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Resveratrol and diabetes: A critical review of clinical studies

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ABSTRACT

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia. The disease results from the defects of insulin secretion and/or action. Resveratrol is a non-flavonoid polyphenol that naturally occurs as phytoalexin. The shell and stem of *Vitis vinifera* L. (Vitaceae) are the richest source of this compound. In addition to various *in vitro* and *in vivo* studies revealing the effectiveness of resveratrol in DM, there are many clinical trials indicating that resveratrol has the potential to benefit in DM patients. The therapeutic action of this compound in relation to diabetes is complex and involves in several beneficial roles. In view of this, clinical studies are necessary to elucidate these roles. In the near future, the use of resveratrol, alone or in combination with current anti-diabetic therapies, might be a conventional approach to effectively manage DM or its complications. This mini-review provides a critical overview of currently available clinical studies examining the effects of resveratrol in DM last decade.

1. Introduction

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia and the incidence of the disease is high throughout the world. It is a common, chronic and serious disease resulting from defects of insulin secretion and/or action. The worldwide prevalence is 285 million in 2010, and by 2030, the number is expected to reach around 438 million. The disease is related to high risk of microvascular and macrovascular complications. DM is a major incumbrance for patients, society, health care systems, as well as economy of a country. Nevertheless, the present treatments have limitations due to their side effects, particularly weight gain and hypoglycemia, or contraindications that limit their use. Clearly, there is a need, for new therapies that might be more effective with acceptable adverse effects [1].

Resveratrol (3,4′,5-trihydroxy-stilbene) [Fig. 1] is a naturally occurring phytoalexin. The richest source of this polyphenol compound is *Vitis vinifera* L. (Vitaceae). This compound is found in different pharmaceutical dosage forms and is recommended as a dietary supplement. Plenty of *in vivo* studies have been reported on its utilities, including DM [1–5]. Resveratrol also exerts glucose-lowering effects in human and in rodent models of obesity and/or diabetes lately. In general, the management of diabetes involves in 3 main aspects: reduction of blood glucose [6], preservation of cells especially in the case of type 2 diabetes mellitus (T2DM) [7], and improvement in insulin secretion from pancreatic β-cells [8]. Literature that exert the beneficial effects of resveratrol in relation to diabetes, comprise all these aspects [9,10]. However, limited clinical data are available on the potential effects of resveratrol.

Type 1 diabetes mellitus (T1DM) which accounts for 5–10% of all diabetic cases is a condition in which pancreatic β-cell destruction generally causes insulin deficiency. In T1DM patients, damage of β −cell destruction leads to insufficient insulin secretion to prevent hyperglycemia. It is well-known that increased blood glucose levels lead to several complications. It is prominent that keeping blood glucose level in normal ranges preserves pancreatic β-cells which is important in type 1 diabetics [12]. *In vivo* studies obviously show that resveratrol reduces blood glucose levels and protects β-cells [13].

T2DM is characterized by impairment in insulin secretion and action. The pathogenesis of T2DM is complicated and both genetic predisposition and environmental conditions involves in the pathogenesis of the disease. Most DM patients have T2DM not T1DM. Both high-calorie diet and low physical activity lead to and exacerbate T2DM. Besides, the incidence of T2DM rises with age and is higher in overweight or obese individuals, dietary style and elevated physical activity may postpone the start of T2DM notwithstanding genetic predisposition. It is recently established that both inflammation and oxidative stress conduce to the exacerbation of insulin dysfunction and to β-cell failure in T2DM. Nevertheless, insulin resistance is one of the main problems in T2DM. Many pharmacologic and nonpharmacologic interventions have been developed based on current understanding of the pathophysiology of T2DM [1].

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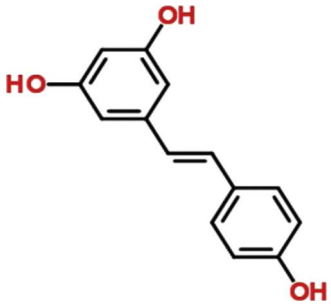

Fig. 1. 2D structure formula of the resveratrol [11].

The antidiabetic effects of resveratrol in DM have been well-reviewed by Oyenihi et al. [14]. It has been shown in the literature that resveratrol impacts both insulin action and pancreatic β cells beneficially and prevents from the complications of the disease [15]. Studies have shown that resveratrol improves biochemical and clinical parameters in both type 1 and type 2 animal models of diabetic nephropathy [16–18]; diabetic neuropathy [19–21]; diabetic retinopathy [22–25]; diabetes-induced hypertension [26,27]; diabetes-induced cardiovascular diseases [28–30] diabetes-induced liver injury [31,32] and T1DM-induced cerebrovascular dysfunction [33].

According to the recent studies on the mode of action of resveratrol in diabetes, resveratrol has shown to activate Sirtuin 1 (SIRT1) pathways. SIRT1, and NAD^+-dependent deacetylase, has been described as an important regulator of many factors influencing T2DM. Studies have revealed that SIRT1 activity and expression were decreased significantly *in vitro* and *in vivo* experimental models of DM [34–38]. Some of the beneficial effects of resveratrol on the regulation of glucose homeostasis is shown to be mediated through the activation of AMPK (Adenosine Monophosphate Activated Kinase). AMPK regulate several significant intracellular processes such as energy metabolism, mitochondrial functions, and cellular homeostasis. Under hyperglycemic conditions, the dysregulation of AMPK activity correlated with insulin resistance and hyperglycemia-associated tissue damage, supporting a key role of AMPK in T2DM [14].

In diabetic rat tissues, resveratrol has been reported to normalize the concentration of oxidative stress indicators such as superoxide anion ($O_2\cdot^-$), hydroxyl radical (OH·), hydrogen peroxide (H_2O_2), malondialdehyde (MDA), thiobarbituric acid reactive substances (TBARS), 8-isoprostane, 8-hydroxydeoxyguanine (8-OHdG), nitro-tyrosine (nitro-Tyr), reduced/oxidized glutathione (GSH/GSSG) ratio, and nitrite/nitrate ratio [30–32,39–42].

Modulation of NF-??B may be a potent treatment and management of DM. Resveratrol administration has been reported to significantly decrease NF-??B activity in the retinas of diabetic rats [25] Resveratrol also ameliorated the elevated levels of inflammatory proteins, TNF-?? (Tumor Necrosis Factor-??), interleukin-6 (IL-6), and COX-2 (cyclooxygenase 2) in relation to NF-??B inhibition and contributed to reduction in neuro-inflammation and protection against functional and behavioral deficits in diabetic neuropathy [43].

Resveratrol significantly upregulates the expression of the nuclear factor-E_2-related factor-2 (Nrf2) target genes NAD(P)H:quinone oxidoreductase 1, γ-glutamylcysteine synthetase, and heme oxygenase-1 [44].

Resveratrol has shown to activate Akt signaling pathway, the effect of resveratrol on increased Akt phosphorylation is independent of prompting insulin secretion, but dependent of increasing insulin receptor substrate phosphorylation [45]. Resveratrol ameliorates lipid and glucose metabolism in T2DM by downregulating proprotein convertase subtilisin/kexin type 9 (PCSK9) [46]. Inhibition of the sphingosine kinase 1 (SphK1-S1P) signaling might be a novel mechanism underlying the antidiabetic nephropathy effects of resveratrol [47].

There is an inverse relationship between absorption and bioavailability of resveratrol. Because it is absorbed high rate through the small intestine. Due to the small nature of the *trans*-resveratrol and the non-polar character, absorption occurs through passive diffusion through the membranes. In addition, there is an evidence that resveratrol is mainly transported across the intestinal epithelium via ATP-dependent binding cassette transporters [48]. The biological activity of resveratrol may be limited by first-pass metabolism. Because of poor bioavailability of resveratrol, resveratrol structural analogs could be synthesized with improved beneficial effects [49]. In a study which chemical instability of resveratrol was improved by liposome-encapsulation, preventing inactivating cis–trans isomerization, poorly soluble natural compounds can be incorporated into liposomes was concluded [50].

Polydatin (resveratrol-3-*O*-β-mono-D-glucoside), known as piceid, is a major active component of *Polygonum cuspidatum* Sieb. et Zucc. and main glycoside of resveratrol. Both resveratrol and polydatin have anti-inflammation, anti-oxidation, cytoprotection in stress conditions, anti-hyperlipidemia, anti-hyperglycemia effects and also other cardiovascular protection properties [46]. The use of polydatin as a natural herbal medicine is greatly limited by its poor water solubility and bioavailability. Therefore, various formulation techniques are applied to enhance the aqueous solubility of poorly water-soluble drugs, including the formulation of amorphous solid forms, nanoparticles, microemulsions, solid dispersions, melt extrusion, salt formation and the formation of water-soluble complexes. The bioavailability of polydatin/cyclodextrines inclusion complexes were effectively improved over free polydatin *in vitro*. The search for an efficient and nontoxic carrier for polydatin has become important in order to further its clinical applications. [51].

Resveratrol might have personally different side effects [52] and not detailed yet gender-dependent effects in the literature. At the same time, consumption of resveratrol of up to 5 g/day may be well tolerated, but dose < 1 g/day consumption may require dosage restriction as it causes side effects [49].

1.1. Literature search methodology

The purpose of this article is to review the literature on resveratrol and its clinical trials in patients with DM in the last 10 years (2007–2017). Pubmed, Science Direct, Google Scholar and ClinicalTrials.gov database were used to search for original articles and clinical trials published in English language with the following key words in combination “resveratrol” and “diabetes mellitus”.

To date, the number of published clinical trials that have examined the effect of RES on insulin sensitivity and DM are limited. Diverse trials are currently ongoing (see Table 1 for an overview of all peer-reviewed published literatures and finalized clinical trials found at ClinicalTrials.gov on resveratrol).

1.2. Clinical trials investigating the effects of resveratrol on molecular mechanisms related to DM

Published *in vivo* studies pointed out that resveratrol increases SIRT1 expression that stimulates PPAR gamma Coactivator 1alpha (PGC1α) activity. Subsequent upregulation of 5′ adenosine monophosphate-activated protein kinase (AMPK) and Glucose transporter type 4, (GLUT4) expression are associated with advanced insulin sensitivity in peripheral tissues. Another study to examine the effect of resveratrol on skeletal muscle SIRT1 expression and energy expenditure in patients with T2DM was conducted. Ten patients with T2DM were randomized in a double-blind fashion to receive 3 g resveratrol or placebo daily during 12 weeks. Both SIRT1 expression and p-AMPK to AMPK expression ratio in the resveratrol group were found to be significantly different compared with the placebo group. The patients treated with resveratrol regulates energy expenditure through increment skeletal muscle SIRT1 and AMPK expression. According to the findings

Table 1
Clinical trials to investigate the value of resveratrol alone or in combination in DM.
[b]Website: ClinicalTrials.gov [67].

Identifier no.	Form and dose of resveratrol	Duration	# of subjects	Year started
22901562[a]	Resveratrol capsules (250 mg/d)	3 months	57	2012
NCT01677611[b]	Resveratrol (3 g/d)	12 weeks	10	2008
NCT00998504[b]	Resveratrol capsules (Resvida®) (150 mg/d)	30 days	10	2009
NCT01302639[b]	Resveratrol	3 months	18	2011
25137036[a]	*trans*-resveratrol (1.5 g/d)	90 days	24	2014
21385509[a]	Resveratrol (10 mg/d)	4 weeks	19	2011
24073011[a]	Resveratrol capsules (1 g/d)	45 days	66	2013
12610000629033[c]	*trans*-resveratrol capsules (10 mg/d)	60 days	24	2014
12613000717752[c]	Resveratrol (1 g/d)	5 weeks	14	2013
27520400[a]	Resveratrol (500 mg/d or 40 mg/d)	6 months	192	2016
NCT01593605[b]	Resveratrol (100 mg/d)	28 days	36	2012
NCT02247596[b]	*trans*-resveratrol (1 g, 3 times/day for 2 weeks)	2 weeks	36	2009
NCT01451918[b]	Resveratrol (1 g/d)	2 weeks	8	2011
NCT01038089[b]	Resveratrol capsules (Resvida®) (90 mg/d and 270 mg/d)	2 weeks	20	2009
NCT00823381[b]	Resveratrol capsules (Resvida™) (75 mg/d)	3 months	58	2009
NCT01150955[b]	Resveratrol (1.5 g/d)	5 weeks	24	2010

[a]PubMed [66].
[b]Website: ClinicalTrials.gov [67].

resveratrol might have beneficial exercise-mimetic effects in patients with T2DM was concluded [53].

Another study was performed to determine if resveratrol improves insulin sensitivity in T2DM patients and to elucidate the mechanism of its action. Nineteen patients enrolled in this double-blind study, randomly divided into 2 groups: a resveratrol group receiving oral 5 mg resveratrol 2 times/day and a control group receiving placebo for 4 weeks. After the 4th week, resveratrol increased the pAkt/Akt ratio in platelets and significantly decreased insulin resistance as well as urinary *ortho*-tyrosine excretion. Nevertheless, it had no effect on parameters that are related to β-cell function. This study revealed that for the first time resveratrol improves insulin sensitivity in human, which might be owing to a resveratrol-induced decrease in oxidative stress that causes a more efficient insulin signaling via the Akt pathway [54].

1.3. Clinical trials investigating the effects of resveratrol on various biochemical parameters in DM

A randomized, open-label and controlled trial was conducted with 62 patients with T2DM. Patients were divided into control and intervention groups. Only oral hypoglycemic agents were given to the control group, while resveratrol (250 mg/d) was given to the intervention group along with their oral hypoglycemic agents for a period of 3 months. Several parameters, including hemoglobin A1c, lipid profile, urea nitrogen, creatinine and protein, were measured at the baseline and at the end of 3 months. In this trial, it was revealed that resveratrol supplementation for 3 months remarkably improved the mean hemoglobin A1c, systolic blood pressure, total cholesterol, and total protein in T2DM. However, there was not a significant change in body weight and high-density lipoprotein (HDL) and low-density lipoprotein (LDL). Resveratrol supplement may be effective in improving glycemic control and could be provided as an adjuvant for the treatment and management of diabetes [1].

In a randomized, double-blind, crossover study, postprandial incretin hormone and glucagon responses in obese human subjects before and after 30 days of resveratrol supplementation was investigated. Postprandial plasma responses of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide and glucagon were measured in 10 obese men who had been given a dietary supplement of resveratrol (Resvida® 150 mg/day) or placebo for 30 days. Based on the findings, the authors suggested that 30 days of resveratrol supplementation did not affect fasting or postprandial incretin hormone plasma levels in obese humans, but suppressed postprandial glucagon responses [9].

A randomized, double-blind, placebo-controlled clinical trial evaluated the effect of resveratrol administration on metabolic syndrome, insulin sensitivity, and insulin secretion. Twenty four patients with the diagnosis of metabolic syndrome in accordance with the International Diabetes Federation criteria was enrolled in this study. After a 75 g dextrose load, glucose and insulin levels were measured. Also, triglycerides and HDL cholesterol concentrations at baseline were evaluated. *trans*-resveratrol (500 mg) was given to 12 patients 3 times daily for 90 days whereas 12 patients received only placebo. Body mass index, fat mass, the area under the curve of insulin, and total insulin secretion were notably decreased after administration of *trans*-resveratrol [55].

There is a relation between impaired regulation of lipid oxidation (metabolic inflexibility) and obesity and T2DM. It is considered that dietary polyphenols might modulate mitochondrial function, substrate metabolism and energy expenditure in human. In a randomized, double-blind cross-over trial, the effects of short-term supplementation of two combinations of polyphenols on energy expenditure and substrate metabolism were investigated in overweight subjects. Eighteen healthy overweight volunteers participated in the study. Combinations of epigallocatechin-gallate + resveratrol and epigallocatechin-gallate + resveratrol + 80 mg/day soy isoflavones or placebo capsules were supplemented twice daily for 3 days. Metabolic flexibility, calculated as the postprandial increase to the highest respiratory quotient achieved, tended to be improved by epigallocatechin-gallate + resveratrol remarkably increased fasting plasma free fatty acid and glycerol concentrations. The investigators concluded that long-term supplementation of these dosages of epigallocatechin-gallate combined with resveratrol may improve metabolic health and body weight regulation [56].

The effect of a proprietary formulation of *trans*-resveratrol on manifestations of diabetic foot syndrome (DFS) was studied in T2DM patients with newly diagnosed diabetic foot ulcers. A pilot clinical trial in which placebo-controlled, examiner-blinded, parallel-group randomized controlled with DFS was performed with 24 patients dividing into the placebo and *trans*-resveratrol treatment groups. Fifty mg of *trans*-resveratrol or placebo capsules were given to patients twice a day for 60 days. Decline in the parameters reflecting diabetic ulcer size was much more prominent in the *trans*-resveratrol group as compared to placebo patients. As a result, it was revealed that *trans*-resveratrol supplementation promoted reduction of the foot ulcer size [57].

A randomized placebo-controlled double-blinded parallel clinical trial aimed to investigate the effectiveness of resveratrol in decreasing blood glucose in the existence of standard antidiabetic treatment in patients with T2DM. In this trial, 66 patients with T2DM were divided into 2 groups: intervention group supplemented with resveratrol at a dose of 1 g/day for 45 days and control group received placebo tablets. Resveratrol treatment remarkably decreased systolic blood pressure,

fasting blood glucose, hemoglobin A1c, insulin, and insulin resistance, whereas significantly increased HDL, when compared to their baseline levels. Nevertheless, the placebo group experienced increased fasting glucose and LDL. There were no changes observed in liver and kidney function markers in the intervention group. According to these findings, resveratrol supplementation given to patients with T2DM showed strong antidiabetic effects [58].

In a double-blind randomized study, the effects of resveratrol administration on GLP-1 secretion, gastric emptying, and glycemic control in T2DM were evaluated. Fourteen patients with diet-controlled T2DM received resveratrol (500 mg twice daily) or a placebo during 5 weeks. After administration of what, it has been observed that there were no effects on GLP-1 secretion, glycemic control, gastric emptying, body weight, or energy intake. The authors concluded that the findings do not support the use of resveratrol for improving glycemic control [59].

A double-blind, randomized, placebo-controlled study aimed to determine whether resveratrol supplementation at 2 different dosages (40 and 500 mg/day) for 6 months reduced the concentrations of C-reactive-protein (CRP) and improved the metabolic pattern of T2DM patients. In this trial, 192 T2DM patients received resveratrol 40 mg/day (Resv40 arm), resveratrol 500 mg/day (Resv500 arm), or placebo for 6-months. The supplementations with 40 mg/day or 500 mg/day resveratrol did neither reduce CRP concentrations, nor improve the metabolic pattern of T2DM patients [60].

A randomized, parallel double-blind study evaluated the effects of resveratrol/leucine and resveratrol/hydroxymethylbutyrate for their ability to control glucose levels in persons without DM, but with impaired fasting glucose. The study involved 36 subjects. It was a 28-day randomized controlled trial of the effects of a nutraceutical preparation on glycemic control in non-diabetic individuals with impaired glucose tolerance [61]. The outcome of the study cannot be reached yet via ClinicalTrials.gov.

A study in which randomized double-blind trial evaluated eligible patients with a body mass index of 30 kg/m^2 or more and venous glucose of < 7.0 and < 11.1 mmol/L at 0 and 120 min respectively on oral glucose tolerance testing following a 12-h fast, *trans*-resveratrol extract from Polygonum cuspidatum was used in the trial. Patients received *trans*-resveratrol for 2 weeks [62]. The results of the study cannot be reached yet at ClinicalTrials.gov.

In a study involving 8 subjects, the effect of resveratrol on DM was assessed. Subjects received resveratrol 500 mg tablets BID for 1 week followed by 1000 mg BID for the second week or placebo and advised to start taking the tablets 14 days prior to the first lipoprotein kinetics study. Then insulin sensitivity was assessed [63]. The results of the study cannot be reached yet at ClinicalTrials.gov.

A non-randomized single group assignment open label pilot study was designed to test the hypothesis that resveratrol (90 mg/day or 270 mg/day for one week) had favorable effects on endothelial function in patients with DM. Resvida® which contains resveratrol was used as a dietary supplement on 20 T2DM patients [64]. The outcome of the study cannot be reached yet at ClinicalTrials.gov.

The purpose of another randomized parallel double-blind study was to compare the effects of the antioxidant resveratrol with diet intervention to detect how each of them affects the following: gene expression profile, cholesterol, how well the hormone insulin works to control blood glucose, and other blood and tissue markers of metabolic and cardiovascular health. In this study, Resvida™ was given to the 58 subjects. Calorie restriction (CR) is a low-calorie diet and has also been connected to health benefits and an extended lifespan. This study was designed to compare the health benefits of both resveratrol and CR and to detect if resveratrol imitates some of the health benefits indicated with CR [65]. The findings of the study cannot be reached yet at ClinicalTrials.gov.

The aim of a randomized parallel double-blind study was to examine potential metabolic efficacies of resveratrol in healthy, but obese men. The researchers were concluded that resveratrol will resist some of the destructive effects of obesity, and as an imitator of CR will give new insight into the primary biochemical pathways supporting human metabolism [66]. The results of the study cannot be reached yet at ClinicalTrials.gov.

2. Conclusion & perspectives

Data from the literature obviously show that resveratrol exerts pleiotropic action in humans. The therapeutic action of this compound in relation to diabetes is complex and involves in various beneficial effects. On account of this, elucidation of these beneficial effects is necessary to perform clinical studies. In addition, a few of the studies described in this review do not clearly improve glycemic index. Thus, the presence of controversial results would require a more extensive investigation. There are a few ongoing clinical trials regarding resveratrol (www.clinicaltrials.gov) which can increase the knowledge about the effects of resveratrol on human health in years to come. Further research should aim at exploring the connection between resveratrol dose and efficacy and should also reveal the pleiotropic mechanisms of actions this agent in DM patients. It is concluded that resveratrol, alone or in combination with current anti-diabetic therapies, might be used in treating diabetes. Additionally, resveratrol molecule could be the scaffold structure for the development of other synthetic compounds for treatment and management of DM.

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Conflict of interests

All authors declare no potential conflicts of interests.

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