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, Shivarathreshwara, Bannimantap Nagar, Mysuru-570015, Karnataka, India

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ABSTRACT
Resveratrol, a non-flavonoid, 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.

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 trans 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 studied 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-κB 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.

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

| Diabetes Cured By Resveratrol | Diabetic Animal Model | 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    | Rat                   | Downregulation of TLR4/MyD88/NF-kB signaling pathway | (Fang et al., 2018) |
| Cardiomyopathy Rat            | Rat                   | SIRT1 activation and increased PGC-1α deacetylation | (Fang et al., 2018) |
| Neuroprotection Rat            | 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    | Mice                  | Inhibition of superoxide dismutase and (-) glutathione and 4-hydroxy-2-nominal levels | (Fang et al., 2018) |
| Cataract Rat                  | Rat                   | Suppress the increase in protein carbonyls  | (Higashi et al., 2018) |
| Vascular Dysfunction Mice     | 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           | 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      | Rat                   | decreased the activity of NF-kB and also the process of apoptosis by regulating their levels in the retina | (Kim et al., 2018) |
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; Zhu and , 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 deacetylation 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 6 action is
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, cholesterol 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)   |
| S. No. | Dosage Form               | Method Of Preparation                      | Complication Addressed                               | Outcomes                                                                 | References                                      |
|-------|---------------------------|--------------------------------------------|------------------------------------------------------|---------------------------------------------------------------------------|------------------------------------------------|
| 1     | Nanoliposome              | a) Dry Film Hydration Method               | Diabetes Mellitus                                     | 1. Stabilizing RSV against trans-to-cis isomerization                     | (Yucel et al., 2018a)                          |
|       |                           | b) Thin Lipid Film Method                  |                                                      | 2. Improving its bioavailability                                          |                                                |
| 2     | Nanocochleates            | Trapping Method                            | Diabetes Mellitus                                     | 1. Not found to be toxic to cells even at the highest concentrations       | (Yucel et al., 2018b)                          |
|       |                           |                                            |                                                      | 2. Improves Solubility and Bioavailability                               |                                                |
| 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             | Microencapsulation                         | 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                  |                                               |
by deacetylation. Sirtuin 4 has ribosyl-transferase 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 decylation 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-κB 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 (Borden 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 17β 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 (phosphorylation 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.

Resveratrol and Glibenclamide

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, anti-
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.

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