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Resveratrol and Its Effects on Diabetes Mellitus

Hatice Tuğçe Berberoğlu [1*], Nurhan Ünüsan [1]

[1] KTO Karatay University, College of Health Sciences, Department of Nutrition and Dietetics, Konya, Turkey

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Abstract

Diabetes mellitus is a chronic disease that causes complications as a result of insulin resistance, insulin deficiency or the combination of both. It is a public health problem of great importance all over the world due to its high prevalence and complications. Resveratrol is a biologically active polyphenolic compound and in recent years, it is one of the most studied nutrients. The effects of resveratrol, which is abundant in foods such as grapes, peanuts, red wine, blueberries and cherries on human health have been studied for a long time. Antioxidant, proinflammatory, anti-carcinogen and their protective effects against heart diseases and obesity have been tried to be elucidated in studies conducted in humans and animals so far. In addition, it is thought that resveratrol may have effects on the development and complications of diabetes, which is an important public health problem in the world. It has been shown to a beneficial effect on diabetes by modulating glucose homeostasis, increasing insulin sensitivity, reducing insulin resistance and contributing to the preservation of pancreatic tissue by activating AMPK, estrogen receptors and SIRT, improving mitochondrial dysfunction, inhibiting protein-tyrosine phosphatase expression in human and animal experimental studies. Even though it has several positive health effects, especially on diabetes, resveratrol is toxic and a safe intake dose has not been clarified yet. Therefore, more studies should be carried out to understand its safe/toxic dose. In this review, the effects of resveratrol's polyphenolic compound on diabetes and glucose metabolism parameters and possible mechanisms of action will be examined.

1. Introduction

Diabetes mellitus is a chronic, broad-spectrum metabolism disorder in which the organism cannot make sufficient use of carbohydrates, fats, and proteins due to insulin deficiency or a decrease in insulin effects, and requires continuous medical care (TEMD, 2020). When diabetes is not managed well, severe damage occurs over time to blood vessels, heart, eyes, kidneys, and nerves. The most common type of diabetes is Type 2 diabetes, and its prevalence is increasing worldwide (WHO, 2021). According to the International Diabetes Federation (IDF), there were approximately 463 million diabetic patients in 2019, and it is estimated that 578 million adult individuals will have diabetes by 2030 and 700 million by 2045 (IDF, 2019). Today, antidiabetic drugs such as Biguanides and sulfonylureas are used in managing diabetes (Huang, Shi, Jiang, Yao & Zhu, 2020). However, due to some critical side effects of these drugs, such as gastrointestinal problems, increased body weight and hypoglycemia (Cheng & Fantus, 2005), researchers have been working on natural compounds that are important for the control of diabetes (Verspohl, 2012). Among these compounds, resveratrol, a natural and biologically active compound, draws attention due to its pleiotropic activity (Szkudelski & Szkudelska, 2015).

Resveratrol, which is in the subclass of stilbene, is one of the polyphenol types. Its chemical structure is in the form of 3,5,4′-trihydroxystylben, and it has two aromatic rings connected by a methylene bridge (Catalgol, Batirel, Taga & Ozer, 2012).

Resveratrol which was first isolated from vine leaves (Langcake & Pryce, 1977), is also abundant in the roots of the Kojo-kon plant for treatment of many diseases such as hypertension, inflammation, and allergies in Japan (Pervaiz, 2003). Siemann et al. found resveratrol in wine for the first time in 1992 (Siemann & Creasy, 1992).

Resveratrol is synthesized in plants in response to stress and protects the plants from the effects of various infections and ultraviolet rays (Dixon, 2001). To date, resveratrol has been detected in 72 plant species, in the seed membrane, shell and embryo of plants (King, Bomser & Min, 2006). Resveratrol found in plants varies depending on the genotype of the plant, water activity, soil temperature, and maturation status (Arora & Strange, 1991). Although *Polygonum cuspidatum* is one of the best sources of resveratrol, it is also found in plants such as grapes, peanuts, red wine, spruce, lily, vine leaves, blueberries, plums, mulberries, cherries, carob, and lemons (Aydın & Erbaş, 2019).

Resveratrol exists in 2 isomeric forms, cis and trans. The trans form has strong therapeutic effects (Nawaz et al., 2017). The trans form can be produced from yeast extracts (*Saccharomyces cerevisiae*) using recombinant technology and is used as a food supplement (Nawaz et al., 2017). Cis form is formed when the trans form is exposed to heat, light, and ultraviolet radiation (Camont et al., 2009).

The health effects of resveratrol have been studied for many years (Aydın & Erbaş, 2019). It has been suggested that resveratrol contributes to the reduced incidence of cardiovascular diseases among the French population, and is named as the French Paradox, due to the consumption of red wine (Nawaz et al., 2017). In addition to its antioxidant, anti-inflammatory, antiviral, anti-aging, and protective

***Corresponding author:** Hatice Tuğçe Berberoğlu
e-mail address: tugceaca@gmail.com

effects against various cancers (Bay Karabulut, 2008), antiplatelet aggregation, protecting cartilage tissue and endothelial function (Oyenihi, Oyenihi, Adeyanju & Oguntibeju, 2016), anti-obesity (de Ligt, Timmers & Schrauwen, 2015), immunomodulator, enhancing cerebrovascular function, neuroprotective (Regitz, Fitzenberger, Mahn, Dußling & Wenzel, 2016), cardioprotective (Li, Xia & Förstermann, 2012), and hepatoprotective (Sadi et al., 2015) properties are also known. It has been reported in previous studies that the positive effects of resveratrol on diabetes in recent years and the results are promising (Szkudelski & Szkudelska, 2015). In this review, we will examine the effects of resveratrol compound on biochemical parameters associated with Diabetes Mellitus and the potential mechanisms underlying these effects.

2. Resveratrol and Diabetes Mellitus

Studies have reported that resveratrol may prevent the development of diabetes and alleviate some diabetes-related complications (Huang et al., 2020). In these studies, it is considered that resveratrol may have important roles in controlling, preventing, or delaying diabetes by improving insulin resistance (Movahed et al., 2013; Szkudelski & Szkudelska, 2015; Thazhath et al., 2016), preventing damage to beta islets in the pancreatic tissue (Lee et al., 2011), and decreasing diabetic complications (Chen et al., 2011; Elbe et al., 2015; Mohammadshahi, Haidari & Soufi, 2014).

2.1. Resveratrol and Diabetic Biomarkers

In a study conducted on diabetic rats, resveratrol has been shown to positively affect metabolic parameters reducing plasma glucose, triglyceride, and insulin levels (Aydın & Erbaş, 2019). In the study of Thazhath et al., it was shown that 5 mg of resveratrol supplementation daily for 28 days reduced HbA1c level (Thazhath et al., 2016). It was found that 1 g resveratrol supplementation daily for 45 days decreased fasting blood glucose-insulin (Movahed et al., 2013), and Goh et al. (2014) showed that resveratrol has a glucose-lowering effect by activating Sirtuin (SIRT)1 and Adenosine Monophosphate-Activated Protein Kinase (AMPK) in individuals with Type 2 diabetes. It was shown that resveratrol supplementation inhibited protein-tyrosine phosphatase expression and decreased insulin, glucose, and lipid concentrations in animals (Sun et al., 2007). In another study, resveratrol administration reduced blood glucose levels in rats whose beta cells were damaged by inducing streptozotocin (Chang, Chang, Huang & Hung, 2012; Jiang et al., 2013). Recently, resveratrol has been found to reduce diabetic ototoxicity in individuals diagnosed with Type 2 diabetes (Erkan et al., 2019).

2.2. Resveratrol and Insulin Resistance/Sensitivity

Resveratrol has been shown to improve insulin resistance (Luo et al., 2017; Wong & Howe, 2018), increase insulin sensitivity (Côté et al., 2015; González-Rodríguez et al., 2015) in animal studies. In addition, it has been shown that it increases insulin sensitivity, glucose tolerance, and mitochondrial biogenesis due to AMPK (Aydın & Erbaş, 2019). In a meta-analysis of 11 randomized controlled trials, a single dose of oral daily resveratrol administration has been shown to reduce blood glucose levels decreasing insulin concentration, HbA1c, HOMA-IR and increasing insulin sensitivity in diabetic individuals for 3 months. However, a similar effect has not been observed in non-diabetic people (Liu,

***Corresponding author:** Hatice Tuğçe Berberoğlu
e-mail address: tugceaca@gmail.com

Zhou, Wang & Mi, 2014). Five mg/d of resveratrol supplementation for 28 days decreased HbA1c level and increased insulin sensitivity (Thazhath et al., 2016). Jimenez-Gomez et al. showed that resveratrol supplementation given for 2 years in rhesus monkeys increased insulin sensitivity in visceral adipose tissue (Jimenez-Gomez et al., 2013). In animal studies, resveratrol has been shown to reduce insulin resistance by causing changes in skeletal muscle, adipose tissue, and liver tissues (Szkudelski & Szkudelska, 2015). It has been shown that resveratrol also decreases the serum insulin level and HOMA-IR value statistically in people with Type 2 Diabetes (Movahed et al., 2013).

2.3. Resveratrol and Diabetic Complications

It was also found that it can prevent the development of hyperglycemia-induced nephropathy (Aydın & Erbaş, 2019). In addition, resveratrol improves sensory-motor disorders associated with diabetic neuropathy by inhibiting nicotinamide adenine dinucleotide phosphate oxidase activity (Chen et al., 2011) reducing oxidative stress (Kumar, Kaundal, Iyer & Sharma, 2007) and lowering pro-inflammatory cytokine levels (Maity, Bora & Sur, 2018). It also reduces diabetic retinopathy by regulating various transcription factors preventing retinal endothelial cell migration and decreasing Vascular Endothelial Growth Factor (VEGF) expression in endothelial tissue (Liu et al., 2013). Also, resveratrol has been shown to reduce diabetes-induced renal damage (Elbe et al., 2015), cardiac complications (Mohammadshahi et al., 2014) and increased neural development along with cognitive functions (Tian et al., 2016).

2.4 Resveratrol and Oxidative Stress, Inflammatory Status

Studies have shown that resveratrol reduces the expression of advanced glycation end-products in the liver and kidneys of diabetic rats, increases antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase and inhibits the production of reactive nitrogen species such as hydrogen peroxide, malondialdehyde and pro-inflammatory cytokines (Aydın & Erbaş, 2019). A study found that serum IL-1, IL-6, and TNF-α levels decreased significantly after the administration of resveratrol in rats with Type 2 Diabetes Mellitus (Chang et al., 2012). In addition, resveratrol supplementation protects pancreatic islet cells by inhibiting NF-κB and other inflammatory cytokine activation and increasing antioxidant enzymes (Palsamy & Subramanian, 2010).

2.5. Resveratrol and Pancreatic Islets

The number of pancreatic islets decrease, insulitis develops, and some degenerative changes occur in Type 1 Diabetes. It was found that resveratrol administration in NOD mice delayed Type 1 Diabetes development and improved the severity of the disease when the disease developed. In addition, the total number of pancreatic islets and non-insulitis and improvement in the general condition of pancreatic islets in NOD mice were reported (Lee et al., 2011).

3. Potential Mechanisms between Diabetes Mellitus and Resveratrol

There are several theories explaining the mechanism of action of resveratrol on diabetes. Firstly, it has

***Corresponding author:** Hatice Tuğçe Berberoğlu
e-mail address: tugceaca@gmail.com

been shown that resveratrol can normalize increased insulin, insulin-like factor, and glucose levels by activating AMPK, estrogen receptors (Wong & Howe, 2018), and SIRT (Côté et al., 2015; Z. Liu, Jiang, Zhang, Liu & Du, 2016) modulating NAD^+/NADH (Luo et al., 2017). SIRT1 and SIRT3 play important roles in improving metabolic disorders such as obesity and diabetes (Szkudelska & Szkudelski, 2010). By activating SIRT1 and SIRT3, resveratrol improves mitochondrial dysfunction that causes the development of insulin resistance and Type 2 Diabetes Mellitus (Pereira et al., 2015; Sharma et al., 2011). Recovery of mitochondrial dysfunction decreases reactive oxygen production and increases fatty acid oxidation (Huang et al., 2020). Secondly, resveratrol has been found to increase insulin sensitivity and prevent insulin resistance by inhibiting protein-tyrosine phosphatase expression (González-Rodríguez et al., 2015; Sun et al., 2007) Resveratrol, the activator of SIRT1, inhibits protein-tyrosine phosphatase and increases insulin sensitivity *in vivo* and *in vitro* (Sun et al., 2007). In addition, resveratrol prevents the destruction of pancreatic tissue by suppressing reactive oxygen species and cytokine release and increasing antioxidant enzyme concentrations. Otherwise, excessive secretion of cytokines damages the pancreatic tissue (Palsamy & Subramanian, 2010). Resveratrol protects pancreatic tissue from free radicals, which has been attributed to resveratrol's increases in antioxidant enzyme levels (Palsamy & Subramanian, 2010). Resveratrol also contributes to the delay of the development of Type 1 Diabetes by preventing the autoimmune destruction of beta cells in the pancreas (Lee et al., 2011).

Resveratrol delays the development of myopathy in the muscle tissue in patients with Type 1 Diabetes by showing an anti-inflammatory effect in muscle tissue and reducing oxidative stress, thus positively affecting glucose metabolism (Chang et al., 2014). Resveratrol contributes to keeping the liver healthy and maintains normoglycemia (Szkudelski & Szkudelska, 2015) by reducing the activity of enzymes that play roles in gluconeogenesis (Palsamy & Subramanian, 2009), and activating glycogen synthase (Chi et al., 2007). In addition, it also improves histological abnormalities in the liver due to its antioxidant and anti-inflammatory effects and by inducing mitochondrial biogenesis in the liver tissue (Szkudelski & Szkudelska, 2015). It is considered that resveratrol improves insulin receptor phosphorylation, IRS-1 protein levels and phosphorylated Akt expression in the skeletal muscle of insulin-resistant animals (Szkudelski & Szkudelska, 2015).

Based on these mechanisms of resveratrol administration in human and animal studies, it is thought that resveratrol may prevent the development of diabetes and diabetic complications, protect pancreatic tissue, maintain optimum glucose, HOMA-IR, insulin levels, reduce insulin resistance, and increase insulin sensitivity.

4. Safe Intake Dose and Toxicity

The data on the toxic and safe intake dose of resveratrol is not yet clear. It has been shown that the oral dose of resveratrol up to 5 g in humans is well tolerated (Cottart, Nivet-Antoine, Laguillier-Morizot & Beaudeux, 2010). Although it is generally well-tolerated in healthy individuals, if taken in large amounts, side effects such as gastrointestinal and

***Corresponding author:** Hatice Tuğçe Berberoğlu
e-mail address: tugceaca@gmail.com

nephrotoxicity have been reported in humans (Poulsen et al., 2013). Additionally, individuals who have health problems tend to be affected by side effects, and there are limited studies among individuals with pathological conditions (Shaito et al., 2020).

High doses of resveratrol up to 1000 mg/d have been shown to increase cardiovascular disease parameters in overweight and elderly individuals. Lower doses had no effects on these parameters (Mankowski et al., 2020). Cottart et al. showed that 0.5 g resveratrol intake may be sufficient to positively affect the effect of insulin and reduce blood glucose level, and it was reported that 0.5 g level may cause moderate and reversible side effects in long-term use (Cottart, Nivet-Antoine & Beaudeux, 2014). In the study of Porte et al., 2g/kg/d resveratrol supplementation for a week caused diarrhea in 6 out of 8 people (la Porte et al., 2010). Resveratrol given orally to rats at 200 mg/kg/d for 90 days had no adverse effects (Johnson et al., 2011). However, another study showed that a resveratrol supplementation of 2-5 grams per day may have mild side effects such as diarrhea and nausea (Muñoz & Bustamante, 2015). In one study, 5.0 g/d of resveratrol was administered to a refractory multiple myeloma patient, and side effects such as nausea, diarrhea, fatigue, kidney toxicity were observed in the patient, and eventually, the patient was lost (Popat et al., 2013). Therefore, prior to human experiments, *in vivo* studies including animal models with different health conditions have been recommended. Ongoing clinical studies are available, but have not yet been published. If published, it is expected that more data will be provided for the use of resveratrol in humans (Shaito et al., 2020). It has been shown to interact with some medications at high doses (1000 mg/day or higher) (Shaito et al., 2020).

In studies conducted on this subject, resveratrol was applied at different doses and times. Generally, short-term results regarding the effects of resveratrol have been observed. Therefore, more comprehensive studies are needed to determine the safe intake and toxic dose of resveratrol (Shaito et al., 2020).

5. Conclusion

It is known that resveratrol, a polyphenolic compound, has anti-inflammatory, antioxidant, and protective effects against obesity, cancer, and various diseases. In recent years, studies have been conducted to examine the effects of resveratrol on diabetes. In these studies, it has been shown that resveratrol activates AMPK and SIRT, protects pancreatic tissue, inhibits protein-tyrosine phosphatase expression, decreases reactive oxygen species and proinflammatory cytokine production, and positively affects insulin signaling, prevents increased blood glucose, HbA1c, insulin levels, and prevents/delays the development of diabetes and the development of diabetes-related complications.

Although the results of the studies regarding the positive effects of resveratrol on health are consistent with each other, studies investigating its toxicity are still limited. Therefore, large-scale, population-based comprehensive and long-term studies are needed to determine the therapeutic or preventive effects of resveratrol in humans, its bioavailability, its possible interactions when used with other treatments and its absorption in the human body.

***Corresponding author:** Hatice Tuğçe Berberoğlu
e-mail address: tugceaca@gmail.com

Conflicts of interest

There are no conflicts of interests to declare.

References

Arora, M. K., & Strange, R. N. (1991). Phytoalexin accumulation in groundnuts in response to wounding. *Plant Science*, *78*(2), 157–163. doi:10.1016/0168-9452(91)90194-d.

Aydın, G. & Erbaş, O. (2019). The effects of resveratrol on human health. *FNG&Demiroğlu Bilim Tıp Dergisi*, *5*(4), 193–201. doi: 10.5606/fng.btd.2019.035.

Bay Karabulut, A. (2008). Resveratrol ve etkileri. *Turkiye Klinikleri Journal of Medical Sciences*, *28*(6 SUPPL.), 166–169.

Camont, L., Cottart, C. H., Rhayem, Y., Nivet-Antoine, V., Djelidi, R., Collin, F., Beaudeux, JL., & Bonnefont-Rousselot, D. (2009). Simple spectrophotometric assessment of the trans-/cis-resveratrol ratio in aqueous solutions. *Analytica Chimica Acta*, *634*(1), 121–128. doi: 10.1016/j.aca.2008.12.003.

Catalgol B., Batirel S., Taga Y., & Ozer N. K. (2012). Resveratrol: French paradox revisited. *Frontiers in Pharmacology*, 2012;3:141. doi: 10.3389/fphar.2012.00141.

Chang, C-C., Yang, M-H., Tung, H-C., Chang, C-Y., Tsai, Y-L., Huang, J-P., Yen, T-H., & Hung, L-M. (2014). Resveratrol exhibits differential protective effects on fast- and slow-twitch muscles in streptozotocin-induced diabetic rats. *The Chinese Journal of Physiology*, *6*(1), 60–67. doi: 10.1111/1753-0407.12072.

Chang, C-C., Chang, C-Y., Huang, J-P., & Hung, L-M. (2012). Effect of resveratrol on oxidative and inflammatory stress in liver and spleen of streptozotocin-induced type 1 diabetic rats. *Chinese Journal of Physiology*, *55*(3), 192–201. doi: 10.4077/CJP.2012.BAA012.

Chen, K-H., Hung, C-C., Hsu, H-H., Jing, Y-H., Yang, C-W., & Chen, J-K. (2011). Resveratrol ameliorates early diabetic nephropathy associated with suppression of augmented TGF-β/smad and ERK1/2 signaling in streptozotocin-induced diabetic rats. *Chemico-Biological Interactions*, 190(1), 45–53. doi: 10.1016/j.cbi.2011.01.033.

Cheng, A. Y. Y., & Fantus, I. G. (2005). Oral antihyperglycemic therapy for type 2 diabetes mellitus. *Canadian Medical Association Journal*, *172*(2), 213–226. doi: 10.1503/cmaj.1031414.

Chi, T. C., Chen, W. P., Chi, T. L., Kuo, T. F., Lee, S. S., Cheng, J. T., & Su M. J. (2007). Phosphatidylinositol-3-kinase is involved in the antihyperglycemic effect induced by resveratrol in streptozotocin-induced diabetic rats. *Life Sciences*, *80*(18), 1713–1720. doi: 10.1016/j.lfs.2007.02.002.

Côté, C. D., Rasmussen, B. A., Duca, F. A., Zadeh-Tahmasebi, M., Baur, J. A., Daljeet, M., Breen, D. M., & Lam T. K. T. (2015). Resveratrol activates duodenal Sirt1 to reverse insulin resistance in rats through a neuronal network. *Nature Medicine*, *21*(5), 498–505. doi: 10.1038/nm.3821.

Cottart, C-H., Nivet-Antoine, V., & Beaudeux J-L. (2014). Review of recent data on the metabolism, biological effects, and toxicity of resveratrol in humans. *Molecular Nutrition & Food Research*, *58*(1), 7–21. doi: 10.1002/mnfr.201200589.

Cottart, C-H., Nivet-Antoine, V., Laguillier-Morizot, C., & Beaudeux, J-L. (2010). Resveratrol bioavailability and toxicity in humans. *Molecular Nutrition & Food Research*, *54*(1), 7–16. doi: 10.1002/mnfr.200900437.

de Ligt, M., Timmers, S., & Schrauwen P. (2015). Resveratrol and obesity: Can resveratrol relieve metabolic disturbances? *Biochimica et Biophysica Acta*, *1852*(6), 1137–1144. doi: 10.1016/j.bbadis.2014.11.012.

Dixon, R. A. (2001). Natural products and plant disease resistance. *Nature*, 411, 843–847. doi: 10.1038/35081178.

Elbe, H., Vardi, N., Esrefoglu, M., Ates, B., Yologlu, S., & Taskapan C. (2015). Amelioration of streptozotocin-induced diabetic nephropathy by melatonin, quercetin, and resveratrol in rats. *Human and Experimental Toxicology*, *34*(1), 100–113. doi: 10.1177/0960327114531995.

Erkan, S. O., Tuhanioğlu, B., Gürgen, S. G., Özdaş, T., Taştekin, B., Pelit, A., & Görgülü, O. (2019). The effect of resveratrol on the histologic characteristics of the cochlea in diabetic rats. *Laryngoscope*, *129*(1), E1–E6. doi: 10.1002/lary.27253.

Goh, K. P., Lee, H. Y., Lau, D. P., Supaat, W., Chan, Y. H., & Koh, A. F. Y. (2014). Effects of resveratrol in patients with type 2 diabetes mellitus on skeletal muscle SIRT1 expression and energy expenditure. *International Journal of Sport Nutrition and Exercise Metabolism*, *24*(1), 2–13. doi: 10.1123/ijsnem.2013-0045.

González-Rodríguez, Á., Santamaría, B., Mas-Gutierrez, J. A., Rada, P., Fernández-Millán, E., Pardo, V., Álvarez, C., Cuadrado, A., Ros, M., Serrano, M., & Valverde, Á. M. (2015). Resveratrol treatment restores peripheral insulin sensitivity in diabetic mice in a sirt1-independent manner. *Molecular Nutrition and Food Research*, *59*(8), 1431–1442. doi: 10.1002/mnfr.201400933.

Huang, D-D., Shi, G., Jiang, Y., Yao, C., & Zhu, C. (2020). A review on the potential of Resveratrol in prevention and therapy of diabetes and diabetic complications. *Biomedicine and Pharmacotherapy*, *125*, 109767. doi: 10.1016/j.biopha.2019.109767.

International Diabetes Federation (2019). *IDF Diabetes Atlas 9th edition*. Retrieved from https://www.diabetesatlas.org/en/

Jiang, B., Guo, L., Li, B-Y., Zhen, J-H., Song, J., Peng T., Yang, X-D., Hu, Z., & Gao H-Q. (2013). Resveratrol Attenuates Early Diabetic Nephropathy by Down-Regulating Glutathione S-Transferases Mu in Diabetic Rats. *Journal of Medicinal Food*, *16*(6), 481–486. doi: 10.1089/jmf.2012.2686.

***Corresponding author:** Hatice Tuğçe Berberoğlu
e-mail address: tugceaca@gmail.com

Jimenez-Gomez, Y., Mattison, J. A., Pearson, K. J., Martin-Montalvo, A., Palacios, H. H., Sossong A. M., Ward, T. M., Younts, C. M., Lewis, K., Allard, J. S., Longo, D. L., Belman, J. P., Malagon, M. M., Navas, P., Sanghvi, M., Moaddel, R., Tilmont, E. M., Helbert, R. L., Morrell, C. H., Egan, J. M., Baur, J. A., Ferrucci, L., Bogan, J. S., Bernier, M., & de Cabo, R. (2013). Resveratrol improves adipose insulin signaling and reduces the inflammatory response in adipose tissue of rhesus monkeys on a high-fat, high-sugar diet. *Cell Metabolism*, *18*(4),533-545. doi: 10.1016/j.cmet.2013.09.004.

Johnson, W. D., Morrissey, R. L., Usborne, A. L., Kapetanovic, I., Crowell, J. A., Muzzio, M. & McCormick, D. L. (2011). Subchronic oral toxicity and cardiovascular safety pharmacology studies of resveratrol, a naturally occurring polyphenol with cancer preventive activity. *Food and Chemical Toxicology*. 49(12):3319-27. doi: 10.1016/j.fct.2011.08.023.King, R. E., Bomser, J. A. & Min, D. B. (2006). Bioactivity of Resveratrol. *Comprehensive Reviews in Food Science and Food Safety*, *5*(3), 65–70. https://doi.org/10.1111/j.1541-4337.2006.00001.x

Kumar, A., Kaundal, R. K., Iyer, S. & Sharma, S. S. (2007). Effects of resveratrol on nerve functions, oxidative stress and DNA fragmentation in experimental diabetic neuropathy. *Life Sciences*, *80*(13), 1236–1244. doi: 10.1016/j.lfs.2006.12.036.

la Porte, C., Voduc, N., Zhang, G., Seguin, I., Tardiff D., Singhal N., & William Cameron, D. (2010). Steady-State Pharmacokinetics and Tolerability of Trans-Resveratrol 2000 mg Twice Daily with Food, Quercetin and Alcohol (Ethanol) in Healthy Human Subjects. *Clinical Pharmacokinetics*, 49(7):449-54. doi: 10.2165/11531820-000000000-00000.

Langcake, P., & Pryce, R. (1977). A new class of phytoalexins from grapevines. *Experientia*, *33*(2), 151–152. doi: 10.1007/BF02124034.

Lee, S. M., Yang, H., Tartar, D. M., Gao, B., Luo, X., Ye, S. Q., Zaghouani, H., & Fang D. (2011). Prevention and treatment of diabetes with resveratrol in a non-obese mouse model of type 1 diabetes. *Diabetologia*, *54*(5), 1136–1146. doi: 10.1007/s00125-011-2064-1.Li, H., Xia, N., & Förstermann, U. (2012). Cardiovascular effects and molecular targets of resveratrol. *Nitric Oxide*, 26(2):102-10. doi: 10.1016/j.niox.2011.12.006.

Liu, K., Zhou, R., Wang, B., & Mi, M. T. (2014). Effect of resveratrol on glucose control and insulin sensitivity: A meta-analysis of 11 randomized controlled trials. *American Journal of Clinical Nutrition*, *99*(6), 1510–1519. doi: 10.3945/ajcn.113.082024.

Liu, X-Q., Wu, B-J., Pan, W. H. T., Zhang, X-M., Liu, J-H., Chen, M-M., Chao, F-P., & Chao, H-M (2013). Resveratrol mitigates rat retinal ischemic injury: The roles of matrix metalloproteinase-9, inducible nitric oxide, and heme oxygenase-1. *Journal of Ocular Pharmacology and Therapeutics*, *29*(1), 33–40. doi: 10.1089/jop.2012.0141.

Liu, Z., Jiang, C., Zhang, J., Liu, B., & Du, Q. (2016). Resveratrol inhibits inflammation and ameliorates insulin resistant endothelial dysfunction via regulation of AMP-activated protein kinase and sirtuin 1 activities. *Journal of Diabetes*, *8*(3), 324–335. doi: 10.1111/1753-0407.12296.

Luo, G., Huang, B., Qiu, X., Xiao, L., Wang, N., Gao, Q., Yang, W., & Hao L. (2017). Resveratrol attenuates excessive ethanol exposure induced insulin resistance in rats via improving NAD+/NADH ratio. *Molecular Nutrition and Food Research*, *61*(11). doi: 10.1002/mnfr.201700087.Maity, B., Bora, M., & Sur, D. (2018). An effect of combination of resveratrol with vitamin D3 on modulation of proinflammatory cytokines in diabetic nephropathy induces rat. *Oriental Pharmacy and Experimental Medicine*, *18*(2), 127–138. doi: 10.1007/s13596-018-0311-4.Mankowski, R. T., You, L., Buford, T. W., Leeuwenburgh, C., Manini, T. M., Schneider, S., Qiu, P., & Anton, S. D. (2020). Higher dose of resveratrol elevated cardiovascular disease risk biomarker levels in overweight older adults – A pilot study. *Experimental Gerontology*, *131*, 110821. doi: 10.1016/j.exger.2019.110821.

Mohammadshahi, M., Haidari, F., & Soufi, F. G. (2014). Chronic resveratrol administration improves diabetic cardiomyopathy in part by reducing oxidative stress. *Cardiology Journal*, *21*(1), 39–46. doi: 10.5603/CJ.a2013.0051.

Movahed, A., Nabipour, I., Louis, X. L., Thandapilly, S. J., Yu, L., Kalantarhormozi, M., Rekabpour, S. J., & Netticadan T. (2013). Antihyperglycemic effects of short term resveratrol supplementation in type 2 diabetic patients. *Evidence-Based Complementary and Alternative Medicine*, 2013:851267. doi: 10.1155/2013/851267.

Muñoz, O., Muñoz, R., & Bustamante, S. (2015). Pharmacological Properties of Resveratrol. A Pre-Clinical and Clinical Review. *Biochemistry & Pharmacology: Open Access*. 4(5):1-9. doi: 10.4173/2167-0501.1000184.

Nawaz, W., Zhou, Z., Deng, S., Ma, X., Ma, X., Li, C., & Shu X. (2017). Therapeutic versatility of resveratrol derivatives. *Nutrients*, *9*(11):1188. doi: 10.3390/nu9111188.

Oyenihi, O. R., Oyenihi, A. B., Adeyanju, A. A., & Oguntibeju O. O. (2016). Antidiabetic Effects of Resveratrol: The Way Forward in Its Clinical Utility. *Journal of Diabetes Research*, *2016*(9737483). doi: 10.1155/2016/9737483.

Palsamy, P., & Subramanian, S. (2009). Modulatory effects of resveratrol on attenuating the key enzymes activities of carbohydrate metabolism in streptozotocin-nicotinamide-induced diabetic rats. *Chemico-Biological Interactions*, *179*(2–3), 356–362. doi: 10.1016/j.cbi.2008.11.008.

Palsamy, P., & Subramanian, S. (2010). Ameliorative potential of resveratrol on proinflammatory cytokines, hyperglycemia mediated oxidative stress, and pancreatic β-cell dysfunction in streptozotocin-nicotinamide-induced diabetic rats. *Journal of Cellular*

***Corresponding author:** Hatice Tuğçe Berberoğlu
e-mail address: tugceaca@gmail.com

Physiology, *224*(2), 423–432. doi: 10.1002/jcp.22138.

Pereira, S., Park, E., Moore, J., Faubert, B., Breen, D. M., Oprescu, A. I., Nahle, A., Kwan, D., Giacca, A., & Tsiani, E. (2015). Resveratrol prevents insulin resistance caused by short-term elevation of free fatty acids in vivo. *Applied Physiology, Nutrition and Metabolism*, *40*(11), 1129–1136. doi: 10.1139/apnm-2015-0075.

Pervaiz, S. (2003). Resveratrol: from grapevines to mammalian biology. *FASEB*, *17*(14), 1975–1985. doi: 10.1096/fj.03-0168rev.

Popat, R., Plesner, T., Davies, F., Cook, G., Cook, M., Elliott, P., Jacobson, E., Gumbleton, T., Oakervee, H., & Cavenagh, J. (2013). A phase 2 study of SRT501 (resveratrol) with bortezomib for patients with relapsed and or refractory multiple myeloma. *British Journal of Haematology*, *160*(5), 714–717. doi: 10.1111/bjh.12154.

Poulsen, M. M., Vestergaard, P. F., Clasen, B. F., Radko, Y., Christensen, L. P., Stødkilde-Jørgensen, H., Møller, N., Pederson, S. B & Jørgensen J. O. L. (2013). High-dose resveratrol supplementation in obese men an investigator- initiated, randomized, placebo-controlled clinical trial of substrate metabolism, insulin sensitivity, and body composition. *Diabetes*, *62*(4), 1186–1195. doi: 10.2337/db12-0975.

Regitz, C., Fitzenberger, E., Mahn, F. L., Dußling, L. M., & Wenzel, U. (2016). Resveratrol reduces amyloid-beta (Aβ1–42)-induced paralysis through targeting proteostasis in an Alzheimer model of Caenorhabditis elegans. *European Journal of Nutrition*, *55*(2), 741–747. doi: 10.1007/s00394-015-0894-1.

Sadi, G., Ergin, V., Yilmaz, G., Pektas, M. B., Yildirim, O. G., Menevse, A., & Akar, F. (2015). High-fructose corn syrup-induced hepatic dysfunction in rats: improving effect of resveratrol. *European Journal of Nutrition*, *54*(6), 895–904. doi: 10.1007/s00394-014-0765-1

Türkiye Endokrinoloji ve Metabolizma Derneği (2020). *Diabetes Mellitus ve Komplikasyonlarının Tanı, Tedavi ve İzlem Kılavuzu.* Retrieved from:https://temd.org.tr/admin/uploads/tbl_kilavuz/20200625154506-2020tbl_kilavuz86bf012d90.pdf

Shaito, A., Posadino, A. M., Younes, N., Hasan, H., Halabi, S., Alhababi, D., Al-Mohannadi, A., Abdel-Rahman, W. M., Eid, A. H., Nasrallah, G. K., & Pintus, G. (2020). Potential adverse effects of resveratrol: A literature review. *International Journal of Molecular Sciences*, *21*(6):2084 . doi: 10.3390/ijms21062084.

Sharma, S., Misra, C. S., Arumugam, S., Roy, S., Shah, V., Davis, J. A., Shirumalla, R. K., & Ray A. (2011). Antidiabetic activity of resveratrol, a known SIRT1 activator in a genetic model for type-2 diabetes. *Phytotherapy Research*, *25*(1), 67–73. doi: 10.1002/ptr.3221.Siemann, E. H., & Creasy, L. L. (1992). Concentration of the Phytoalexin Resveratrol in Wine. *American Journal of Enology and Viticulture*, *43*(1), 49–52.

Sun, C., Zhang, F., Ge, X., Yan, T., Chen, X., Shi, X., & Zhai, Q. (2007). SIRT1 Improves Insulin Sensitivity under Insulin-Resistant Conditions by Repressing PTP1B. *Cell Metabolism*, *6*(4), 307–319. doi: 10.1016/j.cmet.2007.08.014.Szkudelska, K., & Szkudelski, T. (2010). Resveratrol, obesity and diabetes. *European Journal of Pharmacology*,635(1-3):1-8. doi: 10.1016/j.ejphar.2010.02.054.

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

Thazhath, S. S., Wu, T., Bound, M. J., Checklin, H. L., Standfield, S., Jones, K. L., Horowitz, M., & Rayner, C. K. Rayner C. K. (2016). Administration of resveratrol for 5 wk has no effect on glucagon-like peptide 1 secretion, gastric emptying, or glycemic control in type 2 diabetes: A randomized controlled trial. *American Journal of Clinical Nutrition*, *103*(1), 66–70. doi: 10.3945/ajcn.115.117440.

Tian, X., Liu, Y., Ren, G., Yin, L., Liang, X., Geng T., Dang, H., & An, R. (2016). Resveratrol limits diabetes-associated cognitive decline in rats by preventing oxidative stress and inflammation and modulating hippocampal structural synaptic plasticity. *Brain Research*, *1650*, 1–9. doi: 10.1016/j.brainres.2016.08.032.

Verspohl, E. J. (2012). Novel pharmacological approaches to the treatment of type 2 diabetes. *Pharmacological Reviews*, *64*(2), 188–237. doi: 10.1124/pr.110.003319.

World Health Organization (2021). *Diabetes.* Retrieved from https://www.who.int/news-room/fact-sheets/detail/diabetes.

Wong, R. H. X., & Howe, P. R. C. (2018). Resveratrol counteracts insulin resistance-potential role of the circulation. *Nutrients*, *10*(9), 1160. doi: 10.3390/nu10091160.

***Corresponding author:** Hatice Tuğçe Berberoğlu
e-mail address: tugceaca@gmail.com