Chapter 7

Resveratrol in Management of Diabetes and Obesity: Clinical Applications, Bioavailability, and Nanotherapy

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Additional information is available at the end of the chapter

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Abstract

Diabetes is the most common serious metabolic disorder and one of the five leading causes of death worldwide. It is characterized by persistent hyperglycemia coincident with the induction of oxidative stress and alterations in glucose and lipid metabolism–regulating enzymes. Resveratrol has immerged as one of the leading natural ingredients to combat diabetic and its complications. Despite an abundance of laboratory and animal research, there is little clinical evidence to establish resveratrol effectiveness as a therapeutic against diabetes. Further, the poor bioavailability and stability of resveratrol in humans have been a major concern for translating basic science findings into clinical utility. In this review, we embark on large, well-controlled clinical studies to confirm the efficacy of resveratrol in the management of diabetes mellitus and gain a better insight into its biological effects in humans. Further possible methods of increasing the stability and bioavailability for such trials are also discussed.

Keywords: resveratrol, antidiabetic, antioxidant, bioavailability, clinical trials

1. Introduction

Diabetes mellitus (DM) has been an ever-increasing global epidemic and one of the most challenging health problems of twenty-first century. In 2010, more than 285 million people about the world were afflicted with diabetes, and it was then calculated that the number of people with diabetes will increase to 439 million by 2030. Interestingly, the reports of 2015 show that globally 415 million (215.2 million men and 199.5 million women) had DM with a prevalence of 8.8%, and projections indicate that approximately 600 million people would be suffering from diabetic in 2030. In other words, one in eleven people has DM. The economic impact

of diabetes is extensive. A significant component of health care expenditures is attributed to diabetes, and its complications and global spending for treating it in 2015 alone were US$ 673 billion (12% of health expenditure) [1].

Two primary groups of DM are distinguished: (1) autoimmune T1DM or insulin-dependent DM or juvenile DM and (2) T2DM or noninsulin-dependent DM or maturity onset DM. Close to 90% of people with DM around the world have type 2 DM (T2DM) [2].

The treatment of T1DM requires insulin replacement via injections as the pancreatic β-cells are destroyed and do not secrete adequate insulin. On the other hand, T2DM is characterized by insulin resistance and a decreased capacity of insulin secretion by β-cells. Natural/herbal medicines that have claimed to be effectual in the treatment of DM are thus more efficient in the treatment of T2DM [3]. They act either as insulin sensitizers or as substances that reduce the plasma glucose levels.

Further recent inventions on natural products have established a new understanding into the use of antioxidants to combat diabetic complications [4]. Oxidative stress leads to the dysfunction of β-cells and thus plays a crucial role in the pathogenesis of diabetes and its associated complications. In fact, increasing morbidity and mortality rates of T2DM patients are mainly due to the high occurrence and severity of diabetic complications.

Thus, β-cells apoptosis can be protected, and their functions can be preserved by the use of antioxidants [5]. Thus, a potent antioxidant compound is expected to show greater effects on diabetes and its associated complications. Therefore, antioxidant therapy is, a different, innovative but, a fundamental approach for treating diabetic complications [6, 7].

The antioxidant activity and its related health benefits of dietary plant polyphenols are well documented. In recent years, there is growing evidence on the effectiveness of plant polyphenols against the treatment of type 2 diabetes mellitus and its ramifications. Polyphenols may be classified into different groups as a function of the number of phenol rings that they contain and on the basis of structural elements that bind these rings to one another. The main classes include flavonoids, phenolic acids, β-orcinols, stilbenes, and lignans. **Figure 1** illustrates the different groups of polyphenols and their chemical structures reported as antioxidant and antidiabetic activities.

The hypoglycemic effects of polyphenols are mainly ascribed for reducing the intestinal absorption of dietary carbohydrate, for the modulation of carbohydrate and lipid metabolism enzymes, and they stimulate insulin secretion and insulin action and improve β-cell functions by reducing oxidative stress, stress-sensitive signaling pathways, and inflammatory processes [8].

We have already reviewed the antidiabetic effect of least-studied β-orcinol compounds of lichen origin and found in accordance of its antioxidant and antidiabetic effect [9]. The current chapter focuses on the reported antidiabetic effect of stilbenoid type polyphenols. Stilbenoids are phylotaxins and are mainly found in *Vitis vinifera* L., the wine producing grape fruits, together with other plant families, such as Dipterocarpaceae, Gnetaceae, and Fabaceae.

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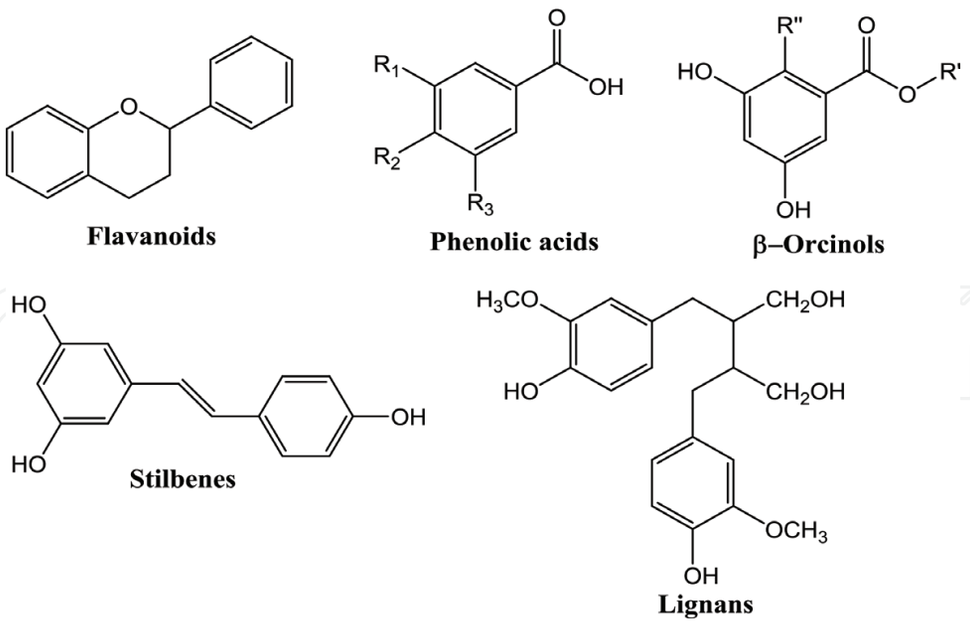

Figure 1. Chemical structure of major classes of polyphenols reported for antioxidant and antidiabetic effects.

The backbone structure of stilbene which is 1,2-diphenylethylene is common, but the type and position of substituents on the rings differ. The hydroxylated derivatives of stilbenes provide the class with a wide variety of polymerization and oligomeric construction. However, the most widely studied hydroxylated stilbenoid is resveratrol (3,5,4′-trihydroxystilbene), which is considered as one of most potent natural biological active compound. The other structural analogs with potentially beneficial medicinal properties include pterostilbene (methylated derivatives), viniferin (glycone derivatives), and hopeaphenol (oligomeric forms—tetramer). Some of the common stilbenoid structures are illustrated in **Figure 2**.

Biological activities of resveratrol have been well examined by a great variety of test systems. Its beneficial properties on humans include neuroprotective, antiviral, antiatherogenic, and estrogen-like growth-promoting effect. Further, its effects on promotion of vasodilatation and prevention of platelet aggregation and its positive effect on the circulatory system especially by increasing production of high-density lipoprotein cholesterol and preventing the development of arteriosclerosis are reported. Furthermore, it was shown that resveratrol is a chemopreventive agent [10]. Due to the wide variety of biological activities shown by this marvel compound, resveratrol-based medicinal chemistry has become rapidly evolving and increasingly active topics in the past decade, covering almost the whole range of therapeutic fields. There are several reports composing the antioxidant, antiinflammatory, and antidiabetic effect of resveratrol. Due to its antiinflammatory and antioxidant effects, resveratrol can mitigate the development of diabetic complications associated with inflammation and oxidative stress. Beneficial effects of resveratrol on the management of blood glucose in diabetes are summarized in **Figure 3**. The aim of this chapter is to highlight the importance of resveratrol along with other stilbenes as an antidiabetic compound with antioxidant properties.

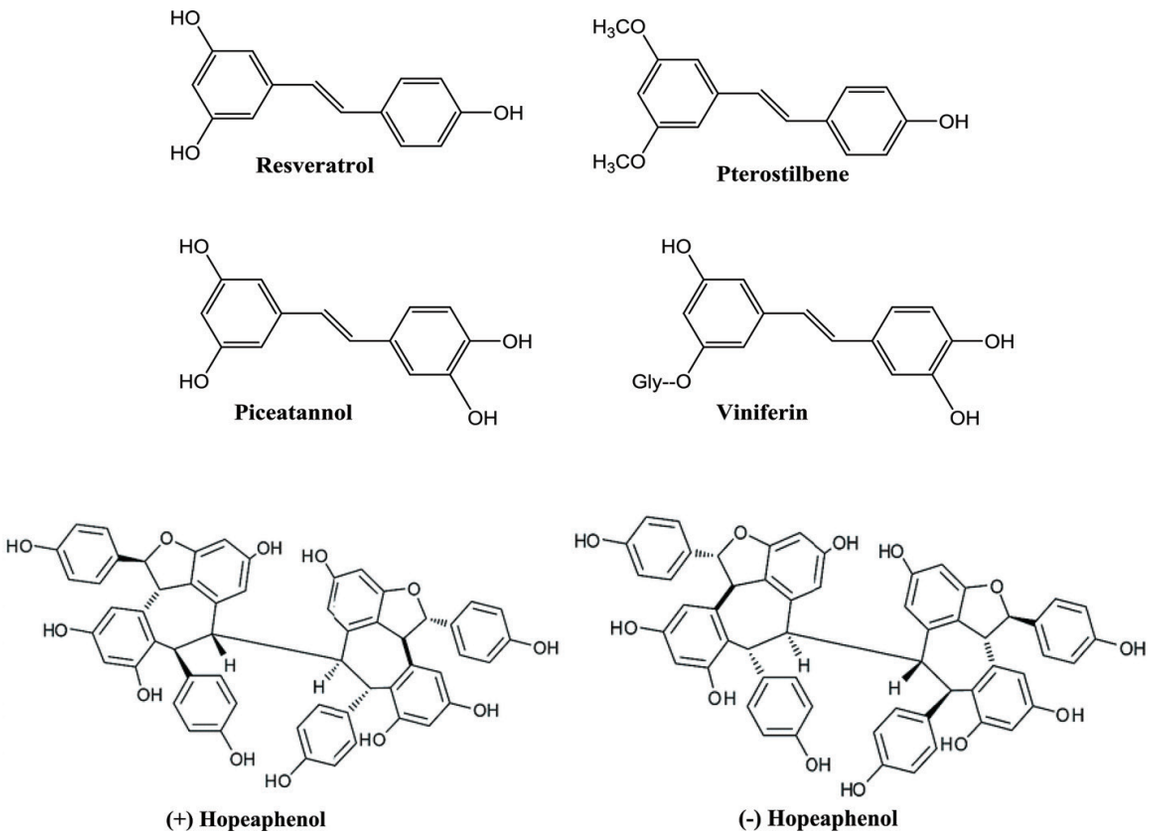

Figure 2. Most common stilbene derivatives reported for antidiabetic activities.

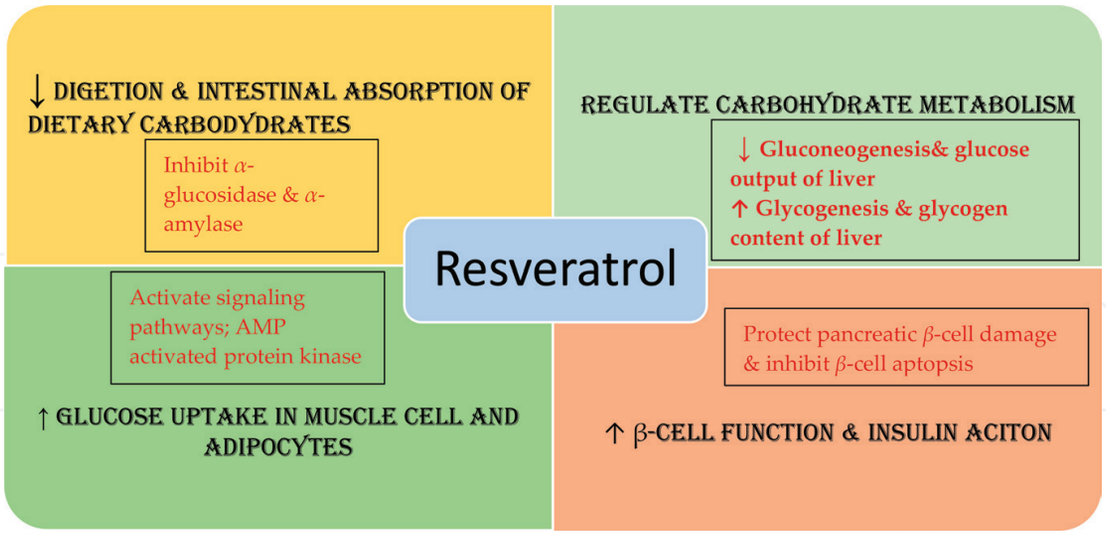

Figure 3. Beneficial effects of resveratrol on the management of blood glucose in diabetes.

2. The role RSV in obesity and diabetes and its molecular mechanism

The appreciable magnitude of scientific evidence is available, which ascribes antidiabetic properties of resveratrol and fights against obesity. There are over 800 publications ascribing

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the hypoglycemic action of resveratrol, through both *in-vivo* and *in-vitro* studies. Multiple modes of action, and diversity of molecular targets, keep resveratrol well ahead of its other natural analogs. Modes of action include inhibition of carbohydrate hydrolyzing enzymes (α-amylase and α-glucosidase), through their role as an effective antioxidants and through their effect on amelioration of insulin sensitivity. The resveratrol improves defective insulin signaling, prevents pancreatic β-cell apotopsis and dysfunction, inhibits abnormal glucose uptake and storage, mitigates hyperlipidemia and dyslipidemia, and thus shows high pharmokinetic potential as antidiabetic agent [11]. The complex physiological action of resveratrol as an antidiabetic agent could be attributed to its capacity to modulate different pathways and to its diversity of molecular targets including phospodiesterases, adenylyl cyclase, kinases, sirtuins, transcription factors, cytokines, and others, some of which are described below.

Pancreatic β-cells are key players in the development of T2DM, as they are required to secrete increasing amounts of insulin so as to compensate for increasing insulin resistance. Consequently, the β-cells come under increasing metabolic stress and finally their function deteriorates. Thus, it is important to find a mean to preserve the health of β-cells.

Cyclic nucleotide phosphodiesterases (PDEs) belong to a class of enzymes that hydrolyze the phosphodiester bonds of cAMP and cGMP to their biologically inactive 5′ derivatives. Cyclic AMP is known as a key mediator of metabolic regulation. Resveratrol acts as PDE inhibitor, leading to increased cAMP levels, which amplifies glucose-induced insulin secretion [12].

Resveratrol triggers cascade of biological pathways that are induced during calorie restriction. Primarily increased cAMP levels activate PKA (protein kinase A), which directly phosphorylates and activates histone deacetylase Sirtuin1 (SIRT1), which increases insulin sensitivity and protects against metabolic damage resulting from a high-fat diet. In detail, SIRT1 catalyzes NAD^+-dependent protein deacetylation, yielding nicotinamide and *O*-acetyl-ADP-ribose. SIRT1 facilitates the conversion of changes in the nutritional status, which it senses via NAD^+ levels, mediates the metabolic stress situations, such as high-fat-diet-induced obesity, and plays a context-dependent role in health span regulation. In addition to the c-AMP mediated pathway, resveratrol also increases SIRT1 activity through an allosteric interaction, resulting in the increase of SIRT1 affinity for both NAD^+ and the acetylated substrate. SIRT1 promotes many beneficial metabolic changes, such as an increase in fatty acid oxidation, gluconeogenesis, and mitochondrial respiration and a decrease in triglyceride synthesis, glycolysis, ROS production, and inflammation. In light of the rising number of patients suffering from metabolic diseases, compounds that activate SIRT1 directly or indirectly offer protection against the onset of metabolic damage and encourage healthy aging [13].

The regulation of glucose uptake and its subsequent utilization is critical for the maintenance of glucose homeostasis. Homeostasis of blood glucose by insulin involves stimulation of glucose uptake by translocation of glucose transporter Glut-4 from intracellular pool to the caveolar membrane system. Resveratrol increases the expression of this glucose transporter Glu-4 and excites the glucose uptake.

Skeletal muscle is the largest organ in the body and contributes to immeasurable features of organismal biology, and its dysfunction stimulates numerous diseases, including diabetes. Skeletal muscle is the main site of glucose disposal after glucose ingestion. Insulin resistance in skeletal muscle is thus the main driver of postprandial hyperglycemia. The transcriptional

coactivator PGC-1α has emerged as a key driver of metabolic programming in skeletal muscle, both in muscle health and disease. PGC-1α has different roles in different tissues, but in nearly every context, PGC-1α stimulates the transcriptional program of mitochondrial biogenesis. PGC-1α dysfunction, and thus mitochondrial insufficiency, contributes to insulin resistance in skeletal muscle. Resveratrol also has proven to enhance the PGC-1α–skeletal muscle protein levels.

Further resveratrol also activates Akt expression, a modulator of insulin-signaling pathway. Akt is the major effector of the IR-IRS-1-PI3K pathway and is activated by phosphorylation. Resveratrol treatment increases the phosphorylation level of Akt, particularly of its Thr308 and Ser473 residues which is essential for its basal and full activation.

Several studies have found that resveratrol has positive effects on inhibiting the insulin secretion from pancreatic β-cells and prevents it from chronic overstimulation, decreases the plasm insulin concentration, and increases the insulin sensitivity. Possible explanations include resveratrol-mediated suppression of cytokine action through decreased DNA binding of nuclear transcription factor κB, production of nitric oxide, and expression of inducible nitric oxide synthesis [14].

2.1. Antioxidant effect of RSV

The advancement in the knowledge of potent antioxidants has uncovered the way for greater insight in the treatment of diabetic complications. The antioxidant activity of resveratrol is well proven, and there is a good accordance between antioxidant and antidiabetic activity of resveratrol. Resveratrol maintains the concentration of intracellular antioxidants in biological systems by dual methods, that is, by acting as scavenger of free radicals and by increasing the activity of antioxidant enzymes such as catalase, glutathione peroxidase, glutathione S-transferase, and glutathione reductase [14]. In a study on isolated liver mitochondria, addition of resveratrol to the incubation medium significantly increased the activity of manganese-containing superoxide dismutase and diminishes ROS generation. Resveratrol acts as a free radical scavenger of ROS and reactive nitrogen species such as superoxide anion ($O2^{\bullet-}$), hydroxyl radical ($OH^{\bullet}$), and hydrogen peroxide, thus, prevent DNA lesions and lipid peroxidation in cell membranes. It has been shown that resveratrol significantly reduced the oxidation of thiol groups in proteins of human platelets [15].

2.2. Effect of RSV on carbohydrate metabolism, through its α-amylase and α-glucosidase inhibitory activities

α-Amylase and α-glucosidase are key enzymes involved in carbohydrate digestion. α-Amylase hydrolyzes starch and glycogen into maltose and ultimately increases the blood sugar. α-Glucosidase hydrolyzes oligosaccharides and disaccharides into glucose, which is absorbed through the gut wall to become blood glucose. Thus, inhibition of the activity of these enzymes is viewed as one of the most effective therapeutic approaches in the reduction of glucose levels in plasma, as a consequence, the suppression of postprandial hyperglycemia.

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Various plant extracts containing resveratrol have been evaluated for α-amylase inhibitory activity and have shown beneficial effects in bringing down the pace of digestion and assimilation of sugars and thereby leading to the effective management of type 2 diabetes by decreasing the postprandial hyperglycemia, some of which are highlighted below.

Antioxidant and α-glucosidase inhibitory potential of reservatrol isolated from *Rumex bucephalophorus* have been reported, which revealed that reservatrol was at least five times more potent α-glucosidase inhibitory activity as compared to standard drug acarbose [16]. A study on peanut extracts correlated the reservatrol content with the α-amylase and α-glucosidase inhibitory activity. The EtOAc extracts of peanuts with higher resveratrol content (3 μg/ml) showed higher α-amylase and α-glucosidase inhibitory activity (4.32 and 5.93%, respectively) as compared to MeOH extract (3.9 and 4.9%) with resveratrol content of (0.5 μg/ml). The standard resveratrol sample showed α-amylase and α-glucosidase inhibitory activity (5.18 and 5.94%) [17].

In another study, resveratrol had shown potent α-glucosidase inhibitory activity against both yeast and mammal α-glucosidase with (IC_{50}, 0.091 mg/ml) and (IC_{50}, 0.12 mg/ml), respectively. The standard drug acarbose showed IC_{50} = 0.247 mg/ml (yeast α-glucosidase) and IC_{50} = 0.013 μg/ml (mammal α-glucosidase) [15]. Piceatannol, with an additional OH group as compared to resveratrol, showed higher α-glucosidase inhibitory activity as compared to resveratrol [18].

In a study, wistar rats when administered with 30 mg/kg BW resveratrol 60 min prior to sucrose- or starch-loading had a delayed absorption of carbohydrates, resulting in significant lowering of postprandial blood glucose concentrations [18].

The structure activity relationship of polyphenols isolated from other plant sources has been extensively reviewed as inhibitors of α-amylase and α-glucosidase. Detailed SAR has revealed that both α-amylase and α-glucosidase share the same properties in terms of structural requirements for inhibition [19]. Studies reveal that inhibitory activity is influenced by a number of hydroxyl groups and their positions, methylation, methoxylation, glycosylation, etc. Broadly, it is considered that hydroxylation of phenols increases the α-amylase inhibitory activity and methoxylation, which blocks the free hydroxyl groups and reduces the inhibitory activity [19]. Apparently, the activity is increased by more phenolic substitutions. Piceatannol with four OH groups showed higher activity than resveratrol with three free hydroxyl groups as for the study of Zhang et al. [18]. This is further evident by the study of Lam et al. [26], where several stilbenoids isolated from seeds of *Syagrus romanzoffiana* were evaluated for inhibitory activity against α-glucosidase *Bacillus stearothermophilus*. Pentahydroxystilbene (5 OH groups) showed higher inhibitory activity (IC_{50} 19.23 μM) as compared to piceatannol with 4 OH groups (IC_{50} 23.24 μM).

Molecular docking studies have revealed that, overall, the inhibitory activity of phenols depends on two parameters: (i) hydrogen bonding capacity of the OH groups of the phenols with the side chains of amino acids such as Asp197 and Glu233, and (ii) planarity of aromatic rings to form an efficient conjugated π-π system with the indole Trp59 of the active site [20].

(+) Hopeaphenol and (−) hopeaphenol oligomer (tetramer) of resveratrol isolated from *Ampelocissus indica* (L.) and *Vateria indica* Linn., respectively, displayed IC_{50} values of 21.21 ± 0.987 and 9.47 ± 0.967 mM in an α-glucosidase inhibitory assay [21], which were higher than the standard acarbose (IC_{50} 81.3 ± 1.10). The compounds showed a concentration-dependent inhibition of both α-glucosidase and α-amylase enzymes. Further, the study also indicated the positive effect of hopeaphenols as antiglycating agents, with IC_{50} values of 81.9 ± 1.176 and 50.96 ± 0.897, respectively, for (+) and (−) isomers which again were less than the ascorbic acid standard (IC_{50} 158.23 ± 0.718). The results indicated that the hopeaphenols can be a promising natural compound in diabetic management [21]. The effect of glucose uptake performed by 2-NBDG in L6 rat skeletal muscle cells using flow cytometry (BD FACS Aria II, USA) showed potent glucose uptake by (+) and (−) hopeaphenol of 31 and 26.4%, respectively [21].

Few reports exist on the *in-vivo* studies of stilbenoids other than resveratrol. Among them is the effect of pterostilbene, which improves glycemic control in insulin-resistant obese rats by increasing hepatic glucokinase activity and increasing skeletal muscle glucose uptake [22]. *In vitro* studies also indicate that pterostilbene protected pancreatic beta cells against oxidative stress and apoptosis [23]. Antihyperglycemic properties of pterostilbene along with other phenolic constituents of *Pterocarpus marsupium* have been reported [24, 25], whereas pterostilbene has been shown to be beneficial in animal models of diabetes and metabolic disorders. Further, the study by Lam et al. also revealed that pentahydroxystilbene (3,3′,4,4′,5′-pentahydroxy-trans-stilbene) possesses significant effect in reducing the postprandial blood glucose level of sucrose-challenged normal wistar rats [26].

2.3. Clinical studies on RSV on diabetic

Although numerous data exist on the beneficial outcomes of resveratrol in diabetic animals and *in vitro*, there are limited studies that have specifically investigated the antidiabetic effects of resveratrol in humans. Further, because of not only a limited number of clinical surveys, but also limited sample size and conflicting data, the use of resveratrol as an effective antidiabetic agent has been delayed [27]. Few of the reported clinical trial data are discussed below.

Glycated hemoglobin (HbA1c) levels reflect glycemic control and can, consequently, be employed as a predictor of the microvascular and macrovascular complications associated with type 2 diabetes. HbA1c levels seem to be determined by postprandial hyperglycemia. Bhatt and colleagues demonstrated that resveratrol (250 mg/day for 3 months) administered along with glibenclamide and/or metformin demonstrated improvement in glycaemic parameters in diabetic patients as compared to metformin or glibenclamide alone [28]. The study reported improvement in HbA1c, systolic blood pressure, and total cholesterol in patients with type 2 DM treated with resveratrol combined with the oral hypoglycemic agents. Recently, Movahed and colleagues also reported [29] that 1 g/day of resveratrol supplementation for 45 days notably reduced fasting blood glucose, HbA1c, insulin, and systolic blood pressure. Brasnyó and colleagues [30] reported an improvement in insulin sensitivity in type 2 diabetic patients after treatment with a much lower dose of resveratrol (5 mg twice daily) for 4 weeks. The study showed that resveratrol did not cause any changes in a glucose-dependent

insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) levels in diabetes patients. However, they did show that resveratrol significantly decreased insulin resistance and blood glucose and delayed glucose peaks after meals. In the study, resveratrol treatment was shown to significantly decrease HbA1c, systolic blood pressure, and total cholesterol. A decrease in oxidative stress assessed by measuring urinary ortho-tyrosine excretion, a bio marker of oxidative stress, was also reported. Nevertheless, the authors found no evidence that resveratrol influenced homeostasis model of assessment of β-cell function (HOMA-β) and therefore suggested that the mechanism of antidiabetic effects might be referable to a reduction in oxidative stress and a more-efficient insulin signaling. Resveratrol activated the Akt insulin signaling pathway by increasing the phosphoAkt:Akt ratio in platelets.

Most significant notice from the above two studies is the extra security of resveratrol as compared to available standard antidiabetic medication [31].

In contrast, in a randomized control trial by Thazhath et al., 500 mg of resveratrol was administration twice daily for 5 weeks in diet-controlled type 2 diabetes. The study revealed no significant improvement in glycemic control [32]. They studied two incretin hormones that affect postprandial hyperglycemia: glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) from the bowel. In healthy people, both hormones stimulate insulin, but in type 2 patients, only GLP-1 can act to stimulate insulin. GLP-1 can also suppress glucagon secretion and energy intake and slow gastric emptying, thereby targeting postprandial hyperglycemia. In rodent models, resveratrol has been shown to upregulate GLP-1 and lower glycemia, but Thazhath et al. found that in human patients, there was no difference between the GLP-1 secretion, fasting glucose level, postprandial glucose level, HbA1c, gastric emptying, body weight, or energy intake in the resveratrol-treated versus the placebo group. As such, resveratrol's efficacy in improving glycemic control is indeterminate. Similarly, resveratrol treatment for 6 months did not improve metabolic parameters in type 2 diabetic patients [33].

Crandall et al. studied older adults with impaired glucose tolerance (IGT), a major risk factor for diabetes as well as cardiovascular disease. They establish that although fasting plasma glucose was unchanged with low dose of resveratrol treatment, peak postmeal glucose and 3-h glucose declined. Further postmeal insulin decreased and insulin sensitivity imporved. Thus, established resveratrol as a promising therapy for insulin resistance [34].

A meta-analysis was carried out by Liu et al. in 2014 [35] and more recently by Zhu et al. in 2017 [36] with the aim of qualitatively comparing the published data on effect of resveratrol on plasma glucose levels, glycated hemoglobin (HbA1c), and insulin sensitivity. A fixed-effect model analysis was carried out to pool the data, nine studies with 283 participants in case by study of Zhu et al. and 388 participants of 11 eligible studies in case of Liu et al. The sample size of studies varied from 8 to 66 participants, with resveratrol dose ranging from 8 mg/d to 3000 mg/d and with duration of intervention differing from 2 weeks to 12 months. Both meta-analysis studies revealed that resveratrol was able to reduce the fasting plasma glucose levels only at high concentrations (1 g/day) as compared with placebo/control in patients with T2DM. Resveratrol was unable to reduce the plasma glucose levels at low concentrations. These studies also revealed that compared to placebo group, the patients who received

resveratrol supplement also showed low insulin levels. Further resveratrol was also effective in reducing the systolic and diastolic blood pressures. However, no significant difference was observed in LDL and HDL levels.

On the other hand, effect of pterostilbene on human type 2 diabetes is yet to be researched. Administration of blueberry (*Vaccinium myrtillus*) and sea buckthorn (*Hippophae rhamnoides*) extract for children with type 1 diabetes for 2 months elicited a reduction in HBA1c levels and an increase in SOD and glutathione peroxidase levels [37]. Since pterostilbene has been isolated from *Vaccinium myrtillus* [38], this effect may be ascribable to the presence of pterostilbene alongside other bioactive compounds in the excerpt.

Some beneficial effects have also been reported in resveratrol treatment in nondiabetic humans. In obese subjects, Timmers and colleagues [39] reported significant improvement in the metabolic profile and general health after resveratrol supplementation for 30 days, thereby describing resveratrol as a calorie restriction mimetic. Resveratrol showed beneficial effects on glucose homeostasis and insulin sensitivity, reduced intrahepatic lipid (IHL) content and expression of inflammatory genes and improved mitochondrial efficiency. These effects may be linked with the activation of AMPK and increased SIRT1 and PGC-1α protein content in the muscle [39].

3. Way forward in clinical utility of resveratrol

One of the major challenges surrounding the clinical utility of resveratrol is achieving its stability and adequate bioavailability at tolerable doses—a common issue in translating promising findings from cell culture and animal models into clinical efficacious drugs. Recent clinical trials proved that resveratrol is well tolerated and pharmacologically safe at doses up to 5 g/day. However, the data on toxicity of resveratrol in long-term experiments are scarce.

Low solubility of resveratrol in water (<0.05 mg/ml), caused by its chemical structure, affects its absorption. Its reported oral bioavailability values range from 20 to 29.8%. After intravenous administration, resveratrol exhibited a very short half-life of 14 min due to rapid metabolism. This poor bioavailability can be ascribed to the rapid conjugation of trans-resveratrol to glucuronic acid and sulfates, producing glucuronides and sulfate conjugates that accumulate in plasma and urine.

In detail, resveratrol is absorbed in a relatively high rate through the small intestine either via passive diffusion due to its nonpolar character or through active diffusion across the intestinal epithelium via cell ATP-dependent binding cassette transporters. Inside the enterocytes of the small intestine and hepatocytes of the liver, the glucuronide and sulfate conjugation of trans-resveratrol to the major metabolites are extensive. This conjugation to sulfates and glucuronides increases resveratrol's aqueous solubility, reduces flux across membranes, preventing nonpolar molecules from interacting with essential macromolecules, and allows excretion by the kidneys via urine. The extensive metabolism to glucuronide and sulfate conjugates during absorption is well described and decreases circulating levels of free trans-resveratrol.

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Thus, metabolism of resveratrol ultimately results in relatively small amounts of free trans-resveratrol in the plasma to be delivered to other tissues. Strategies to increase bioavailability from oral delivery of resveratrol are generally focused on increasing the rate of resveratrol absorption into the enterocytes and decreasing intracellular metabolism [40]. Further, the photostability of the resveratrol itself must also be considered when developing formulations, as resveratrol is sensitive to both heat and UV light. New approaches to increase the bioavailability of resveratrol can help to actualize its potentials as a therapeutic agent in DM and related complications.

Different approaches have been utilized by various researchers to increase the stability and bioavailability, some of which are discussed below.

3.1. Co-administration of resveratrol with other phenolic compounds

One simple approach to enhance bioavailability has been the consumption of resveratrol in combination with other phenolic compounds that play as the substrate for enzymes involved in resveratrol metabolism; such compounds which have demonstrated the positive effects are piperine, quercetin, etc. [41]. Combined effect of resveratrol along with curcumins was evaluated by Rouse et al. on animal models and human islet cell lines. Beneficial effects were demonstrated on insulin secretion by these naturally occurring polyphenols. However, the study revealed that the combination of resveratrol along with curcuminoids either did not yield any additional benefits or reduced the beneficial effects observed with the individual treatments. It would be noteworthy to test the combined effect of these two well-studied compounds on human models along with cinnamon and another known natural compound effective for diabetics. Further, clinical data are available on co-administration of resveratrol with various food and beverage, which contain subsequent amounts of other polyphenols such as grape juice, etc.; unfortunately, neither of these studies included a control condition to determine whether food or beverages enhanced or impaired bioavailability compared to resveratrol itself [41]. Due to 3-hydroxyl groups, resveratrol rapidly undergoes glucuronidation or sulphation. The presence of two methoxy groups in the pterostilbene structure makes it more lipophilic and thus more bioavailable and also more metabolically stable because it has only one free hydroxyl group available for glucuronidation or sulphation. However, the data also reveal that more the free hydrozyl groups, it shows better activity in *in-vitro* assays. Furthermore, administration of pterostilbene in a clinical trial at a dose of 125 mg twice daily for 6–8 weeks was found to be safe and did not evoke any remarkable adverse reactions. Still, there are no clinical studies on the antidiabetic effect of pterostilbene on diabetic patients and its co-treatment with resveratrol.

3.2. Prodrugs and resveratrol formulations to increase the stability and bioavailability

Another approach to increase the absorption of resveratrol in the gastrointestinal tract is improving the material properties of resveratrol used in the oral dosage, given the rapid metabolism of resveratrol. This is the basis for SRT501, the patented formulation of micronized oral version of resveratrol that may have higher bioavailability. In this process, resveratrol is

microionized to particle sizes <5 μm, mixed with flavorings, colorings, and emulsifying agents such as docusate sodium and mixed with water for ingestion. The small particle size with the emulsifiers in solution theoretically increases surface area for intestinal absorption while also improving suspension properties [42].

Another approach to maximize the bioavailability of free trans-resveratrol is to develop resveratrol prodrugs, which could be used to improve the anti-diabetic efficacy of resveratrol. Assuming that maximizing free trans-resveratrol is the primary goal, resveratrol prodrug generates *in vivo* resveratrol through enzymatic reactions. Some of these technologies have been investigated in animal studies with no report in humans. Metabolism of prodrugs into resveratrol in tissues of interest can maximize tissue concentration and can be beneficial in the treatment of tissue specific complications in diabetic patients. Targeted delivery of resveratrol prodrugs into tissues of interest via delivery systems such as liposome-mediated delivery or nanotechnological approaches may result in the improved therapeutic effect. Also, intravenous injection as an option to the traditional oral route of administration of resveratrol may bypass gastrointestinal absorption, conjugation, and hepatic metabolism, therefore resulting in increased bioavailability and improved results in diabetic patients.

3.3. Nanotechnological approaches to enhance the stability and bioavailability of resveratrol

A routine of recent surveys have concentrated on applying nanotechnology to improve the bioavailability of resveratrol and have generally demonstrated improved stability and bioavailability with minimal side effects compared to oral dosing. Nanoformulations can improve resveratrol's solubility and transport across the plasma membrane and therefore enhance its effects within cells.

The nanoencapsulation methods include polylactic coglycolic acid nanoparticles [43, 44], carboxymethyl chitosan nanoparticles [45], solid lipid nanoparticles [46], and cyclodextrin nanoparticles [47]. Studies revealed sustained release profiles, which enhanced plasma bioavailability compared to free resveratrol. Nanoencapsulation was also effective in improving the solubility and stability of resveratrol. All the same, no clinical or paraclinical studies have been done to determine the efficacy of resveratrol nanovectors against antidiabetic potential.

Nanovectors delivering resveratrol have been described by Singh and Pai that drew a sustained release of trans-resveratrol from orally administered polylactic-co-glycolic acid nanoparticles (drug encapsulation efficiency more than 78%, with a molecule size of about 170 NM) [43]. The same authors encapsulated resveratrol in Eudragit RL 100 nanoparticles with a drug incorporation efficiency of 84% and the average size of 180 nm. *In vivo* studies in a rat model showed prolonged plasma levels up to 16 h, in comparison with the free drug being cleared within 6 h [44]. Zu et al. developed carboxymethyl chitosan nanoparticles as a carrier for resveratrol [45]. These nanoparticles (155 nm-sized, with an encapsulation efficiency of 44%) improved the solubility of resveratrol, thereby greatly affecting the antioxidant activity of the drug. Additionally, resveratrol-loaded solid lipid nanoparticles were synthesized with a controlled release profile, due to an initial burst release of 40% caused by the active

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principle associated with the particle shell and a subsequent prolonged release of the drug located in the lipid matrix. In this system, the efficiency of the cellular uptake depended on the molecular interactions with the biological membrane organization, lipid rafts, and the actin cytoskeleton invaginations for the receptor-mediated entrance [48]. Resveratrol-loaded solid lipid nanoparticles have been also prepared by Pandita et al. with a drug incorporation efficiency of 89% and an average diameter of 134 nm [46]. This drug delivery system showed prolonged release *in vitro* up to 120 h in a Wistar rat model, enhancing plasma bioavailability compared to a free drug suspension. Finally, cyclodextrins-resveratrol complexes have been used to increase the concentration of polyphenol in aqueous solution while maintaining its biological activity. For example, spherical cyclodextrin-based nanosponges showed increasing solubility and stability, together with good drug encapsulation efficiency, compared to free resveratrol [48].

4. Conclusion

There is a large body of evidence indicating resveratrol as an antidiabetic agent. Numerous studies have demonstrated that resveratrol can prevent, attenuate, or reverse diabetic dysfunction through diverse mechanisms and multiple molecular targets, which lead to pleiotropic therapeutic action in the whole organism. The exerted effects include inhibition of carbohydrate hydrolyzing enzymes (α-amylase and α-glucosidase) resulting in improved glycemic control, antioxidant properties, and antiinflammatory properties, which ultimately ameliorates diabetes and its complications. Resveratrol enhances insulin sensitivity and decreases insulin resistance, by changes in expression and activity of phosphodiesterases, kinases, AMPK, and SIRT1 in different tissues, which ultimately leads to protection of pancreatic β-cells from deterioration.

Despite widespread use of resveratrol as a nutritional supplement and the fact that animal models have provided a strong case for resveratrol as an antidiabetic agent, however, due to limited number of well-designed human clinical trials and various other limitations, this compound is still under investigation as an antidiabetic drug. The poor stability and bioavailability of resveratrol in humans have been a major concern for translating basic science findings into clinical utility [49].

From the 11 human clinical trial data available on effect of resveratrol as antidiabetic agent, all studies have shown positive effect of resveratrol in reducing the fasting plasma glucose level at higher concentration. But still there remain many discrepancies such as on the Hb1AC levels. The origins of these discrepancies are not definitively known but may be due to different quantification techniques (e.g., HPLC vs. MS/MS, etc.), different formulations and dosing protocols, and differing sample size, dosage duration, and effects of other drugs/materials used in combination with resveratrol. In addition, inter-bioavailability of resveratrol can vary from person to person, which may cause inconsistent physiological responses between individuals and limited clinical applicability. Thus, further well-defined clinical trials should exploit the efficacy of resveratrol itself or when used in combination with other antidiabetic

drugs (e.g., metformin, etc.) or with other known antidiabetic natural products (curcumins, cinamaldedhye, etc.) as a potential pharmaceutical intervention.

A number of approaches have been developed to improve the stability and bioavailability of resveratrol, including consumption with various foods containing multiple polyphenols and micronized powders, combining it with additional phytochemicals, controlled release devices, and nanotechnological formulations. Animal studies demonstrate that these advanced formulations could improve tolerability in humans while also increasing its bioavailability; nonetheless, these nanotechnological and other advanced approaches are yet to be attempted in humans [41]. A combinational approach, as well as improved formulations of resveratrol, may help to overcome the challenge of maintaining an effective concentration at the site of action for an appropriate period, which needs to be confirmed by human studies.

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