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Original article

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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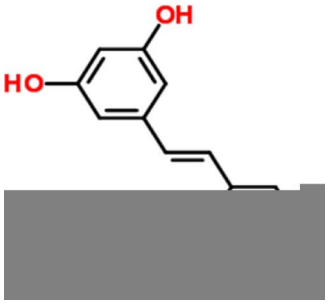

Fig. 1. 2D structure formula of the resveratrol [11].

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

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