HR. Modulation of growth and immunity by dietary supplementation with resveratrol in young chickens receiving conventional vaccinations. *American Journal of Veterinary Research*. 2014;**75**:752-759

