The effect of resveratrol on live weight, serum biochemistry and tissue antioxidant enzymes in rats

ABSTRACT

The aim of this study is to determine the effects of resveratrol used in adding it to drinking water. The study was carried out with 24 Wistar albino male 20 days rats for 40 days. The study design was determined as one control and two trial groups (each group with 2 parallels and each parallel with 4 rats). The first group was given a basal ration and drinking water. The second group was given the basal ration and drinking water with 10 mg/kg resveratrol; and the third group was given the basal ration and drinking water 20 mg/kg resveratrol. In serum biochemistry parameters, significant decreases were observed in serum Aspartate aminotransferase (AST) enzyme activity, blood urea nitrogen (BUN), albumin, total protein and globulin concentrations and increase in albumin/globulin ratio in groups given resveratrol ($p<0.05$). Regardless of the dose, an increase in the concentration of glutathione (GSH) from the antioxidant parameters was observed in the liver; In the kidney, an increase was observed in the Res10 group. In addition, a decrease in muscle superoxide dismutase (SOD) activity and an increase in muscle and kidney catalase (CAT) activity were observed. A decrease was observed in malondialdehyde (MDA) concentrations, which is a parameter of lipid peroxidation in the kidney. As a result, it was determined in the present study that resveratrol has antioxidant effects regardless of the way of use, and it was concluded that this additive can be used for various purposes.

Keywords: Antioxidant, rat, resveratrol, serum biochemistry, water

INTRODUCTION

Resveratrol (3,5,4'-trihydroxytrans-stilbene) is a polyphenolic compound found in 72 plants, mainly grapes and peanuts (Joe et al., 2002). This compound exists in two isomeric forms. Most of the transform is found in the peel of grapefruit. The synthesis of this form can be stimulated by ultraviolet (UV) light, puncture and fungal infection. The cis form is produced from the transform. It is usually absent or barely detectable in grapes. However, it was reported that it occurs during wine production (Moreno et al., 2008). Harada et al. (2011) found the average concentration of resveratrol in red wine as 4.7 mg/L.

Resveratrol was reported to have numerous pharmacological effects, including antioxidant, preventing cancer, anti-coagulation and inflammation, anti-aging, hypoglycemic and hypolipidemic effects (Nosá et al., 2014; Singh et al., 2015; Xie et al., 2013). It also shows antiestrogenic activity by inhibiting platelet aggregation (Stivala et al., 2001). Adrenaline induced by resveratrol has been reported to have a lipolytic effect (Szkudelska et al., 2009). Resveratrol is also reported to provide a decrease in inflammation through inhibition of prostaglandins and cyclooxygenase-2 (COX 2) (Shankar et al., 2007).

How to cite this article
Özbilgin, A., Gümüş, R., Ekici, M., Ercan, N. (2023). The effect of resveratrol on live weight, serum biochemistry and tissue antioxidant enzymes in rats. *Journal of Advances in VetBio Science and Techniques*, *8*(2), 112-120. https://doi.org/10.31797/vetbio.1293543

Research Article

Abdullah Özbilgin[1a]
Recep Gümüş[1b]
Mehmet Ekici[2c]
Nazlı Ercan[3d]

[1] Sivas Cumhuriyet University Faculty of Veterinary Medicine Department of Animal Nutrition and Nutritional Disorders, Sivas, Türkiye

[2] Sivas Cumhuriyet University, Faculty of Veterinary Medicine, Department of Physiology, Türkiye

[3] Sivas Cumhuriyet University, Faculty of Veterinary Medicine, Department of Biochemistry, Türkiye

ORCİD-

[a]0000-0002-1675-3176
[b]0000-0002-8812-191X
[c]0000-0002-7473-3579
[d]0000-0002-2163-6214
[e]0000-0003-3542-3743

Correspondence
Abdullah Özbilgin
abdullahozbilgin@gmail.com

Article info
Submission: 06-05-2023
Accepted: 14-07-2023
Publication: 30-08-2023

e-ISSN: 2548-1150
doi prefix: 10.31797/vetbio
http://dergipark.org.tr/vetbio

This work is licensed under a Creative Commons Attribution 4.0 International License

In mouse modeling studies, the addition of resveratrol was reported to increase the concentrations of SOD and glutathione peroxidase (GPx), while reducing the concentration of MDA (Liu et al. 2012). Similarly, there are studies that report resveratrol increasing the concentration of antioxidant enzymes such as CAT, SOD and GSH-Px (Khan et al., 2013; Şahin et al., 2012). The antioxidant activity of resveratrol can also inhibit the oxidation of low-density lipoproteins (LDL). Therefore, it was also reported to prevent endothelial damage associated with cardiovascular disease (Frankel, 1993; Nigdikar et al., 1998). It was also reported that resveratrol increases the phosphorylation levels of proteins involved in the insulin signaling pathway in the liver in obese mice (Hong et al., 2014).

This study, unlike other studies, was designed on the hypothesis that Resveratrol would have positive effects by adding it to water instead of feed. In this context, the effects of Resveratrol on live weight change, feed consumption, serum biochemistry and antioxidant parameters in animals that consumed Resveratrol and those in the control groups will be examined.

MATERIALS AND METHODS

Animal and treatment groups

The study was performed with 24 Wistar albino male post weaned 20-day-old rats for 40 days. Resveratrol in the study (molecular formula C14H12O3, Cas no.: 501-36-0, purity: 99.13%, Chem-Impex International Company, USA) was provided from the market. The study design was determined as one control and two trial groups (each group with 2 parallels and each parallel with 4 rats). *Ad libitum* feed and water were given to the control and experimental groups. The first group (control) was given a basal ration and drinking water with 0 mg/kg resveratrol. The second group was given the basal ration and drinking water with 10 mg/kg resveratrol; and the third group was given the basal ration and drinking water 20 mg/kg resveratrol. The study was conducted in accordance with the dosage recommended by the OECD (1995). The rations used in the experiment were formulated according to the recommendations of NRC (1994). At the end of the study, the animals were weighed at beginning and the end to determine their live weight changes.

Biochemical parameters analysis

At the end of the study, blood taken from animals (eight per group, total of 24) was separated from serum with a centrifuge device (Hettich - Eba 200, Germany) at 3000 rpm for 10 minutes. Glucose, total protein, albumin, globulin, creatinine, BUN, total bilirubin, total cholesterol, AST, gamma glutamyl transferase (GGT) levels in blood serum were determined by analyzing in a biochemistry device (Mindray 200, China) with an auto analyzer device.

Antioxidant parameter analysis

At the end of the study, the blood serum, liver and muscle tissue homogenates were prepared. CAT, SOD, GSH and MDA for lipid peroxidation enzyme levels among the supernatant antioxidant parameters obtained from serum and tissue homogenates were determined by enzyme-linked immunosorbent assay (ELISA) testing device using commercial kits.

Statistical analysis

In the study, arithmetic mean was used as descriptive statistics for groups and standard error was used as a measure of prevalence. Conformity of data to normal distribution was determined by Kolmogorov-Smirnov test. One-way analysis of variance (ANOVA) was used to determine the significance of differences in body weight changes, biochemical parameters and antioxidant parameters between groups, and Tukey and Tamhane's T2 multiple comparison test was used to determine differences between groups.

Analysis results were decided according to the significance level of $p<0.05$. The data were analyzed using the IBM SPSS Statistic V 21.0 package program.

RESULTS

There was no statistical difference between the groups depending on the effect of resveratrol on the parameters of live weight and feed utilization rate at the beginning and end of the study ($p>0.05$) (Table 1).

Table 1. The effect of resveratrol on body weight and daily body weight gain in rats.

Parameters	Control	Res10	Res20	p value
Initial live weight, g	52.50±0.93	51.25±0.75	52.50±1.31	0.610
Finish live weight, g	146.38±1.16	139.75±4.90	145.25±4.60	0.460
Daily live weight gain, g	2.68±0.05	2.53±0.14	2.65±0.13	0.620

There was a significant reduction in parameters of BUN, AST, albumin, total protein, globulin and albumin/globulin ratio among serum biochemistry parameters depending on resveratrol ($p<0.05$). There was no statistical difference between the experimental groups in terms of creatinine, total cholesterol, GGT, total bilirubin, glucose parameters ($p>0.05$) (Table 2).

Table 2. The effect of resveratrol on serum biochemical parameters in rats.

Analyzes	Control	Res10	Res20	p value
Creatinine, mg/dL	0.50±0.03	0.51±0.06	0.37±0.06	0.140
BUN, mg/dL	28.38±1.77^{a}	26.25±1.31^{ab}	20.75±2.28^{b}	0.020
Total cholestrol, mg/dL	72.09±3.51	59.54±4.48	47.65±5.31	0.070
AST, U/L	154.80±4.45^{a}	130.71±5.17^{b}	93.00±7.99^{c}	0.001
GGT, U/L	1.00±0.01	1.25±0.25	1.50±0.29	0.530
Total Bilirubin, mg/dL	0.10±0.02	0.08±0.01	0.08±0.02	0.670
Albumin, g/dL	3.30±0.06^{a}	3.23±0.13^{ab}	2.18±0.35^{b}	0.002
Total Protein, g/dL	6.23±0.11^{a}	5.84±0.25^{a}	4.14±0.76^{b}	0.010
Globulin, g/dL	2.93±0.07^{a}	2.61±0.12^{ab}	1.79±0.40^{b}	0.010
Albumin/globulin, g/dL	1.13±0.02^{b}	1.24±0.03^{ab}	1.58±0.21^{a}	0.050
Glucose, mg/dL	144.38±7.20	146.25±5.88	128.60±7.43	0.220

BUN: Blood urea nitrogen, AST: Aspartate aminotransferase, GGT: Gamma glutamyl transferase. $^{a-c}$: The difference between values with different letters on the same line is significant

Among the experimental groups within the scope of antioxidant parameters, GSH enzyme in liver tissue; GSH, MDA and CAT enzymes in kidney tissue; SOD and CAT enzyme concentrations in muscle tissue; statistically significant differences were found. ($p<0.05$). There was no statistical difference in serum GSH, MDA, SOD and CAT enzyme concentrations ($p>0.05$) (Table 3).

DISCUSSION

Resveratrol was first used in Chinese and Japanese traditional medicine for the treatment of inflammation, allergies and hypertension diseases (Smoliga et al., 2013). Unlike previous studies, the current study tries to determine the effects of application in the form of adding resveratrol to water in varying dosages instead of dietary supplements.

There are many studies on the effect of resveratrol on live weight and feed consumption (Carbo' et al., 1999; Dal-Pan et al., 2010; He et al., 2019; Juan et al., 2002; Pallouf et al., 2019; Sridhar et al., 2015; Turner et al., 1999; Zhang et al., 2014, 2017). In this study; Juan et al. (2002)

found that 2g/kg of resveratrol has no negative effect on growth in rats; Turner et al. (1999) and Carbo' et al. (1999) reported that oral administration of 20 mg/kg of resveratrol for 28 days did not affect body weight or growth rate. In a resveratrol-administered study, no change in feed consumption was determined in mice fed with a diet high in fat and sugar for 12 months (C57BL/6) (Pallouf et al., 2019). A study conducted on different species reported that the addition of 0.5% and 1.0% resveratrol to the diets of broilers exposed to aflatoxin caused a decrease in body weight and feed consumption during a 5-week period but did not affect the feed conversion rate (Sridhar et al., 2015). It was reported that the addition of resveratrol to broiler rations at different rates (200, 400 and 800 mg/kg) does not affect the feed performance parameters (Zhang et al., 2014). In the current study, a similar effect to those of previous studies was found (Carbo' et al., 1999; Sridhar et al., 2015). However, He et al., (2019) reported that the addition of resveratrol at different levels (200, 350, 500 mg/kg) in broiler chickens under heat stress affects the average daily feed consumption and increases body weight. Zhang et al., (2017) reported that the average daily feed consumption, average live weight and feed utilization rate increased with the addition of resveratrol to broiler diets under heat stress. There are also studies reporting that dietary resveratrol supplementation (in the resveratrol groups of 100 and 400 mg/kg) caused a reduction in feed consumption, and claiming that this effect may be due to the softness of resveratrol (Dal-Pan et al., 2010).

Table 3. The effect of resveratrol supplementation on antioxidant and peroxidant enzyme concentration in liver, kidney, muscle and serum tissues of rats.

Samples	Enzymes	Control	Res10	Res20	p value
Liver	GSH U/mL	39.26±9.38^{c}	148.48±16.94^{b}	340.48±17.94^{a}	0.001
	SOD U/mL	65.17±3.23	66.08±1.23	65.97±2.45	0.960
	MDA nmol/mL	4.69±0.44	6.33±0.89	4.92±0.76	0.280
	CAT U/mL	0.04±0.01	0.07±0.02	0.05±0.01	0.330
Kidney	GSH U/mL	72.81±4.80^{ab}	82.78±5.59^{a}	55.72±2.22^{b}	0.020
	SOD U/mL	75.38±2.23	71.65±1.58	74.16±1.56	0.360
	MDA nmol/mL	15.18±1.49^{a}	13.94±0.59^{a}	5.44±0.33^{b}	0.001
	CAT U/mL	0.05±0.01^{b}	0.14±0.01^{a}	0.15±0.01^{a}	0.001
Muscle	GSH U/mL	80.00±6.57	53.37±2.60	51.11±4.96	0.300
	SOD U/mL	86.53±0.62^{a}	81.43±1.02^{b}	80.15±1.98^{ab}	0.020
	MDA nmol/mL	11.23±0.87	8.89±0.38	9.76±1.40	0.340
	CAT U/mL	0.04±0.01^{c}	0.11±0.01^{b}	0.51±0.07^{a}	0.001
Serum	GSH U/mL	49.45±1.61	46.67±3.01	60.94±5.56	0.110
	SOD U/mL	86.27±1.69	89.16±0.22	89.38±0.20	0.070
	MDA nmol/mL	3.10±0.28	3.85±0.48	4.20±0.30	0.100
	CAT U/mL	0.04±0.01	0.03±0.01	0.06±0.01	0.310

GSH: Glutation peroxidase, SOD: Super oxide dis mutase. MDA: Malondialdehyde, CAT: Catalase, $^{a-c}$: The difference between values with different letters on the same line is significant.

Routine blood parameters are widely used to study the effects of various factors on the body (Chand et al., 2018). Serum glucose, triglyceride and total protein parameters, which are generally used for this purpose, reflect sugar, fat and protein metabolism (Ghasemi and Nari, 2020; Hu et al., 2021). Especially serum triglyceride and cholesterol parameters are accepted as key

factors of lipid metabolism balance (Helkin et al., 2016). In a study conducted in quails, it was stated that 100, 200 and 400 mg/kg of resveratrol supplementation in the ration did not affect glucose, triglyceride and total protein levels in serum (Ölmez et al., 2020). In another study, it was stated that 400 mg/kg resveratrol added to the broiler ration did not affect glycogen, lactate and lactate dehydrogenase (LDH) values in breast meat (Zhang et al., 2018). Again, in a study conducted in sheep, it was reported that 450 and 900 mg/kg doses of curcumin added to the diet did not affect serum glucose, triglyceride and total cholesterol levels (Jiang et al., 2019). The serum biochemical profile provides valuable information about the health and immune status of animals, and serum BUN, creatine and creatine kinase levels are very important for kidney function (Comba et al., 2016). Increased blood urea level and creatinine may result from increased protein catabolism and/or adequate conversion of ammonia to urea (Badgujar et al., 2015). In a study, it was suggested that increased serum creatinine and urea levels as a result of fipronil intoxication reflect the toxicity, as well as seriously jeopardizing the kidney's capacity to filter wastes from the blood, and this may be an indicator of kidney damage (Mossa et al., 2015). In the current study, the fact that resveratrol added to water statistically lowers serum BUN, creatinine, albumin, total protein and globulin concentration may mean that it has no negative effects on the kidneys.

There are many biochemical studies on the use of resveratrol in animal trial studies (Poulsen et al., 2013; Wilson et al., 1996). In a study conducted in rats, it was reported that the injection of resveratrol in two doses of 20 and 40 mg/kg for 21 days did not change the ratio of cholesterol due to high-density lipoprotein (HDL) or LDL (Juan et al., 2002). Ghanim et al. (2010) reported in a study conducted on sick and healthy people that resveratrol supplementation of 40 mg for 6 weeks did not change the cholesterol (total, LDL and HDL) and triglycerides levels in the trial groups compared to the control group. When hypercholesterolemic rabbits were given resveratrol, no differences in lipoprotein levels were found (Wilson et al., 1996). Zhang et al. (2017) reported that the addition of resveratrol to broiler rations affected triglyceride and total protein concentrations and decreased glucose concentration. He et al. (2019) reported that resveratrol supplementation reduced serum glucose and total protein concentrations, while triglyceride concentrations did not change. Unlike previous studies, the current study found that Resveratrol supplementation reduces the level of total cholesterol, but that it also reduces the level of total protein similar to previous studies. The data in the current study are supported by studies which report that resveratrol also inhibits the oxidation of LDL and prevents cardiovascular diseases associated with endothelial damage (Frankel et al., 1993; Nigdikar et al., 1998).

There are many studies which report that resveratrol has antidiabetic effects (Bhatt et al., 2012; Hausenblas et al., 2014). Poulsen et al. (2013) reported that resveratrol supplementation prevents diseases such as diabetes, cancer and fatty liver, and also reduces insulin resistance (Szkudelski and Szkudelska, 2015). Although it was not statistically significant, the current study determined that the concentration of glucose decreased in direct proportion to the resveratrol ratio. It was reported to facilitate glycemic index control in diabetic animals given a diet with Resveratrol, to decrease serum LDL and triglyceride levels significantly, and to increase high-density lipoprotein (HDL) levels. In the same study, it was stated that animals given resveratrol was improved tolerance to glucose, but did not produce changes in liver and kidney function parameters (Raskovic et al., 2019).

In the evaluation of liver enzymes, Alema´n et al. (1998) reported that the AST concentration in rats given resveratrol was significantly higher than in the control group, but that the alanine aminotransferase (ALT) concentration did not

change. Another study showed that resveratrol (20 mg/kg daily for 4 weeks) inhibited dimethylnitrosamine-induced elevation of serum alanine transaminase, aspartate transaminase, alkaline phosphatase, and bilirubin (Lee et al., 2010). However, Upadhyay et al. (2008) reported that serum ALT and AST concentrations decreased significantly in a study conducted on Swiss albino mice with 10 mg/kg of resveratrol for 1-4 weeks. Likewise, the current study observed that the serum AST concentration decreased, in contrast to some previous studies. It is believed that this effect occurs similar to the positive effects of resveratrol on triglycerides, cholesterol and glycemic index.

The use of antioxidants in diet and skin care products has increased its popularity in the last few years. Intensive research has been conducted on resveratrol in recent years. Resveratrol is considered a very powerful antioxidant, which makes it a unique product. Research has shown that the polyphenols found in wines are some of the most powerful antioxidants, several times more powerful than vitamins A, C and E. Idebenone, the ubiquinone analogue, is considered the strongest topical antioxidant. However, recent studies have shown that resveratrol has about 17 times higher potency than Idebenone (Baxter, 2008). It was reported that the addition of Resveratrol to broiler rations helps them increase their antioxidant activity, and also contributes to the development of protein and total antioxidant capacity in plasma (Sridhar et al., 2015). Khan et al. (2013) and Şahin et al. (2012) reported that resveratrol increases the regulation of antioxidant enzymes such as CAT, SOD and GSH-Px, reducing oxidative stress and inflammation. There are studies, which report that resveratrol can increase the expression of various antioxidants, but it reduces the enzyme level and MDA content (Xia et al., 2017; Zhang et al., 2017). Şahin et al. (2010) reported that the serum MDA level was not affected in oviparous quails after the addition of resveratrol. In contrast to this study, Liu et al. (2014) stated that the addition of 400 mg/kg of Resveratrol to chicklet rations increased antioxidant capacity and reduced MDA content. In the presented study observed increases in GSH (liver), and CAT (muscle and kidney) concentrations. In general, a slight increase in serum MDA concentration, which is a lipid peroxidation parameter, was observed. A decrease was observed GSH and MDA concentration in muscle tissue, while it did not change SOD concentration in kidney tissues.

CONCLUSION

As a result, in this study, it was aimed to determine the effects of resveratrol, which is used in various ways, by adding it to drinking water. There was no change in terms of live weight and daily live weight gain parameters as a result of resveratrol. In serum biochemistry parameters, however, a significant decrease was observed in urea, BUN, albumin, total protein, globulin and albumin/globulin ratios. It is thought that these decreases may occur due to the fact that resveratrol is structurally condensed with protein structures. There was also a significant decrease in the liver enzyme AST. A general increase in GSH levels among antioxidant parameters in the liver was observed, regardless of the dosage. Additionally, a very slight decrease was observed in the muscle tissue in SOD parameter. In general, a decrease was observed in MDA concentrations in the kidney tissue, a parameter of lipid peroxidation. It is believed that the increase in antioxidant enzyme levels and the decrease in MDA concentration are due to the antioxidant aspect of resveratrol. As a result, it was determined in the current research that resveratrol has antioxidant effects without depending on the usage patterns; and it was concluded that this additive can be used for various purposes.

ACKNOWLEDGMENT

Conflict of interest: The authors declared that there is no conflict of interest.

Ethical statement: This study was carried out per Cumhuriyet University's approved ethical rules (protocol no. 2021/422 date: 20/04/2021).

REFERENCES

Alema´n, C.L., Ma´s, R.M., Rodeiro, I., Noa, M., Herna´ndez, C., Mene´ndez, R., Ga´mez, R. (1998). Reference database of the main physiological parameters in Sprague-Dawley rats from 6 to 32 months. *Laboratory Animals*, *32*(4), 457–466. https://doi.org/10.1258/002367798780599802

Badgujar, P.C., Pawar, N.N., Chandratre, G.A., Telang, A.G., Sharma, A.K. (2015). Fipronil induced oxidative stress in kidney and brain of mice: protective effect of vitamin E and vitamin C. *Pesticide Biochemistry and Physiology*, *118*, 10-18. https://doi.org/10.1016/j.pestbp.2014.10.013

Baxter, R.A. (2008). Anti-aging properties of resveratrol: Review and report of a potent new antioxidant skin care formulation. *Journal of Cosmetic Dermatology*, *7*, 2–7.

Bhatt, J.K., Thomas, S., Nanjan, M.J. (2012). Resveratrol supplementation improves glycemic control in type 2 diabetes mellitus. *Nutrition Research*, *32*(7), 537-541. https://doi.org/10.1016/j.nutres.2012. 06.003

Carbo´, N., Costelli, P., Baccino, F.M., Lo´pez-Soriano, F.J., Argile´s, J.M. (1999). Resveratrol, a natural product present in wine, decreases tumor growth in a rat tumor model. *Biochemical and Biophysical Research Communications*, *254*(3), 739–743. https://doi.org/10.1006/bbrc.1998.9916

Chand, N., Naz, S., Rehman, Z., Khan, R.U. (2018). Blood biochemical profile of four fast-growing broiler strains under high ambient temperature. *Applied Biological Chemistry*, *61*(3), 273-279. https://doi.org/10.1007/s13765-018-0358-4

Comba, B., Cinar, A., Comba, A., Gencer, Y.G. (2016). Effects of ACTH application on kidney function tests, the electrolytes and hematological parameters in rats. *Ankara Üniversitesi Veteriner Fakültesi Dergisi*, *63*(3), 229-233.

Dal-Pan, A., Blanc, S., Aujard, F. (2010). Resveratrol suppresses body mass gain in a seasonal non-human primate model of obesity. *BMC Physiology*, *10*(11). https://doi.org/10.1186/1472-6793-10-11

Frankel, E.N., Waterhouse, A.L., Kinsella, J.E. (1993). Inhibition of human LDL oxidation by resveratrol. *Lancet*, *341*(8852), 1103-1104. https://doi.org/10.1016/0140-6736(93)92472-6

Ghanim, H., Sia, C.L., Abuaysheh, S., Korzeniewski, K., Patnaik, P., Marumganti, A., Chaudhuri, A., Dandona, P. (2010). An antiinflammatory and reactive oxygen species suppressive effect of an extract of Polygonum cuspidatum containing resveratrol. *Journal of Clinical Endocrinology and Metabolism*, *95*(9), E1-E8. https://doi.org/10.1210/jc.2010-0482

Ghasemi, H.A., Nari, N. (2020). Effect of supplementary betaine on growth performance, blood biochemical profile, and immune response in heat-stressed broilers fed different dietary protein levels. *Journal of Applied Poultry Research*, *29*(2), 301-313. https://doi.org/10.1016/j.japr.2019.11.004

Harada, N., Zhao, J., Kurihara, H., Nakagata, N., Okajima, K. (2011). Resveratrol improves cognitivefunction in mice by increasing production of insulin-like growth factor-I in the hippocampus. *Journal of Nutritional Biochemistry*, *22*(12), 1150-1159. https://doi.org/10.1016/j.jnutbio.2010.09.016

Hausenblas, H.A., Schoulda, J.A., Smoliga, J.M., Schoulda, S. (2014). Resveratrol treatment as an adjunct to pharmacological management in type 2 diabetes mellitus-systematic review and meta-analysis. *Molecular Nutrition and Food Research*, *59*(1), 147-159. https://doi.org/10.1002/mnfr.201400173

He, S., Li, S., Arowolo, M.A., Yu, Q., Chen, F., Hu, R., He, J. (2019). Effect of resveratrol on growth performance; rectal temperature and serum parameters of yellow-feather broilers under heat stress. *Animal Science Journal*, *90*(3), 401-411. https://doi.org/10.1111/asj.13161

Helkin, A., Stein, J.J., Lin, S., Siddiqui, S., Maier, K.G., Gahtan, V. (2016). Dyslipidemia part 1-review of lipid metabolism and vascular cell physiology. *Vascular and Endovascular Surgery*, *50*(2), 107-118. https://doi.org/10.1177/1538574416628654

Hong, H.J., Kang, W., Kim, D.G., Lee, D.H., Lee, Y., Han, C. (2014). Effects of resveratrol on the insulin signaling pathway of obese mice. *Journal of Veterinary Science*, *15*(2), 179-185. https://doi.org/10.4142/jvs.2014.15.2.179

Hu, H., Bai, X., Xu, K., Zhang, C., Chen, L. (2021). Effect of phloretin on growth performance, serum biochemical parameters and antioxidant profile in heat-stressed broilers. *Poultry Science 100*(8), 101217. https://doi.org/10.1016/j.psj.2021.101217

Jiang, Z., Wan, Y., Li, P., Xue, Y., Cui, W., Chen, Q., Mao, D. (2019). Effect of curcumin supplement in summer diet on blood metabolites, antioxidant status, immune response, and testicular gene expression in Hu sheep. *Animals*, *9*(10), 720. https://doi.org/10.3390/ani9100720

Joe, A.K., Liu, H., Suzui, M., Vural, M.E., Xiao, D., Weinstein, I.B. (2002). Resveratrol induces growth inhibition, S-phase arrest, apoptosis, and changes in biomarker expression in several human cancer cell lines. *Clinical Cancer Research*, *8*(3), 893–903.

Juan, M.E., Vinardell, M.P., Planas, J.M. (2002). The daily oral administration of high doses of trans-resveratrol to rats for 28 days is not harmful. *Journal of Nutrition*, *132*, 257-260. https://doi.org/10.1093/jn/132.2.257

Khan, M.A., Chen, H.C., Wan, X.X., Tania, M., Xu, A.H., Chen, F.Z., Zhang, D.Z. (2013). Regulatory effects of resveratrol on antioxidant enzymes: A mechanism of growth inhibition and apoptosis induction in cancer cells. *Molecular Cell*, *35*(3), 219-225. https://doi.org/10.1007/s10059-013-2259-z

Lee, E.S., Shin, M.O., Yoon, S., Moon, J.O. (2010). Resveratrol inhibits dimethylnitrosamine-induced hepatic fibrosis in rats. *Archives of Pharmacal Research*, *33*, 925-932. https://doi.org/10.1007/s12272-010-0616-4

Liu, G.S., Zhang, Z.S., Yang, B., He, W. (2012). Resveratrol attenuates oxidative damage and ameliorates cognitive impairment in the brain of senescence-accelerated mice. *Life Science*, *91*(17-18), 872–877. https://doi.org/10.1016/j.lfs.2012.08.033

Liu, L.L., He, J.H., Xie, H.B., Yang, Y.S., Li, J.C., Zou, Y. (2014). Resveratrol induces antioxidant and heat shock protein mRNA expression in response to heat stress in black-boned chickens. *Poultry Science*, *93*(1), 54-62. https://doi.org/10.3382/ps.2013-03423

Moreno, M., Castro, E., Falqué, E. (2008). Evolution of trans- and cis- resveratrol content in red grapes (Vitis vinifera L. cv Menciá; Albarello and Merenzao) during ripening. *European Food Research and Technology*, *227*(3), 667-674. https://doi.org/10.1007/s00217-007-0770-1

Mossa, A.T.H., Swelam, E.S., Mohafrash, S.M. (2015). Sub-chronic exposure to fipronil induced oxidative stress, biochemical and histopathological changes in the liver and kidney of male albino rats. *Toxicology Reports*, *2*, 775-784. https://doi.org/10.1016/j.toxrep.2015.02.009

Nigdikar, S.V., Williams, N.R., Griffin, B.A., Howard, A.N. (1998). Consumption of red wine polyphenols reduces the susceptibility of low-density lipoproteins to oxidation in vivo. *American Journal of Clinical Nutrition*, *68*(2), 258-265. https://doi.org/10.1093/ajcn/68.2.258

Nosáľ, R., Drábiková, K., Jančinová, V., Perečko, T., Ambrožová, G., Číž, M., Lojek, A., Pekarová, M., Šmidrkal, J., Harmatha, J. (2014). On the molecular pharmacology of resveratrol on oxidative burst inhibition in professional phagocytes. *Oxidative Medicine and Cellular Longevity*, *2014*, 706269. https://doi.org/10.1155/2014/706269

NRC (1994). Nutrient Requirements of Poultry. 9th Edn., National Academy Press, Washington, DC. USA.

OECD (Organization for Economic Cooperation and Development). (1995). Guidelines for testing chemicals. Repeated dose 28-d oral toxicity study in rodents, No. 407. Paris, France.

Ölmez, M., Şahin, T., Makav, M., Karadağoğlu, Ö. (2020). Effect of resveratrol supplemented to japanese quail (Coturnix coturnix japonica) rations on performance and some biochemical parameters. *Kafkas Üniversitesi Veteriner Fakültesi Dergisi*, *26*(6), 807-812. https://doi.org/10.9775/kvfd.2020.24542

Pallauf, K., Chin, D., Gunther, I., Birringer, M., Luersen, K., Schultheiss, G., Vieten, S., Krauss, J., Bracher, F., Danylec, N., Soukop, S.T., Kulling, S.E., Rimbach, G. (2019). Resveratrol, lunularin and dihydroresveratrol do not act as caloric restriction mimetics when administered intraperitoneally in mice. *Scientific Reports*, *9*(1), 4445. https://doi.org/10.1038/s41598-019-41050-2

Poulsen, M.M., Jorgensen, J.O., Jessen, N., Richelsen, B., Pedersen, S.B. (2013). Resveratrol in metabolic health: An overview of the current evidence and perspectives. *Annals of the New York Academy of Sciences*, *1290*(1), 74-82. https://doi.org/10.1111/nyas.12141

Rasković, A., Ćućuz, V., Torović, L., Tomas, A., Gojković-Bukarica, L., Ćebović, T., Milijašević, B., Stilinović, N., Cvejić Hogervorst, J. (2019). Resveratrol supplementation improves metabolic control in rats with induced hyperlipidemia and type 2 diabetes. *Saudi Pharmaceutical Journal*, *27*(7), 1036–1043. https://doi.org/10.1016/j.jsps.2019.08.006

Shankar, S., Singh, G., Srivastava, R.K. (2007). Chemoprevention by resveratrol: molecular mechanisms and therapeutic potential. *Frontiers in Bioscience – Landmark*, *12*(12), 4839-4854. https://doi.org/10.2741/2432

Singh, C.K., Ndiaye, M.A., Ahmad, N. (2015). Resveratrol and cancer: Challenges for clinical translation. *Biochimica et Biophysica Acta (BBA)*, *1852*(16), 1178-1185. https://doi.org/10.1016/j.bbadis.2014.11.004

Smoliga, J.M., Sage, C.E., Campen, M.J. (2013). A healthier approach to clinical trials evaluating resveratrol for primary prevention of age-related diseases in healthy populations. *Aging*, *5*(7), 495-506. https://doi.org/10.18632/aging.100579

Sridhar, M., Suganthi, R.U., Thammaiah, V. (2015). Effect of dietary resveratrol in ameliorating aflatoxin B1-induced changes in broiler birds. Journal of Animal Physiology and *Animal Nutrition*, *99*(6), 1094-1104. https://doi.org/10.1111/jpn.12260

Stivala, L., Savio, M., Carafoli, F., Perucca, P. (2001). Specific structural determinants are responsible for the antioxidant activity and the cell cycle effects of resveratrol. *Journal of Biological Chemistry*, *276*(25), 22586-22594. https://doi.org/10.1074/jbc.M101846200

Szkudelska, K., Nogowski, L., Szkudelski, T. (2009). Resveratrol, a naturally occurring diphenolic compound, affects lipogenesis, lipolysis and the antilipolytic action of insulin in isolated rat adipocytes. *Journal of Steroid Biochemistry and Molecular Biology*, *113*(1-2), 17-24. https://doi.org/10.1016/j.jsbmb.2008.11.001

Szkudelski, T. and Szkudelska, K. (2015). Resveratrol and diabetes: From animal to human studies. *Biochimica et Biophysica Acta - Molecular Basis of Disease*, *1852*(6), 1145-1154. https://doi.org/10.1016/j.bbadis.2014.10.013

Şahin, K., Akdemir, F., Orhan, C., Tuzcu, M., Hayirli, A., Şahin, N. (2010). Effects of dietary resveratrol supplementation on egg production and antioxidant status. *Poultry Science*, *89*(6), 1190-1198. https://doi.org/10.3382/ps.2010-00635

Şahin, K., Orhan, C., Akdemir, F., Tuzcu, M., Iben, C., Şahin, N. (2012). Resveratrol protects quail hepatocytes against heat stress: Modulation of the Nrf2 transcription factor and heat shock proteins. *Journal of Animal Physiology and Animal Nutrition*, *96*(1), 66-74. https://doi.org/10.1111/j.1439-0396.2010.01123.x

Turner, R.T., Evans, G.L., Zhang, M., Maran, A., Sibonga, J.D. (1999). Is resveratrol an estrogen agonist in growing rats? *Endocrinology*, *140*(1), 50–54. https://doi.org/10.1210/endo.140.1.6460

Upadhyay, G., Singh, A.K., Kumar, A., Prakash, O., Singh, M.P. (2008). Resveratrol modulates pyrogallol-induced changes in hepatic toxicity markers, xenobiotic metabolizing enzymes and oxidative stress. *European Journal of Pharmacology*, *596*(1-3), 146-152. https://doi.org/10.1016/j.ejphar.2008.08.019

Wilson, T., Knight, T.J., Beitz, D.C., Lewis, D.S., Engen, R.L. (1996). Resveratrol promotes atherosclerosis in hypercholesterolemic rabbits. *Life Science*, *59*(1), 15–21. https://doi.org/10.1016/0024-3205(96)00260-3

Xia, N., Daiber, A., Förstermann, U., Li, H. (2017). Antioxidant effects of resveratrol in the cardiovascular system. *British Journal of Pharmacology*, *174*(12), 1633-1646. https://doi.org/10.1111/bph.13492

Xie, H.C., Han, H.P., Chen, Z., He, J.P. (2013). A study on the effect of resveratrol on lipid metabolism in hyperlipidemic mice. *African Journal of Traditional*, *11*(1), 209-212.

Zhang, Z., Gao, L., Cheng, Y., Jiang, J., Chen, Y., Jiang, H., Yu, H., Shan, A., Cheng, B. (2014). Resveratrol; a natural antioxidant; has a protective effect on liver injury induced by inorganic arsenic exposure. *BioMed Research International*, *2014*, 1-7. https://doi.org/10.1155/2014/617202

Zhang, C., Zhao, X., Wang, L., Yang, L., Chen, X., Geng, Z. (2017). Resveratrol beneficially affects meat quality of heat-stressed broilers which is associated with changes in muscle antioxidant status. *Animal Science Journal*, *88*(10), 1569-1574. https://doi.org/10.1111/asj.12812

Zhang, C., Yang, L., Zhao, X., Chen, X., Wang, L., Geng, Z. (2018). Effect of dietary resveratrol supplementation on meat quality, muscle antioxidative capacity and mitochondrial biogenesis of broilers. *Journal of the Science of Food and Agriculture*, *98*(3), 1216-1221. https://doi.org/10.1002/jsfa.8576