Review Article

International Journal of Research in Pharmaceutical Sciences

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

Recent Review on Role of Resveratrol in Diabetes and its Complication

Dhruval Nandurkar, Manohar M, Gowda D.V.*

Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Shivarathreeshwara, Bannimantap Nagar, Mysuru-570015, Karnataka, India

Article History:

Received on: 20.08.2019
Revised on: 06.11.2019
Accepted on: 13.11.2019

Keywords:

Resveratrol,
Diabetes,
Curcumin,
SIRT1 signaling pathway,
Polyol Signaling Pathway

Abstract

Resveratrol, a non-flavanoid, is a trans-stilbene derivative and is a compound of great interest because of its wide pharmacological actions in disease such as cancer, diabetes and its complications, cardiac diseases etc. Resveratrol has been working effectively by acting as an antioxidant and interfere in the generation of free radicals, which in turn is the main cause of various diseases. Resveratrol has shown very effective in Diabetes and its complications such as Diabetic Retinopathy, Coronary Artery Disease, Diabetic cardiomyopathy, vascular dysfunction, Chronic Renal Failure and others. Though the main challenge comes in formulating Resveratrol as it has low solubility, low stability and less bioavailability. This review focuses on antioxidants being an essential class of compounds in the treatment of diabetes. Role of various antioxidants being studied along with showcasing their combined effect with resveratrol and also the mechanism of resveratrol in diabetes and its complications. Lastly, it also highlights various formulations of resveratrol which have shown improvement in solubility, stability and bioavailability. Thus Resveratrol is identified as an essential compound in the treatment of diabetes and its complications.

*Corresponding Author

Name: Gowda D.V.
Phone:
Email: dvgowda@jssuni.edu.in

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i2.2069

Production and Hosted by

IJRPS | www.ijrps.com

INTRODUCTION

Resveratrol is a non-flavonoid polyphenolic compound with chemically containing 3,5,4 trihydroxy trans-stilbene Figure 2. In 1940, it was first identified by Michio Takaoka from Hellebore roots. Resveratrol after that became commonly used to prepare wine from grapes, berries. It was also extracted from peanuts, soy and dark chocolate. The activities of Resveratrol has been related to the structure to a great extent. Resveratrol occurs in two different stereo forms namely as cis isomer and trans isomer where only tans form is active (Catalgol *et al.*, 2012).

Antioxidants are widely researched for the treatment of varieties of diseases. These antioxidants act by interfering with the free radical generations which is one of the leading causes for most of the diseases such as diabetes and their complications Figure 1,Table 1 renal diseases, cardiac disease and various others too. Antioxidants such as curcumin, resveratrol, berberine, quercetin and combinations of these are topics of interest in research. But these antioxidants mentioned above have both beneficial effects and limitations to a certain extent. Out of the mentioned antioxidants, Resveratrol has been researched and has potentially shown a high safety profile. Resveratrol has also shown to have the potential to target a number of diseases from Cancer to Diabetes Table 2. More focus has been given to the anti-diabetic action of resveratrol and is stud-

ied extensively.

Resveratrol act by more than one mechanism in these diseases, such as decreasing the glucose level in blood in diabetes or vasodilation in the case of cardiac disease. The Resveratrol mainly exerts its action by interfering in various pathways such as the SIRT1 signaling pathway, NK-kB Signalling Pathway, AMPK signaling pathway, or by increasing Akt phosphorylation and decreasing free radical generation (Oyenihi *et al.*, 2016),Figure 3.

Pharmacologically resveratrol is an emerging molecule for curing various diseases. But for researchers, the main challenges come in formulating of resveratrol into an effective formulation as various problems need to be tackled, such as the low biological half-life of resveratrol with rapid metabolism and degradation in the body, labile nature of it, and very less oral bioavailability. So novel formulation has been formulated to stabilize and protect resveratrol from degradation, enhancing its solubility in water to improve its bioavailability, to achieve a sustained release, and ultimately to target resveratrol to specific locations via multiparticulate forms and colloidal carriers Table 3.

Role of antioxidants in diabetes mellitus

Antioxidants act primarily by decreasing oxidative stress and act on the free radical generation. They are available from various dietary sources and enhance our defense mechanism. In the elimination of reaction species of oxygen, various non-enzymatic and enzymatic mechanisms are involved. Vitamin E decreases the peroxidation of fatty acids. Vitamin E exists as eight different forms, which are fat-soluble of which tocopherol A is present in Sunflower. Vitamin C plays a predominant function in enhancing the production of nitric oxide in epithelial cells. Diabetes interferes in oxidative stress and the free radical generation, which may act as a typical target for inhibition. Antioxidants, as discussed above, act on scavenging the free radicals and act by various mechanisms. Antioxidants also act by inhibiting the formation of ROS and enhance antioxidants defense enzyme capabilities. Antioxidants supplementation may improve the endothelial dysfunction in Type 2 DM by enhancing eNOS expression and mitochondrial function and suppressing vascular NADPH oxidase activity. In the Case of Diabetic complications, proper management of blood pressure and glucose level along with antioxidant therapy, is needed. Antioxidants therapy can be given along with substrates, enzymes, other drugs, biologic substrates, etc. There exist a large number of the cellular defense mechanism of various antioxidants to scavenge free radicals. In enzymatic system antioxidant system, enzymes such as copper, manganese, zinc, glutathione reductase, peroxidase and catalase may remove Reactive oxygen species, preventing their excessive deposition and unwanted effects, whereas, in non-enzymatic antioxidants system, it involves scavenger compounds that are produced in the body. During rigorous exercise, the level of oxidative stress increases and that tends to up-regulate antioxidants defense mechanisms in various tissues. Exogenous antioxidants compensate for lower plasma antioxidants level as studied in TypeII DM and also in pre-diabetic individuals. Vitamins (C, E and A) and carotenoids are derived from diet and are considered to a great extent. Ascorbic acid and Tocopherol are showing good antioxidant properties. These vitamins are mainly present in vegetables and fruits, which is one-way to guarantees health benefits.

Along with vitamins, some polyphenols have also been researched recently and have been proved to show antioxidants effects. In vegetables, these constituents are present in the form of phenolic acids, phenol and flavonoids. Coenzyme Q has shown to act by decreasing oxidative stress by two mechanisms i.e., "Recoupling" mitochondrial oxidative phosphorylation and quenching ROS. Another example is Alpha-lipoic acid, which also acts by radical scavenging mechanism.

According to a study, it was found that lipoic acid suppresses glucose transit in muscle cells by activating the translocation of GLUT-4. Lipoic acid has also shown a protective action in cultured adipocyte cells. Similarly, lipoic acid has increased insulin-mediated glucose uptake in patients with Type 2 DM by modulating insulin sensitivity. Some of the drugs have also shown the antioxidant effect -eg gemfibrozil, statins, thiazolidinediones.

List of Antioxidants and their Combination Proved to be effective in Diabetes and its Complication.

Quercetin (QE) and Resveratrol (RS)Flavanoids like Quercetin and Resveratrol are phenolic compounds that have shown verities of activity such as anti-diabetic, anti-oxidant, anti-hypertensive, neuroprotective, anti-inflammatory, etc. The main source of these antioxidants is fruits and vegetables. Both resveratrol and quercetin have shown to elevate the lifespan of the organism by decrease cell death.

Quercetin (QE) and Resveratrol (RS)

Flavanoids like Quercetin and Resveratrol are phenolic compounds that have shown verities of activity such as anti-diabetic, anti-oxidant, anti-

Table 1: Resveratrol in treatment of Diabetes and its complications as studied in various Animal Model

Diabetes Complication Cured By Resveratrol	Diabetic Animal Model used	Mechanism	Reference
Ischemia-Reperfusion Injury	Rat	Increase in the level of ATP and phosphocreatine in the heart of TYPE II diabetic patient during reperfusion	(Fourny *et al.*, 2019)
Coronary Heart Disease	Rat	Downregulation Of TLR4/MyD88/NF-kB signaling pathway	(Fang *et al.*, 2018)
Cardiomyopathy	Rat	SIRT1 activation and increased PGC-1α deacetylation	(Fang *et al.*, 2018)
Neuroprotection	Rat	Prevention of hypertrophy of the nNOS-IR, HuC/D-IR, and CALR-IR neuronal subpopulations and Prevent the neuronal loss	(Fang *et al.*, 2018)
Chronic Renal Failure	Mice	Inhibition of superoxide dismutase and (-) glutathione and 4-hydroxy-2-nominal levels	(Fang *et al.*, 2018)
Cataract	Rat	Suppress the increase in protein carbonyls	(Higashi *et al.*, 2018)
Vascular Dysfunction	Mice	Reduced the activity of HFD-induced extravasation Recovery of the phosphorylated form of Akt and eNOS expression in the thoracic aorta healing through Sirt1/ER pathway	(Fang *et al.*, 2018)
Muscle Atrophy	Mice	activating catabolic signaling pathways	(Wang *et al.*, 2018)
acute pulmonary thromboembolism-induced pulmonary artery hypertension	Rat	elevated the expression of eNOS (P<0.01) and enhanced the expression of p-p38 and VGEF	(Fang *et al.*, 2018)
Diabetic Retinopathy	Rat	decreased the activity of NF-kB and also the process of apoptosis by regulating their levels in the retina	(Kim *et al.*, 2018)

hypertensive, neuroprotective, anti-inflammatory, etc. The main source of these antioxidants is fruits and vegetables. Both resveratrol and quercetin have shown to elevate the lifespan of the organism by decrease cell death.

Quercetin has proven beneficial effects such as:

1. Normalise blood glucose level
2. Augment liver glycogen content and enzyme
3. Reduce serum cholesterol
4. Improve antioxidant activity and prevent oxidative damage

Resveratrol has shown antidiabetic effects and improvement in insulin release and has shown significant effect when administered along with Quercetin in animal models.

Berberine

Berberine is a component obtained from traditional Chinese herb *Coptidis Rhizoma* has shown hypolipidemic effects against hypercholesteremia and Type 2 DM. However, a high dose of berberine has shown to have few adverse effects such as constipation, diarrhea and flatulence. Though all of these adverse effects disappeared in one week after a decline in berberine dosage. In previous studies, it was established that Berberine could resist oxidative stress-induced apoptosis or cellular senescence by upregulation of sirtuin 1 (SIRT1) expression at a low dosage (Zhu *et al.*, 2013, 2017).

SIRT1 was regarded as a master metabolic sensor by inhibiting the caloric intake in mammals which proved beneficial. Resveratrol, a chemical activator of SIRT1, also showed improvement in lipid metabolism in the pathologic state, such as obesity, type II diabetes and atherosclerosis. Level of ROS are elevated in cells incubated in both low and high concentrations of curcumin, moreover signaling pathway tend to increase in less concentration. This intends to prevent diabetic complications by reducing oxidative stress.

Curcumin

Curcumin has been researched in the treatment of various diseases such as diabetes and its complications too. Mainly research has shown that Curcumin may act by regulating inflammatory factors such as NK-kB. These factors deregulate various pathways involving proteins such as AMPK and SIRT1, which helps in insulin production and a decrease in glucose level AMPK is phosphorylated by curcumin and metabolism of lipid is enhanced. Glucose and deacetylating of PGC1-α were found to be regulated by SIRT1 (Yang *et al.*, 2013; Zendedel, 2018). PGC1-α and PPAR-γ help in modulating actions pertaining to the metabolism of fatty acid, the formation of glucose, etc.. But still, research of curcumin in diabetes by various mechanisms is running.

Resveratrol

Resveratrol has shown its antioxidant effects by various mechanisms (Szkudelski and Szkudelska, 2015; Berman *et al.*, 2017).

Along with resveratrol, pterostilbene has been researched for the treatment of diabetes. Nutraceuticals are considered for treatment because of safety and efficacy.

Resveratrol in the act by SIRT-1 Pathway by regulating Foxo-1 Signalling by decreasing glucose in the body by utilizing it. Foxo-1 transactivates the PDK-4 enzyme. So compounds such as Curcumin, Berberine and resveratrol have already been studied and have shown activity against diabetes.

These molecules also increase glucose uptake and increase insulin release by increasing phosphodiesterase activity and so is an essential target in diabetes treatment (Mccubrey *et al.*, 2017). Melatonin also acts on SIRT-1 and interferes with aging.

Resveratrol has shown in interfering with estrogen receptors, which is one way, has an indirect relation with diabetes (Li *et al.*, 2018). Has told above resveratrol effects in diabetes has already been researched in rats, which are made diabetic by streptozocin. And also in mice, and high-fat diet mice, in some studies even in a human volunteer. In a few studies, resveratrol has also shown to act on insulin resistant and increase insulin levels Table 2.

Resveratrol and 17β-estradiol

17β-Estradiol action in diabetes has already been proved along with resveratrol as discussed in various diabetic animal models (Catanuto *et al.*, 2009; Li *et al.*, 2018), in diabetic humans, and also in rats with Type 1 D. But estrogen has some interference in studies, so its effect was removed by removing both ovaries. Various parameters such as T-AOC (plasma total antioxidant capacity), FPI (Fasting Plasma insulin level), etc... were studied.

Role of Resveratrol in SIRT1 Signalling

Recent studies have shown that Resveratrol acts through a SIRT1 signaling pathway. Sirtuins are enzymes acts through NAD-dependent deacetylation and deacylation of protein and play a vital role in the various biological process such as aging, inflammation, etc. About 7 Type of sirtuin has been researched (Houtkooper *et al.*, 2012; Yamagata and Yoshizawa, 2018). Sirtuin 3 and sirtuin

Table 2: Resveratrol in treatment of Diabetes and its complications as studied in cell line studies and human trials

Condition	Study Carried On	Dose and Duration	Outcome	Reference
Diabetic cardiomyopathy	H9c2 cardiac myoblast cells		prevents autophagy alleviates apoptosis attenuates HG/PA-induced apoptosis	(Fang *et al.*, 2018)
Bone Health	Type 2 Diabetic Patient		Enhanced Bone density prevention of bone mass reduction	(Fang *et al.*, 2018)
Type 2 Diabetic	Human	250mg/day + oral antidiabetic for 3 months	(i)↓HbA1c (ii) Cholesterol, LDL, HDL, cholesterols and body weight remains unaffected	(Fang *et al.*, 2018)
Type 2 Diabetic	Human	500mg twice daily for 45 days	(i) Decreased fasting blood glucose, HbA1c, insulin and insulin resistance (ii)↑HDL level	(Lv *et al.*, 2019)
Type 2 Diabetic	Human	5mg twice daily for 4 weeks	(i) Improved insulin sensitization (ii) Increased in the ratio of pAkt: Akt found in platelets	(Lv *et al.*, 2019)
Type 2 Diabetic	Human	50mg twice daily for 60 days	i)Decrease in size of foot ulcer and lower the level of plasma fibrinogen	(Lv *et al.*, 2019)
Coronary Artery Disease	Human	RSV-enriched grape extract for 12 months (8mg/day in initial 6 months and 16 mg/day in the later 6 months)	(i)HbA1c, serum glucose level, blood pressure and lipids remain unaltered (ii) ↓ IL-6, IL-1β and TNF-α expression	(Lv *et al.*, 2019)

Table 3: Formulations of resveratrol

S. No.	Dosage Form	Method Of Preparation	Complication Addressed	Outcomes	References
1	Nanoliposome	a) Dry Film Hydration Method b) Thin Lipid Film Method	Diabetes Mellitus	1. Stabilizing RSV against trans-to-cis isomerization 2. Improving its bioavailability	(Yucel *et al.*, 2018a)
2	Nanocochleates	Trapping Method	Diabetes Mellitus	1. Not found to be toxic to cells even at the highest concentrations 2. Improves Solubility and Bioavailability	(Yucel *et al.*, 2018b)
3	Self Emulsifying Drug Delivery System		antidiabetic, cardioprotective, and antitumor activities	Enhanced Solubility in Propylene glycol	(Yucel *et al.*, 2018b)
4	resveratrol loaded hyaluronic acid-DPPC microparticles	Spray Drying	diabetic foot wounds	The enhanced wound healing process	(Gokce *et al.*, 2017)
5	Nanoparticle	co-precipitation method	prophylaxis of myocardial infarction types 1 and 2 diabetes, and tumors	Increased bioavailability	(Yucel *et al.*, 2018b)
6	Nanosuspension	high-pressure homogenization technique	antidiabetic, cardioprotective, and antitumor activities	Enhanced Solubility and enhanced dissolution, thereby enhancing the bioavailability	(Pando *et al.*, 2013)
7	Cyclodextrin		Neuroprotection, antidiabetic	Enhanced solubility, thermal stability and antioxidant activity	(Gokce *et al.*, 2012; Reis *et al.*, 2013)
8	Microcapsules	Microen -capsulation	antidiabetic	Increased (Bioavailability, solubility and stability)	(Caddeo *et al.*, 2008)
9	Niosomes	Mechanical agitation followed by sonication	antidiabetic	Increased solubility and bioavailability	(Ahmed *et al.*, 2013)
10	Transfersome and ethosomes	Thin lipid film hydration method (rota evaporator)	Cardiovascular disease		(Peng *et al.*, 2010)
11	Nanosponges	Solubilization technique	antidiabetic	Increase Stability and cytotoxicity	(Peng *et al.*, 2010)
12	Microsphere	Chemical crosslinking method	Cardiovascular Disease	Increased Photostability, heat stability and solubility	

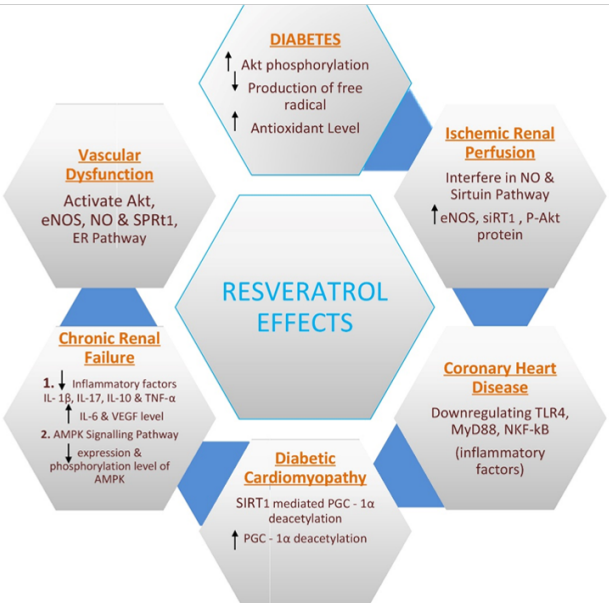

Figure 1: Effects of Resveratrol in Diabetic and its Complications

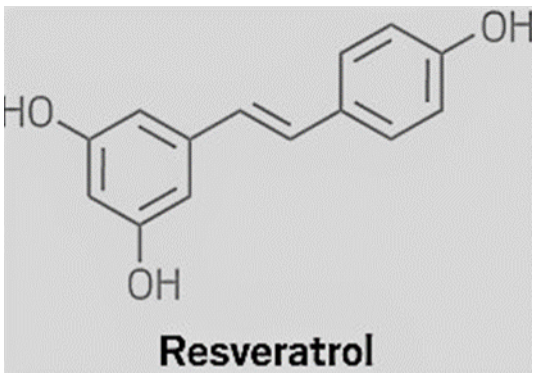

Figure 2: Structure of Resveratrol

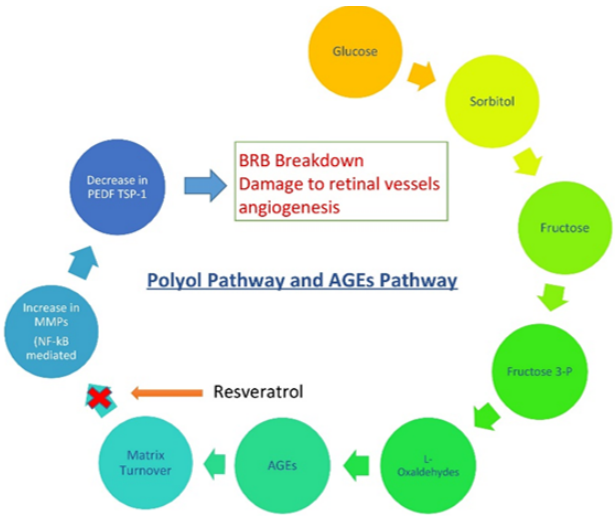

Figure 3: Role of Resveratrolin the polyol pathway and AGEs Pathway

6 action is by deacetylation. Sirtuin 4 has ribosyltransferase action and sirtuin 5 act by desuccination and demalonylation. Sirtuin 6 acts by hydrolyzation action on fatty acyl chains. SIRT7 acts by selective deacetylation activity by histone protein. Sirtuins act by deacetylation and deacylation of transcription factors. Out of 7 Sirtuins, Sirtuin 1 is studied mostly in liver tissue and skeletal muscle. Activation of this or its overexpression helps in diabetic treatment. This Studies also suggest that it can help in obesity treatment too. It also regulates enzymes pertaining to gluconeogenesis, such as glucose-6-phosphatase. Studies have shown that Sirtuin 1 increases gluconeogenesis by decreasing the expression of G6-pc and Pack-1 in the liver.

The metabolic role of sirt1 in β-cells of the pancreas

Insulin is secreted by β-cells of islets of Langerhans in the pancreas. Any dysfunction in these pancreatic cells leads to diabetes. Sirtuins elevate the transcription of uncoupling proteins 2, which decreases the secretion of insulin. Sirtuin 1 protects β-cells from the damage caused by cytokine by increasing NK-kB Signalling Pathway. This shows a Sirtuin act in insulin secretion. In autoimmune Diabetes, Treg cells have an essential role and sirtuin regulate the production of these cells, so it is believed that sirtuin malfunction may be the underlying cause for autoimmune diabetes. Sirtuin has desired effects in diabetic treatment. Sirtuin has also been shown an effect on the oxidation of various fatty acids (Bordone *et al.*, 2005; Kim *et al.*, 2018). Dysfunction in the signaling of insulin is commonly referred to as insulin resistance (Kim *et al.*, 2018). During this condition, oxidation of lipids does not take place, so lipid gets deposited. All the research and studies carried through years in various animal models and also in human volunteer has finally proved that SIRT-1 and other sirtuins too may be a potential target in the treatment of Diabetes.

Current trends of Resveratrol in Diabetes

Resveratrol and 17B estradiol

A study was carried out by Yunxia .et.al; to study effects of resveratrol and 17β- estradiol on streptozotocin (STZ) induced type 1 diabetes where female mice were given 0.1. 1, 10mg/kg of resveratrol and 0.01, 0.1, 1mg/kg of 17β-estradiol by subcutaneous route for 4 weeks and it was found that there was inhibition of the increase of blood glucose level and also increase of plasma malondialdehyde. The increase in the level of plasma antioxidant capacity and plasma insulin was also detected. Along with these effects, a significant change in the level of expression of GLUT4, IRS-1 and p-ERK (phosphory-

lation of extracellular signal-regulated kinase) was also seen.

Resveratrol and Berberine

Various researchers study combinations of Resveratrol and berberine. One of them includes the study of monotherapy of Resveratrol and Berberine and Combination of both on a high fat diet-induced hyperlipidemic mice. The concentration of resveratrol and berberine were 20 mg/kg/day, oral and 30 mg/kg/day, oral respectively. This was concluded that the combination of two was much more effective than monotherapy alone. There was a decrease in lipoprotein-cholesterol by 31.6% and total serum cholesterol by 27.4% on a combination of resveratrol and berberine while monotherapy of resveratrol decreased the level by 6.6% and 8.4% and berberine to 9.8% and 10.5% respectively. Thus the combination is an effective therapy for hyperlipidemia in associated obese diseases such as type II diabetes.

Resveratrol and Quercetin

Research on a combination of Resveratrol and Quercetin on streptozotocin (STZ)-induced diabetic rats for the treatment of diabetes was carried. Here 50 male Sprague-Daley rats were divided into five groups; standard control, 50 mg/kg STZ-induced diabetic, and three (30 mg/kg QE, 10 mg/kg RS, and combined) compound-treated diabetic groups and upon combined administration of both compound there was decrease in serum blood glucose level, increase in insulin level significantly.

Resveratrol and Metformin

Resveratrol and Metformin combination decreased the glucose, triglyceride level and also obesity. It also improved renal function and liver function to some extent. For this Diabetic mice were treated with resveratrol (20 mg/kg/day), metformin (150 mg/kg/day) and combined metformin/resveratrol therapy for 5 weeks and tissue analyses and biochemical parameters, functional liver enzymes (AP, AST and GGT) and renal parameters (urea and uric acid) were examined. So Combined therapy may act as an effective way to treat diabetes and its renal complications.

CONCLUSION

Resveratrol is a nonflavonoid polyphenolic compound with chemically containing 3, 5, 4 trihydroxy trans-stilbene. Studies carried out by researchers have shown Resveratrol being essential in the treatment of Diabetes and its various complications. Resveratrol has shown acting as an antioxidant, antitumor, and cardioprotective. Various in-vitro and animal models have been studied and the effects of resveratrol have experimented.

Along with these experiments, human trials of resveratrol have also been performed. To overcome the stability and low bioavailability, various novel formulations have been prepared. However, there is a need for extensive research for resveratrol and development of novel formulations even in combination with other antioxidants which will prove to be effective in the treatment of Diabetic Complications.

REFERENCES

Ahmed, R. Z., Patil, G., Zaheer, Z. 2013. Nanosponges - a completely new nano-horizon: pharmaceutical applications and recent advances. *Drug Development and Industrial Pharmacy*, 39(9):1263–1272.

Berman, A. Y., Motechin, R. A., Wiesenfeld, M. Y., Holz, M. K. 2017. The therapeutic potential of resveratrol: a review of clinical trials. *Npj Precision Oncology*.

Bordone, L., Motta, M. C., Picard, F., Robinson, A., Jhala, U. S., Apfeld, J., Guarente, L. 2005. Sirt1 Regulates Insulin Secretion by Repressing UCP2 in Pancreatic β Cells. *PLoS Biology*, 4(2).

Caddeo, C., Teskac, K., Sinico, C., Kristl, J. 2008. Effect of resveratrol incorporated in liposomes on proliferation and UV-B protection of cells. *International Journal of Pharmaceutics*, 363(1-2):183–191.

Catalgol, B., Batirel, S., Taga, Y., Ozer, N. K. 2012. Resveratrol: French Paradox Revisited. *Frontiers in Pharmacology*, 3:1–18.

Catanuto, P., Doublier, S., Lupia, E., Fornoni, A., Berho, M., Karl, Elliot, S. 2009. 17 β-estradiol and tamoxifen upregulate estrogen receptor β expression and control podocyte signaling pathways in a model of type 2 diabetes. *Kidney International*, 75(11):1194–1201.

Fang, W., Wang, C., He, Y., Zhou, Y., Peng, X., Liu, S. 2018. Resveratrol alleviates diabetic cardiomyopathy in rats by improving mitochondrial function through PGC-1α deacetylation. *Acta Pharmacologica Sinica*, 39(1):59–73.

Fourny, N., Lan, C., Sérée, E., Bernard, M., Desrois, M. 2019. Protective effect of resveratrol against ischemia-reperfusion injury via enhanced high energy compounds and eNOS-SIRT1 expression in type 2 diabetic female rat heart.

Gokce, E., Korkmaz, Dellera, Sandri, Bonferoni, Ozer, O. 2012. Resveratrol-loaded solid lipid nanoparticles versus nanostructured lipid carriers: evaluation of the antioxidant potential for dermal applications. *International Journal of Nanomedicine*,

pages 1841–1850.

Gokce, E. H., Tanrıverdi, S. T., Eroglu, I., Tsapis, N., Gokce, G., Tekmen, I., Ozer, O. 2017. Wound healing effects of collagen-laminin dermal matrix impregnated with resveratrol loaded hyaluronic acid-DPPC microparticles in diabetic rats. *European Journal of Pharmaceutics and Biopharmaceutics*, 119:17–27.

Higashi, Y., Higashi, K., Mori, A., Sakamoto, K., Ishii, K., Nakahara, T. 2018. Anti-cataract Effect of Resveratrol in High-Glucose-Treated Streptozotocin-Induced Diabetic Rats. *Biological and Pharmaceutical Bulletin*, 41(10):1586–1592.

Houtkooper, R. H., Pirinen, E., Auwerx, J. 2012. Sirtuins as regulators of metabolism and healthspan. *Nature Reviews Molecular Cell Biology*, 13(4):225–238.

Kim, M. J., An, H. J., Kim, D. H., Lee, B., Lee, H. J., Ullah, Chung, H. Y. 2018. Novel SIRT1 activator MHY2233 improves glucose tolerance and reduces hepatic lipid accumulation in db/db mice. *Bioorganic & Medicinal Chemistry Letters*, 28(4):684–688.

Li, Y., Huang, J., Yan, Y., Liang, J., Liang, Q., Lu, Y., Li, H. 2018. Preventative effects of resveratrol and estradiol on streptozotocin-induced diabetes in ovariectomized mice and the related mechanisms. *PLOS ONE*, 13(10).

Lv, W., Zhang, J., Jiao, A., Wang, B., Chen, B., Lin, J. 2019. Resveratrol attenuates hIAPP amyloid formation and restores insulin secretion ability in the hIAPP-INS1 cell line via enhancing autophagy. *Canadian Journal of Physiology and Pharmacology*, 97(2):82–89.

Mccubrey, J. A., Lertpiriyapong, K., Steelman, L. S., Abrams, S. L., Yang, L. V., Murata, R. M., Cervello 2017. Effects of resveratrol, curcumin, berberine and other nutraceuticals on aging, cancer development, cancer stem cells and microRNAs. *Aging*, 9(6):1477–1536.

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*, pages 1–14.

Pando, D., Gutiérrez, G., Coca, J., Pazos, C. 2013. Preparation and characterization of niosomes containing resveratrol. *Journal of Food Engineering*, 117(2):227–234.

Peng, H., Xiong, H., Li, J., Xie, M., Liu, Y., Bai, C., Chen, L. 2010. Vanillin cross-linked chitosan microspheres for controlled release of resveratrol. *Food Chemistry*, 121(1):23–28.

Reis, S., Neves, Lúcio, Martins, Lima 2013. Novel resveratrol nano delivery systems based on lipid nanoparticles to enhance its oral bioavailability. *International Journal of Nanomedicine*, 177.

Szkudelski, T., Szkudelska, K. 2015. Resveratrol and diabetes: from animal to human studies. *Biochimica et Biophysica Acta*, (6):1145–1154. BBA) - Molecular Basis of Disease.

Wang, D., Sun, H., Song, G., Yang, Y., Zou, X., Han, P., Li, S. 2018. Resveratrol Improves Muscle Atrophy by Modulating Mitochondrial Quality Control in STZ-Induced Diabetic Mice. *Molecular Nutrition & Food Research*, 62(9):1–32.

Yamagata, K., Yoshizawa, T. 2018. Chapter Four - Transcriptional Regulation of Metabolism by SIRT1 and SIRT7. *International Review of Cell and Molecular Biology*, 335:143–166. 1st edn.

Yang, Y., Duan, W., Lin, Y., Yi, W., Liang, Z., Yan, J., Jin, Z. 2013. SIRT1 activation by curcumin pretreatment attenuates mitochondrial oxidative damage induced by myocardial ischemia-reperfusion injury. *Free Radical Biology and Medicine*, 65:667–679.

Yucel, C., Karatoprak, G. S., Aktas, Y. 2018a. Nanoliposomal Resveratrol as a Novel Approach to Treatment of Diabetes Mellitus. *Journal of Nanoscience and Nanotechnology*, 18(6):3856–3864.

Yucel, C., Karatoprak, G. S., Atmar, A. 2018b. Novel Resveratrol-Loaded Nanocochleates and Effectiveness in the Treatment of Diabetes. *Fabad Journal of Pharmaceutical Sciences*, 43(2):35–44.

Zendedel, E. 2018. Impact of curcumin on sirtuins: A review. *Journal of Cellular Biochemistry*, 119(12):10291–10300.

Zhu, X., Guo, X., Mao, G., Gao, Z., Wang, H., He, Q., Li, D. 2013. Hepatoprotection of Berberine Against Hydrogen peroxide-induced Apoptosis by Upregulation of Sirtuin 1. *Phytotherapy Research*, 27(3):417–421.

Zhu, X., Yue, H., Guo, X., Yang, J., Liu, J. 2017. The Preconditioning of Berberine Suppresses Hydrogen Peroxide-Induced Premature Senescence via Regulation of Sirtuin 1. *Oxidative Medicine and Cellular Longevity*, 2017. Article ID: 2391820.