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Mariana Nathuê Lôbo Prata
Department of Pharmacology, Institute of Biological Sciences, ICB-UFMG, Av. Antônio Carlos, 6627, Pampulha, CEP 31.270-100, Belo Horizonte, MG, Brazil

Cristina da Costa Oliveira
Department of Pharmacology, Institute of Biological Sciences, ICB-UFMG, Av. Antônio Carlos, 6627, Pampulha, CEP 31.270-100, Belo Horizonte, MG, Brazil

Ives Charlie-Silva
Department of Pharmacology, Institute of Biological Sciences, ICB-UFMG, Av. Antônio Carlos, 6627, Pampulha, CEP 31.270-100, Belo Horizonte, MG, Brazil

Thiago R Lima Romero
Department of Pharmacology, Institute of Biological Sciences, ICB-UFMG, Av. Antônio Carlos, 6627, Pampulha, CEP 31.270-100, Belo Horizonte, MG, Brazil

Andrea de Castro Perez
Department of Pharmacology, Institute of Biological Sciences, ICB-UFMG, Av. Antônio Carlos, 6627, Pampulha, CEP 31.270-100, Belo Horizonte, MG, Brazil

Correspondence
Andrea de Castro Perez
Department of Pharmacology, Institute of Biological Sciences, ICB-UFMG, Av. Antônio Carlos, 6627, Pampulha, CEP 31.270-100, Belo Horizonte, MG, Brazil

Anti-inflammatory effects of resveratrol

Mariana Nathuê Lôbo Prata, Cristina da Costa Oliveira, Ives Charlie-Silva, Thiago R Lima Romero and Andrea de Castro Perez

Abstract
Diabetes is characterized by the absence of insulin or impairment of its action, which consequently lead to chronic hyperglycemia. Numerous complications emerge as a consequence of this metabolic alteration, resulting in complications of the circulatory system, vascular endothelium lesions and, consequently, the appearance of an inflammatory process and secondary diseases. Our objective is to review the anti-inflammatory action of resveratrol in chronic complications caused by Diabetes Mellitus. Several studies indicate that its anti-inflammatory action is due to the inhibition of several pro-inflammatory pathways and consequently the reduction of pro-inflammatory markers such as cytokines, chemokines and adhesion molecules. Resveratrol was able to reduce the inflammatory effects caused by Diabetes Mellitus, and improved nephropathy, neuropathy, hepatopathy, retinopathy, insulitis, among others, being a potential pharmacological tool and/or medicament.

Keywords: *Vitis vinifera*; wine; resveratrol; diabetes; inflammation.

1. Introduction
Nowadays there is a demand for food that, in addition to nourishment, will protect and preserve the organism from diseases [1].
Among them antioxidant compounds with proven beneficial effect on health like wine, one of the most consumed and noble alcoholic beverages has been studied [2]. The first reports of wine consumption occurred around 7000 years ago, in the Mediterranean, but its beneficial effects were evidenced in 1992 with the publication of the "French paradox" [3]. This study showed that although the high consumption of saturated fats, the cardiovascular disease (CVD) mortality was relatively low in France compared to other countries, due to the moderate and regular use of wine [4].
There are many substances in wine, and resveratrol is the compound that draws most attention for its antioxidant and anti-inflammatory properties. It can benefit the cardiovascular system, inhibit platelet aggregation, decrease inflammation, and improve homeostasis and insulin sensitivity [5] in addition to lipolytic activity in adipose cells [6].
Diabetes mellitus (DM) is a metabolic disorder characterized by defects in insulin secretion and / or insulin resistance, that result in chronic hyperglycemia [7]. There are two main types of DM, type 1, an autoimmune disease caractherized by destruction of pancreatic β cells resulting in insulin shortage, and type 2, characterized by reduction of insulin sensitivity (resistance), which may be accompanied by impairment of its secretion [8]. Patients with DM are more likely to acquire vascular diseases and secondary diseases due to vascular endothelial injury and, subsequently, induction of inflammatory mediators [9].
The aim of this review is to investigate the anti-inflammatory action of resveratrol in DM, as well as the reduction of related secondary diseases.

2. Resveratrol
2.1 Chemical structure and properties
The word resveratrol comes from Latin, where "res" means "coming from", "veratrum" which is the plant to which the compound was first detected, and "ol" which emphasizes the presence of the alcohol group in its molecular structure [10].
Chemically known as 3,5,4'-trihydroxystilbene, resveratrol is a compound that has two phenols rings linked by a styrene double bond [11], which allows two geometric isomers: being *trans* the biologically and physiologically active form [12]. However, when exposed to ultraviolet radiation, the trans-isomer tends to be altered to its less active cis-isomer [12, 13].

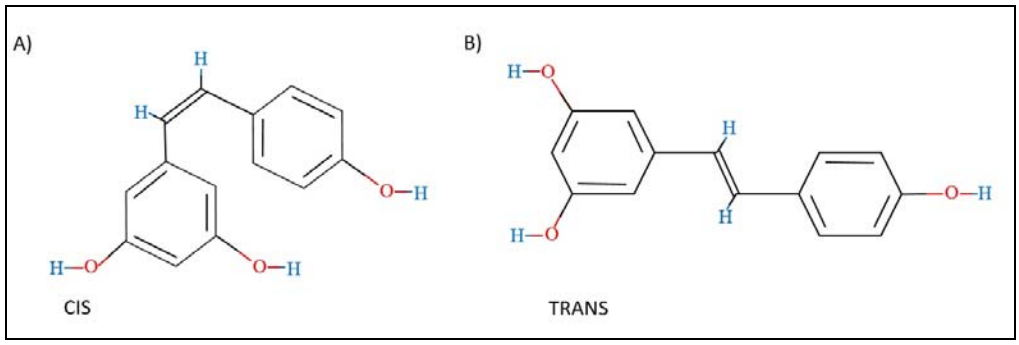

Fig 1: Chemical structure of cis-resveratrol (A) and trans-resveratrol (B) isomers.

Resveratrol was first identifield from the roots of the plant *Veratrum grandifolorum* O. Loes in 1940 [14] and from the roots of a traditional Chinese, Korean and Japanese plant *Polygonum cuspidatum* in 1963 [15].

This polyphenol is a phytoestrogen produced by a large variety of plants, including peanuts and berries (figure 3), but the most outstanding is grape and its industrialized products, such as red wine [13].

Classified as a phytoalexin, the role of resveratrol in plants is to protect them from external damage, such as ultravioleta radiation, ozone exposure and fungal or attack [11]. The content of resveratrol may vary depending on the different sources and the various factors such as climate, cultivation, level of plant infections caused by fungi and exposure to ultraviolet radiation [16].

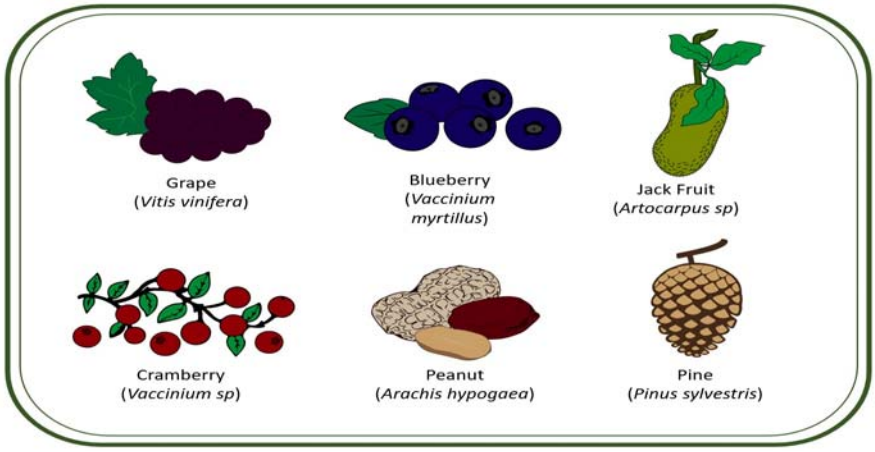

Fig 2: Sources of resveratrol.

3.2. Physiological effects of resveratrol

Several studies and evidence indicate that moderate consumption of red wine promotes cardioprotective effect, either short or long term, leading to the suggestion that resveratrol could be responsible for the beneficial properties of red wine. Resveratrol may act on numerous molecular targets (figure 3) such as cell oxidation, inflammation, carcinogenesis, cell division cycle and apoptosis [11].

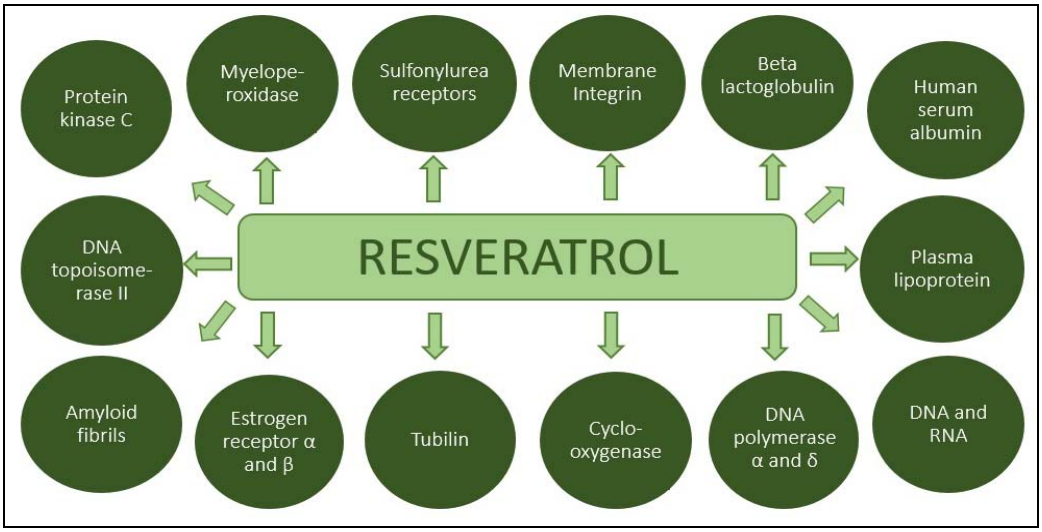

Fig 3: Molecular targets of resveratrol.

In vitro, resveratrol associated with lipoproteins was shown to inhibit low-density lipoprotein (LDL) oxidation [17], significantly reduced adiposity mass in mice, and also improved lipid metabolism, inflammatory risk factors and antigen-positive macrophages of atherosclerosis [18]. Resveratrol has also been used to inhibit the progression stage of carcinogenesis in rats, being effective in blocking *in vivo* the three stages of carcinogenesis: initiation, promotion and progression [19].

Resveratrol has shown cardioprotective effects due to total cholesterol and LDL reduction, inhibition of platelet aggregation, decrease the progression of atherosclerosis and CVD, and antioxidant/anti-inflammatory actions. The anti-inflammatory activity of resveratrol is related to a decrease of pro-inflammatory markers such as cytokines, chemokines and adhesion molecules [20].

It was reported that resveratrol has anti-inflammatory activity by acting on the NF-kβ pathway [21,22,23,24], as well as reducing inflammatory cytokines, such as TNF-α [21,23,24,25, 26], IL-1β [22,26], IL-6 [21,23,25], COX [24,26], PCR [21], among other inflammatory mediators.

4. *Diabetes Mellitus* and inflammation

Hyperglycemia of DM occurs due to lack of insulin or impairment of its action. It occurs with the decrease of glucose uptake mainly by the muscle, with reduced glycogen synthesis associated with liver glucose release. Them glucose can be lost through urine (glycosuria), with consequent loss of water and dehydration, causing osmotic diuresis (polyuria), which induces increased water intake (polydipsia) [8]. According to the Diabetes American Association (2016) [7] DM is usually diagnosed based on plasma glucose levels, such as fasting blood glucose [≥126 mg/dL (7.0 mmol/L)], oral glucose tolerance test [≥ 200 mg/dL (11.1 mmol/L)] and the level of hemoglobina A1c [Hb A1 ≥ 6.5%(48 mmol/mol)] [7].

It is becoming increasingly clear that DM can cause an inflammatory process, which contributes to the emergence of secondary diseases, affecting the vascular endothelium [27-29], generating platelet hyperreactivity and, consequently, activating the cascade of inflammatory mediators [9]. According to KANTER *et al*. (2012) [27], monocytes, the body's defense phagocytic cells, isolated from humans with DM1 secrete elevated levels of proinflammatory cytokines, such as IL-6 and IL-1β that can trigger cardiovascular problems such as atherosclerosis. The authors emphasized that, during cell differentiation in the presence of a hight-glucose concentration, the macrophages promote high levels of PGE2 [27].

PICCIRILLO *et al*. (2004) [28] reported that elevated inflammatory mediators due to DM results in an increased risk of CVD and aterosclerosis, possibly due to the progression of vascular changes. Patients with DM can have elevated levels of acute phase proteins, such as C-reactive protein (CRP) and α1-acid glycoprotein (α1-GPA). At the beginning of DM, the inflammatory reaction results in an increase in cytokines, including TNF-α, interleukin 1 (IL-1) and interleukin-6 (IL-6). Low concentration of insulin in the hepatic portal system blood, increases inflammatory protein production by the liver, which are normally inhibited by insulin. Another mechanism include an increased oxidative stress induced by hyperglycemia, resulting in a phenomenon called glycation. Glycation consists of the union between a protein and a carbohydrate (in this case glucose), generating products that can induce activation of macrophages, which will increase the synthesis of IL-1 and TNF-α and consequently, increase oxidative stress and acute phase proteins. Another mechanism would be related to cytokines derived from adipose tissue such as IL-6, with subsequent production of CRP by the liver, that induces macrophages formation and release of inflammatory mediators. The latter mechanism would be more common in DM2 due to obesity [28].

Abdominal obesity leads to insulin resistance due to metabolic products derived from lipids and cytokines. Consequently, it can lead to endothelial dysfunction and abnormal insulin action on muscles, adipose tissue and endothelial cells [29] and formation of leptin, adiponectin, TNF-α and IL-6 [30]. Obesity facilitates the infiltration of macrophages into adipose tissue and production of IL-6 and TNF-α and CRP [30].

After binding to the receptor to allow glucose into tissues, insulin stimulates phosphatidylinositol 3-kinase pathway that regulates the production of insulin-mediated nitric oxide. When this pathway is dysfunctional, insulin-mediated endothelium-dependent vasodilation does not occur. The MAPK pathway, that seems to mediate endothelial cells migration, stimulating proinflammatory responses, due to hyperinsulinemia is also activated [29].

Several studies demonstrate new strategies in the regulation of the inflammatory processes associated with DM, in order to prevent secondary diseases associated with DM and improve insulin action and resveratrol is among these possible pharmacological targets.

5. Effect of resveratrol in the inflammatory processes of Diabetes Mellitus

Several studies have hypothesized and demonstrated that resveratrol has a beneficial role in prevention and also in relieving complications correlated to DM. Table 1 below presents 11 articles on the use of resveratrol in the context of inflammatory processes related to DM:

Table 1: Use of resveratrol in the improvement of inflammatory processes related to Diabetes Mellitus.

Species	Model	Secondary disease	Dose	Mechanism and effects	References
Male Sprague-Dawley rats (250-270 g)	DM was induced by streptozotocin (STZ) at a dose of 55 mg/kg (i.p.)	Neuropathy	Resveratrol 10 and 20 mg / kg for 2 weeks	Resveratrol restored sciatic nerve flow. It also decreased levels of pro-inflammatory mediators, such as TNF-α, IL-6, COX-2, the cascade of NF-kβ, decreasing neuropathy caused by DM.	KUMAR & SHARMA, 2010 [31]
Wistar rats (160-180 g)	Diabetic animals induced by streptozotocin (50 mg / kg body weight) i.p.	Hepatocyte dysfunction	Oral suspension of resveratrol (5mg / kg body weight / day) compared to glyclazide	Resveratrol demonstrated a decrease in NF-kβ and NO, decreased proinflammatory cytokines, protected	PALSAMY; SIVAKUMAR; SUBRAMANIAN, 2010 [32]

	and nicotinamide (110 mg/kg body weight)		(5 mg / kg body weight) for 30 days	hepatocytes from oxidative damage mediated by hyperglycemia compared to those not treated with resveratrol	
19 caucasian male patients (older than 18 years)	Diagnosed with DM2	Metabolic effects through insulin resistance	Double-blind study: one group received 5 mg resveratrol oral capsules twice daily, and the other group received placebo for 4 weeks	Resveratrol improved insulin sensitivity in humans by decreased oxidative stress and the Akt pathway	Brasnyó; Molnár; Mohás; Markó; Laczy ; Cseh; *et al.,* 2011 [33]
Wistar rats (160-180 g)	Diabetic animals induced by streptozotocin (50 mg / kg body weight) i.p. and nicotinamide (110 mg/kg body weight)	Nephropathy	Oral suspension of resveratrol (5mg / kg body weight / day) compared to glyclazide (5 mg / kg body weight) for 30 days	Resveratrol effectively protected oxidative damage in the kidneys of diabetic rats. It decreased pro-inflammatory markers, such as TNF-α, IL-1β, IL-6 and NF-kβ	PALSAMY & SUBRAMANIAN, 2011 [34]
Seventy-five patients (18 to 80 years old).	Patients with diabetes, obesity or other cardiovascular risk factors such as hypertension, active smoking, or overweight / obesity (body mass index greater than 30 kg / m2) who used statins	High risk of CVD	Triple-blinded, randomized, parallel, dose–response, placebo-controlled, 1-year follow-up trial. 3 groups: placebo, grape supplement lacking resveratrol and resveratrol 8 mg oral capsules, once daily for the first 6 months and 2 capsules daily for the next 6 months	Resveratrol improved inflammation and fibrinolytic disorder; It significantly decreased C-reactive protein (CRP), TNF-α, the plasminogen activator inhibitor type 1 (PAI-1) and increased IL10 and adiponectin compared to the control group and the group that used resveratrol-free grape supplement	Tomé-Carneiro; Gonzálvez; Larrosa; Yáñez-Gascón; García-Almagro; Ruiz-Ros; *et al.,* 2012 [35]
Wistar rats (220–310 g)	DM was induced by streptozotocin at a dose of 50 mg / kg body weight (i.p.). Then, induction of cerebral ischemia by occlusion of the bilateral carotid artery followed by reperfusion	Cerebral ischemia	Injection i.p. of resveratrol at a dosage of 5, 10, 20, 30 mg / kg. Application before reperfusion. In a select group, 20 mg / kg to evaluate markers of oxidative and inflammatory stress	Resveratrol dosage of 5, 10, 20, 30 mg / kg showed dose-dependent reduction of brain injury. 20 mg / kg of resveratrol reduced levels of oxidative stress markers, significantly increased levels of antioxidant and anti-inflammatory markers.	PRABHAKAR, 2013 [36]
Male Sprague-Dawley rats (160–180 g) and human endothelial cell line culture	Rats were fed high-fat, sugar-rich diet (HFD). Endothelial cells EA.hy926 with high glucose (25 mmol/L)	Vascular inflammatory injury (atherosclero-sis)	Rats: Resveratrol was administered intragastrically the dose of 50 mg/kg once daily for 24 weeks; Culture: 10 nmol/L and 100 nmol/L of resveratrol were incubated for 24 or 48 hours	Rats: Resveratrol regulated the metabolism of glucose and lipids, protected vessels from plaque formation and improved insulin action. Both rats and endotelial cell line culture: Resveratrol attenuated the action of NF-kβ, IL-1β, IL-6 and TNF-α, whereas in rats it was in the carotid artery and thoracic aorta	Zheng; Zhu; Chang; Cao; Dong; Li; *et al.*, 2013 [9]
Rat Mesangial Cell (RMC) and male FVB mice (26–30 g)	RMCs were cultured with 25 mM D-glucose (high glucose, HG). Mice were injected intraperitoneally with streptozotocin (50 mg/kg daily) i.p	Nephropathy	RMC: Resverarol (25 μM). Mice: Oral gavage administration of resveratrol (10mg / kg / day) for 12 weeks	In vitro, lower rates of NF-k β were seen with resveratrol treatment compared to untreated culture. *In vivo*, a significant improvement was observed in the glomeruli of DM animals treated with resveratrol and significant decrease in NF-k β indices	Xu; Wang; Cui; Yuan; Sun; Wu; *et al et al*., 2014 [37]
Wistar rats (115 g)	Hyperlipidic diet. Fragments of the myocardium of the rats used in Western blot analysis	Myocardium inflammation	20 mg / kg / day of resveratrol for 8 weeks	Resveratrol increased the phosphorylation of the insulin receptor, reduced TNF-α, NF-kβ, reduced pro-inflammatory molecules and improved insulin sensitivity	Luciano; Marques; Pieri; Souza; Lira; Souza, 2014 [5]
Human umbilical vein	Endothelial cells: stimulated with palmitate (PA) to	Endothelial dysfunction (aortic	Endothelial cells: resveratrol (0.1–10 μmol/L).	Incubation of aortas of rats with resveratrol restored the vasodilator responses to	Liu; Jiang; Zhang; Liu B; Du, 2016 [38]

endothelial cell line EA.hy926 Male Sprague-Dawley rats (200–250 g)	induce insulin resistance Rats: Diabetes was induced by fructose feeding. Rat´s Aortic rings was incubated with palmitate	constriction and relaxation) and insulin signaling	Rats: Resveratrol (5 or 20 mg/kg per day, p.o.) or metformin (100 mg/kg per day, p.o.). Aortic rings were pretreatment with 0.1–10 μmol/L resveratrol	insulin in a concentration-dependent manner. In endotelial cells, resveratrol reduced phosphorylation of IKKβ and NF-κβ and levels of PAI-1, TNF-α and IL-6	
Male Sprague-Dawley rats (200–250 g)	60 mg/kg streptozotocin (i.p.)	Diabetic encéphalo-pathy	Five groups of 15 animals each: control, diabetic control, diabetic + resveratrol 10 mg/kg, diabetic+ resveratrol 20 mg/kg, and control+ resveratrol 20 mg/kg, once a day for 8 weeks	SYN and GAP-43 expression were reduced in the hippocampus of DM rats. However, resveratrol (10, 20 mg/kg) improved neuronal injury and cognitive performance by attenuating oxid stress and inflammation	Tian; Liu; Ren; Yin; Liang; Geng; *et al*., 2016 [39]

KUMAR & SHARMA (2010) [31] conducted a study with streptozotocin induced diabetes in Sprague-Dawley rats. Streptozotocin is a glucosamine-nitrosurea used to induce DM type 1 in experimental models, inducing cytotoxic effects in pancreatic cell that contain glucose transporters GLUT-2 [40]. Alkalinization of cellular DNA and activation of poly-ADP ribose synthetase (important in nuclear alterations and DNA repairs) causes lethal NAD depletion, decreasing ATP levels and subsequent inhibition of insulin synthesis and secretion [40]. The animals treated with resveratrol at both doses (10 and 20 mg / kg / day) had restored blood flow and exhibited an improvement of sciatic nerve condutance. Resveratrol at both doses inhibited elevation of TNF-α, IL-6, malodialdehyde (MDA), NF-kβ and COX-2 levels [31].

NF-kβ is present in macrophages and is also found in the cytoplasm, bound to an inhibitory protein, Iκβ. When stimulated, phosphorylation of Ikβ occurs, releasing NF-kβ, which is directed to the nucleus, producing numerous transcription factors [41]. NF-kβ is involved in the activation of genes that act on several inflammatory target genes, such as tumor necrosis factor-α (TNF-α), interleukin 1β (IL-1β), both pro-inflammatory cytokines and nitric oxide synthase (iNOS), which forms nitric oxide (NO), causing vasodilation, increasing vascular permeability [42]. NF-kβ can be inhibited by the silent information regulator T1 (SIRT1). SIRT1 regulates innumerable signaling pathways, as well as metabolism, apoptosis, endotelial functions, cellular senescence, and also inflammation. It interacts by deacetylating the RelA/p65 subunit of NF-kβ, inhibiting the proinflammatory cytokines transcription [43].

Diabetic neuropathy progresses within six weeks in streptozotocin-induced animals due to reduced blood flow in the nerve and high levels of NF-kβ and proinflammatory IL-6, TNF-α and COX-2. The inhibitor kappa β (Ikβ) maintains inactive NF-kβ in the cytoplasm under physiological conditions. Resveratrol inhibits Ikβ phosphorylation, preventing NF-kβ activation [31].

PRABHAKAR (2013) [36] investigated the cerebroprotective role of resveratrol in DM in diabetic Wistar rats (streptozotocin induction) with carotid artery ischemia-reperfusion injury. There was a significant reduction of cerebral infarction in DM animals treated with resveratrol as well as reduced MDA (a lipid peroxidation product) levels and significantly increase of endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) levels compared to the control group [36].

In ischemia-reperfusion injury, brain cells are exposed to free radicals and inflammatory and oxidative processes. Physiologically, SOD and CAT play a key role in the elimination of free radicals preventing cellular damage. Resveratrol strengthened the mechanisms of oxidative defense and reduced lipid peroxidation [36].

Reactive oxygen species (ROS) associated with inflammation may induce and aggravate ischemia. The condition may be worsened when it is associated with DM, as it can also increase the release of ROS and inflammatory mediators. Treatment with resveratrol reduced oxidative stress and inflammation at central level demonstrating resveratrol neuroprotection [36] and, corroborating KUMAR & SHARMA (2010) [31] studies demonstrating peripheral neuroprotection in rats.

TIAN *et al*. (2016) [39] conducted a study to investigate the effects of resveratrol on the structural synaptic plasticity of the hippocampus of STZ induced diabetic. Two molecular targets involved in structural synaptic plasticity were chosen: SYN and GAP-43. The cognitive performances (learning and memory) in the diabetic group were markedly deteriorated, the expression of SYN and GAP-43 were reduced and TNF-α and IL-1β mRNA levels were increased in the hippocampus of diabetic rats compared to the non-diabetic control group and resveratrol treated groups (10 and 20 mg/kg, once a day for 8 weeks) [39].

Oxidative stress and inflammation are involved in the cognitive deficiency associated with DM. Hyperglycemia results in increased glycation phenomena (AGEs), that induce formation of reactive oxygen species (ROS), and neuronal damage. ROS can further activate NF-κB through the activation of the MAP kinase pathway and consequently trigger proinflammatory cytokines, known to arise in several neuropathological states. It is perceived that the brain is another target lesion site of DM, leading to cognitive dysfunction and synaptic problems. Therefore, the use of resveratrol may be an ideal choice to complement the treatment of these problems [39].

LUCIANO *et al*. (2014) [5] showed increased insulin sensitivity of obese animals treated with resveratrol. Phosphorylation of the insulin receptor IRS1 and Akt were significantly greater in obese animals treated with resveratrol than in obese untreated rats. Resveratrol also decreased TNF-α and NF-κβ levels [5].

Obesity leads to insulin resistance. TNF-α activates IKKα and IKKβ, promoting phosphorylation of the insulin receptor on serine [5]. The insulin receptor can be tyrosine phosphorylated, generating GLUT-4 translocase response and glucose uptake into the cell but it can also be phosphorylated on serine, with signal transmission decreased (inhibitory phosphorylation). This causes a negative feedback and may lead to insulin resistance [44]. The activation of the insulin pathway by resveratrol may also induce SIRT1, which helps to control physiological levels of glucose by modulating insulin

receptors, protection of pancreatic β cells, inhibition of the NF-kβ pathway and reduction of inflammatory mediators and also be involved in the secretion of adiponectin [5].

When diabetes was induced in rats by fructose feeding resveratrol inhibited IKKβ / NF-κB-dependent inflammation by regulating the AMPK and SIRT1 pathways, improving endothelial dysfunction and facilitating insulin signaling. It also suppressed the production of PAI-1, modulating the balance between the PI3K and MAPK insulin pathways in the endothelium in inflammatory conditions [38].

It was also demonstrated a hepatoprotective action by resveratrol through the blockade of oxidative stress mediated by hyperglycemia and levels of proinflammatory cytokines [32]. Excessive increase of blood glucose can lead to necrosis, inflammation, and oxidative stress in liver tissues. The inflammatory response is mediated by proinflammatory cytokines, such as TNF-α and IL-1β. NF-κβ, in addition increases NO by activation the nitric oxide synthase expression, which increases levels of lipid peroxidation and oxidation of LDL. TNF-α, IL-1β, IL-6, NF-κβ and NO in hepatic tissues were significantly elevated in the DM group compared to the control group. Resveratrol, by attenuating proinflammatory cytokines to near normality, reduced oxidative damage mediated by inflammation [32].

The liver is a metabolic organ mainly involved in regulation of glucose metabolism. Insulin impairment induces elevated hepatic glucose production through glycogenolysis, resulting in hyperglycemia and increased liver markers such as AST, ALT and ALP and bilirubin. Resveratrol significantly decreased these hepatic markers in Wistar rats [32].

The effect of resveratrol on a hypoglycemic drug, glyclazide, was compared. Proliferative glycemia and mediator levels were significantly reduced with the use of resveratrol as well as the glycated group compared to the untreated DM group [34]. Adiponectin is a protein secreted mainly by adipose tissue and acts to improve insulin sensitivity, and has anti-inflammatory properties by reducing TNF-α and IL-6 [45]. Adiponectins values were significantly reduced and levels of TNF-α, IL-1β, IL-6 and NF-ßβ were significantly increased in DM mice. Elevated levels of TNF-α and IL-6 may correlate with reduced levels of adiponectins. Resveratrol restored adiponectin levels [34].

TNF-α is cytotoxic at the gromerular and epithelial cells levels, capable of generating free radicals, inducing direct renal damage. IL-1β increases the synthesis of prostaglandin in mesangial cells leading to intraglomerular abnormalities. Both can increase NO levels and cause oxidative stress. IL-6 affects the dynamics of the extracellular matrix and increases the endothelial permeability, which may cause thickening of the gromerular basement membrane. NF-kβ can trigger this cascade. Therefore, resveratrol may present antioxidant and anti-inflammatory mechanisms [34].

Nephroprotective action of resveratrol in vitro, was also demonstrated by XU *et al*. (2014) [37] with culture of mesangial cells of rats exposed to high glucose concentrations, and *in vivo*, with male mice with DM induction. Resveratrol decreased NF-kβ activation *in vivo* and in vitro. Kidney weight was significantly increased in the DM group, but not in animals treated with resveratrol [37]. NF-kβ promotes the expression of a number of genes involved in inflammation, such as PAI-1 and ICAM-1. PAI-1 promotes thrombus formation and rupture of unstable atherogenic plaques [46] and ICAM-1 (a member of the glycoprotein family of cell adhesion molecules that bind to the lymphocyte cell surface), resulting in the migration of neutrophils during the final phase of inflammation [47]. Resveratrol decreased PAI-1 and ICAM-1 activity by direct or independent NF-kβ pathway. Therefore, resveratrol inhibits the induction of renal mesangial cell proliferation through the regulation of NF-kβ and, thereby, attenuate kidneys inflammation caused by DM, both *in vitro* and *in vivo* [37].

Resveratrol also inhibited the inflammatory processes through the activation of NF-kβ pathway in Sprague-Dawley rats and in human endothelial cells EA.Hy926 culture with high concentration of glucose from increased TNF-α, ICAM-1, MCP-1 expression, by decreasing NF-kβ [9], responsible for the formation of the atherosclerotic plaque in the vascular wall [48]. The study showed suppressed nuclear translocation of NF-kβ, with decreased expression of mRNA and inflammatory proteins such as TNF-α, ICAM-1 and MCP-1, by resveratrol. However, the specific site of action of resveratrol has not yet been elucidated it may be through activation of AMP- protein kinase (AMPK), silent information regulator T1 (SIRT1) and peroxisome proliferator-activated receptor (PPAR) γ co-activator 1α (PGC-1α). These sites play a role in the regulation of lipid and glucose homeostasis and in the control of the inflammatory process [9].

After 4 weeks, resveratrol significantly decreased insulin resistance in humans, decreasing glycemia levels, by either two mechanisms: indirectly, through a reduction of oxidative stress and inflammation or directly through Akt phosphorylation, without affecting β-pancreatic cells, improving insulin signaling [33]. Insulin binds to a membrane-specific receptor, leading to tyrosine phosphorylation of various substrates, including IRS-1 and IRS-2, by activating phosphatidylinositol 3-kinase (PI3-k). This protein triggers the recruitment and activation of Akt near the plasma membrane, inducing uptake of glucose via GLUT-4 transporters [49].

Another study involving humans was conducted by TOMÉ-CARNEIRO and collaborators (2012) [35]. This randomized, triple-blind, placebo-controlled study of 75 patients aged 18 to 80 years with diabetes, obesity, or other cardiovascular risk factors such as hypertension, smoking, or overweight/obesity (1 year). There was significant decrease in inflammatory mediators such as CRP, TNF-α, PAI-1, ICAM, IL-6 and increased IL-10 and adiponectin, improving fibrinolytic and inflammatory status in patients taking statin and the group taking grapes supplented with resveratrol as compared to control or the group with grapes and no resveratrol [35].

TOMÉ-CARNEIRO *et al.* (2012) [35] described this nutraceutical intervention containing resveratrol in the improvement of inflammatory conditions in patients with chronic diseases, including DM. BRASNYÓ *et al*. (2011) [33] demonstrated an improvement in insulin sensitivity through the activation of Akt. Statin activation of these pathways has been reported to decrease PAI-1, and the increase in adiponectin has been reported to activate this pathway. There was synergism between statins and resveratrol, which did not occur between statins and grape supplement without resveratrol. This strengthens the hypothesis that resveratrol accounts for the anti-inflammatory action found in red wine [35]. This study confirms the long-term efficacy of polyphenol in humans [35].

6. Conclusion

Wine is a millenarian beverage that has cultural, religious and socio-economic importance, but nowadays it has aroused interest in health, especially after the "French Paradox" report.

Resveratrol is one of the most important substances present in red wine, precisely because of its health benefits. Resveratrol has numerous biological effects, among them anti-inflammatory, antiproliferative, antiplatelet and anti-oxidant action.

Thus, it may be used as a therapy in combating the various complications associated to DM, including nephropathy, neuropathy, liver disease, atherosclerosis, cardiovascular diseases, reduction of insulin resistance and other inflammatory problems. These results are clinically important reinforcing the benefits that a polyphenol may have to prevent such complications.

Resveratrol is a potential pharmacological tool to treat the inflammatory process caused by DM, however it is understood that further studies and tests on the subject are necessary, especially in humans.

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