Resveratrol for the Management of Diabetes and its Downstream Pathologies

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Abstract

Over the past 10 years more than 10,000 papers and *in vitro* investigations have been published that identify or analyse various critical pathways and biological processes through which the phytoalexin resveratrol has been shown to attenuate the metabolic dysfunctions, acute symptomatology and the consequential downstream pathologies related to type 2 diabetes. More recently, several clinical trials have confirmed resveratrol's potential to substantially enhance the therapeutic effects of the pharmaceutical metformin hydrochloride, particularly related to glucose management, insulin sensitivity and cardioprotection. Metformin is the most commonly prescribed type 2 diabetes treatment worldwide; consequently, any compound with the ability to safely and effectively augment its therapeutic effects warrants intensive investigation. This paper elucidates the principal modes of action that underly resveratrol's promising potential as an effective adjunct treatment for patients currently being administered metformin.

Keywords

Resveratrol, diabetes, diabetes management, metformin, metformin adjunct, glucose homeostasis, cardiovascular protection, adjuvant therapy

Disclosure: Moola Joghee Nanjan has no conflicts of interest to declare. James Betz is an employee of Biotivia Labs LLC.
Received: 24 January 2014 **Accepted**: 12 March 2014 **Citation**: *European Endocrinology*, 2014;10(1):31–5 *DOI:10.17925/EE.2014.10.01.31*
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Support: The publication of this article was supported by Biotivia.

Diabetes is a metabolic disorder, characterised by hyperglycaemia and associated disturbances, which results from defects in insulin secretion, action or a combination of both. Type 1 diabetes is associated with complete or relative insulin deficiency related to autoimmune-mediated destruction of pancreatic β-cells. Type 2 diabetes is associated with variable degrees of insulin resistance, impaired insulin secretion, moderate to severe β-cell apoptosis and increased hepatic glucose production.[1] Insulin and glucagon are the primary hormones that maintain glucose homeostasis by controlling its concentration in blood. When the blood glucose level increases, insulin-mediated signalling lowers it by enhancing glucose uptake in the skeletal muscle, adipose tissue and kidneys, and by promoting its utilisation and storage in the liver. When the blood glucose level decreases, glucagon raises it by promoting glucose production and release in the liver, and by increasing lipolysis from adipose tissue. Compounds that target glucose-regulating processes in the pancreas, liver, skeletal muscles and adipose tissues can, therefore, affect glucose homeostasis.[2] Insulin and oral anti-diabetic agents including sulphonylureas, biguanides, thiazolidinediones and α-glucosidase inhibitors, are the conventional pharmaceutical agents used to treat diabetes.[3] All these hypoglycaemic agents, however, have adverse side effects of varying severity and only alleviate symptoms, while failing to target their cause. Efforts have been made in recent years to identify natural compounds that may promote glucose homeostasis through regulation and modulation of cellular and extracellular pro-diabetic biochemical, nutritional, epigenetic and enzymatic pathways, processes and effects, without associated adverse reactions. In this connection, resveratrol, a naturally occurring polyphenol, has been widely studied for its beneficial effects in maintaining glucose homeostasis, and hence treating diabetes and its accompanying complications. The *in vitro* and *in vivo* evidence underlying resveratrol's ability to attenuate blood glucose levels and reduce hypertension, inhibit insulin resistance and beneficially modify the ratio of plasma high-density lipoproteins (HDLs) to low-density lipoproteins (LDLs) and triglycerides, clearly identify this compound as a potentially effective and safe adjunct treatment of type 2 diabetes for patients who are being treated with metformin and related glucophage-type drugs, as well as those who manage their symptoms primarily by dietary strategies and regular physical exercise.

What is Resveratrol?

Resveratrol, trans-3,5,4-trihydroxystilbene, is a naturally occurring phytoalexin produced by certain spermatophytes in response to injury.[4] Grape vines, berries and peanuts are dietary sources of this compound, with good concentrations in the leaf epidermis and skin of grape berries.[5,6] The principal natural source for commercial extraction of resveratrol is the Japanese giant knotweed, or polygonum-cuspidatum plant rhizome. Resveratrol can also be obtained by synthesis in the laboratory, and can occur in multiple forms. The lioforms, trans and cis, exhibit different biological properties. The trans conformation possesses numerous well-established health benefits. Less is known about the cis isomer; however, it has not been as widely associated with potential disease chemoprevention and treatment.

Resveratrol is rapidly absorbed from the intestine, allowing its distribution, primarily in the liver, kidneys, brain, lungs and muscles. Removal of

Table 1: Resveratrol and the Management of Diabetes – Cell Culture and Animal Studies

Ref.	Model and Period	Parameters Analysed	Results and Conclusions
20	*In vitro* mouse 3T3 –L1 adipocyte cell culture; *in vivo* male rhesus monkey; (2-year period)	Total cholesterol, LDL-C and HDL-C; protein extraction; Western blot and immunoprecipitation; gene expression; histology; immunocytochemistry; enzyme-linked immunosorbent assay; citrate synthase activity and hydrogen peroxide determination	↓ Adipocyte size, ↑ SIRT1 expression, ↓ NF-κB activation and improves insulin sensitivity in visceral WAT from HFS-fed animals
21	*In vivo* SD rats; STZ-induced type 2 diabetes model; dose 40 mg/kg IP; (24-week period)	Vascular permeability assay; histological examinations; immuno-histochemical staining; qRT-PCR analysis; Western blot analysis; cell culture and viability assay; inhibition of NF-κB p65 activation by small interfering RNA and PDTC in cultured endothelial cells	↓ NF-κB, ↓ IL-1β and ↓ IL-6 in blood; ↓ TNFα, ↓ ICAM-1 and ↓ MCP-1 expressions in vascular wall
22	*In vitro* RINm5F pancreatic cells from MG-induced apoptosis	ROS measurement; assay for cell apoptosis; Western immuno blotting; detection of insulin protein expression in RINm5F cells	Inhibits MG-mediated expression of CCAAT/ enhancer-binding protein C/EBP-β activates the expression of Nrf2
23	*In vitro* cell culture-3T3-LI pre-adipocytes; *in vivo* C57BL/6J female mice; diet regulation; (6-week period)	Oil red O staining; RT-PCR; glucose uptake into C2C12 cells; Western blot analysis; oral GTT; ITT; measurement of glucose uptake into skeletal muscle	Inhibits adipocyte differentiation, ↑ glucose uptake in the myotubes
24	*In vivo* male, 5-week-old db/db and db/dm (non-diabetic control) mice (12-week period)	GTT and ITT; immunohistochemical staining; Masson's trichrome staining; beta-cell mass in pancreatic islet; plasma and urinary ROS markers	Improves glucose tolerance at 2 hours in db/db mice; ↑ pancreas weight and beta-cell mass; ↓ islet fibrosis and urinary 8-OHdG levels
25	*In vivo* male C57BL/6J mice; (24-week period)	Isolation and batch incubation of islets, morpho metric evaluation; pancreatic insulin content; apoptosis by TUNEL TG measurements in pancreas; RT-PCR; IPGTTs; analysis of protein expression by Western blot analysis; oxidative stress damage	↓ The levels of glucose, ↓ lipid metabolism, ↓ beta cell mass, ↓ lipid content, ↓ oxidative stress; promotes SIRT1 expression islets; beneficial effect on the ratios of expressions of Bcl-2/Bax and levels of malondialdehyde/↑ glutathione peroxidase
26	*In vitro* mesangial cells-glomeruli of SD rats	SIRT1 activity assessment; Western blot analysis; intracellular ROS assay; mitochondrial superoxide generation determination; MnSOD activity assay; determination of activities of mitochondrial complexes I and III; measurement of mitochondrial membrane potential; ATP content determination; MtDNA content detection	↓ Hyperglycaemia-induced increase in ROS production and mitochondrial superoxide generation and stimulates MnSOD activity; reverses the mitochondrial complex III activity and restores the hyperpolarisation of $\triangle\varphi$m, ↑ ATP production and preserve the mtDNA content
27	*In vivo* STZ-induced model; male wistar rats; dose 55 mg/kg IP; (30-day period)	Blood glucose and body weight; determination of lipid peroxidation; CAT and SOD activities; vitamin C NPSH content; δ-ALA-D; biochemical analysis; protein determination	Prevents the ↑ CAT, ↑ SOD and ↑ δ-ALA-D and the levels of nonprotein thiols and vitamin C; ↓ serum ALT, ↓ AST and ↓ rGT activities, ↓ levels of urea, ↓ creatinine, ↓ cholesterol and triglycerides (to normal levels)
28	*In vitro* cell culture THP-1 cell line	Trypan blue exclusion assay; immunostaining; preparation of nuclear fraction; measurement of HDAC activity using ELISA; Western blot analysis; measurement of intracellular superoxide production; small interfering RNA transfection assays	↓ HG-induced superoxide production via upregulation of SIRT1, induction of FOXO3a and inhibition of p47phox in monocytes
29	*In vivo* male SD rats; STZ-induced model (8-week period)	Plasma biochemistry; isolation of glomeruli; assessment of kidney morphology and estimation of glomerular volume by light microscopy; immunohistochemical staining for TGF-β1, fibronectin and collagen IV in glomeruli; Western blot analysis; electron microscopy	Urinary albumin excretion, glomerular hypertrophy and expressions of fibronectin, collagen IV and TGF-β in the glomeruli were alleviated; ↓ the thickness of the glomerular basement membrane to the original thickness; ↑ Increases nephrin expressions to normal levels; Inhibits phosphorylation of smad2, smad3 and ERK1/2 in diabetic rat kidneys

8-OHdG = 8-hydroxy-2'-deoxyguanosine; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ATP = adenosine triphosphate; CAT = catalase; δ-ALA-D = delta-aminolevulinic acid dehydratase; ELISA = enzyme linked immunosorbent assay; ERK1/2 = extracellular signal-regulated protein kinases 1/2; GTT = glucose tolerance test; HDAC = histone deacetylase; HDL-C = high-density lipoprotein cholesterol; HFS = high fat sucrose; HG = high glucose; ICAM-1 = intercellular adhesion molecule-1; IL = interleukin; IPGTT = intraperitoneal glucose tolerance test; IP = intraperitoneal; ITT = insulin tolerance test; IV = intravenous; LDL-C = low-density lipoprotein cholesterol; MCP-1 = monocyte chemoattractant protein 1; MG = methylglyoxal; MnSOD = manganese superoxide dismutase; MtDNA = mitochondrial DNA; NF-κB = nuclear factor kappaB; NPSH = non protein thiol; PDTC = pyrrolidine dithiocarbamate; qRT-PCR = quantitative reverse transcription polymerase chain reaction; rGT = r-glutamyltranspeptidase; SD = Sprague Dawley; RNA = ribonucleic acid; ROS = reactive oxidative stress; RT = real time; SIRT1 = sirtuin 1; SOD = superoxide dismutase; STZ = streptozotocin; TG = triglyceride; TGF-β1 = transforming growth factor beta 1; TNFα = tumour necrosis factor-alpha; TUNEL = terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling; WAT = white adipose tissue.

resveratrol from the body occurs mainly through renal excretion. Resveratrol is known to impact numerous mechanisms and pathways within the body, including inhibition of lipid peroxidation, free radical scavenging, alteration of eicosanoid synthesis, modulation of lipid metabolism, improvement of insulin sensitivity, anti-inflammatory activity, signalling pathways, mitochondrial processes and both pro-oestrogenic and anti-oestrogenic activity.[7–9]

Resveratrol and Diabetes

The exact cellular and molecular mechanism of the aetiology and the progression of diabetes is still not fully understood. There is increasing evidence, however, that oxidative stress plays a crucial role in the pathogenesis of diabetes and its complications, and that the β-cell dysfunction is closely related to it and possibly exacerbated by the weakened antioxidant defense of the pancreatic islets.[10] Among other activities, resveratrol has been reported to possess potent antioxidant properties,[11–14] and so it has become an attractive therapeutic agent in the treatment of diabetes and its associated complications. The first known use of grape extract for the benefit of human health dates back over 3,000 years. Drakshasava, an Ayurvedic medicine whose main constituent is *vitis vinifera* L, is prescribed as a cardiotonic in India:[15] a major portion of this extract is resveratrol. In addition to its antioxidant properties, resveratrol appears to beneficially modulate an array of

Table 2: Resveratrol and the Management of Diabetes – Clinical Studies

Ref	Cohort (n)	Form of RSV and Duration	Dose and Schedule	Conclusions
31	Type 2 diabetes patients with hypertension (35)	RSV-enriched grape extract capsule; 1 year	8 mg/day to 16 mg/day; 1 per day for first 6 months; 2 per day for last 6 months	Long-term supplementation with a grape extract containing resveratrol downregulates the expression of key pro-inflammatory cytokines with the involvement of inflammation-related miRs in circulating immune cells of hypertensive-medicated patients with type 2 diabetes and supports beneficial immunomodulatory effect
32	Type 2 diabetes patients (66)	Capsule; 45 days	1 g/day; 500 mg/day twice daily	↓ Systolic blood pressure, ↓ fasting blood glucose, ↓ HbA_{1c}, ↓ insulin and ↓ insulin resistance ↑ HDL level
33,34	Type 2 diabetes patients (62)	Capsule; 3 months	250 mg/day; single	↓ HbA_{1c}, ↓ systolic blood pressure, ↓ body weight lipid profile and total protein in type 2 diabetes
35	Type 2 diabetes patients (19)	Capsule; 4 weeks	10 mg/day; 5 mg/day twice daily	↓ Insulin resistance, ↓ urinary ortho-tyrosine excretion; ↑ pAkt:Akt ration in platelets

Akt = protein kinase B; HbA_{1c} = glycated haemoglobin; HDL = high-density lipoprotein; miRs = microRNAs; pAkt = phosphorylated protein kinase B; RSV = resveratrol.

biological mechanisms at the cellular and extracellular levels that have been identified as having chemopreventive properties with respect to a significant number of chronic diseases, particularly those commonly associated with ageing and obesity.[16,17] Moreover, resveratrol's ability to activate sirtuins 1–7 (SIRT1–7), particularly SIRT1, a prolific, highly conserved NAD+-dependent lysine deacylase,[18] either indirectly via the intermediary coenzyme NAD+ at low doses, or directly at high doses, identifies this molecule as a prime candidate for adoption as a potential pharmacological agent targeted towards the cellular and extra-cellular dysfunctions and abnormalities underlying type 2 diabetes, obesity and other mitocondrial-mediated metabolic pathologies. Given the low level of patient compliance with behaviour-modification-based type 2 diabetes remedial strategies, such as diet and regular vigorous physical exercise,[19] clearly there exists a mandate for development of non-toxic, efficacious and affordable treatments to stem the accelerating escalation in the incidence of this disease worldwide.

Table 1 summarises some of the recent cell culture and animal studies that have been undertaken on the benefits of treating diabetes and its accompanying complications with resveratrol. The data clearly reveal several clinically relevant aspects. Among the major findings are that chronic resveratrol administration provides a safe approach to reduce chronic inflammatory properties associated with obesity while restoring insulin responsiveness in visceral white adipose tissue (WAT),[20] attenuates the inflammatory injury of the vascular wall,[21] attenuates methylglyoxal (MG)-induced oxidative stress in pancreatic cells with increase in insulin levels,[22] reduces oxidative-stress obesity pathologies and improves glucose tolerance.[23] Resveratrol attenuates β-cell loss, inhibits oxidative stress, improves glucose tolerance,[24] decreases plasma glucose levels, potentiates lipid metabolism, improves β-cell mass lipid content and diminishes oxidative stress, in addition to promoting SIRT1 expression. Furthermore, resveratrol effectively reduces reactive oxidative stress (ROS) and maintains mitochondrial function and enhances mitogenesis via SIRT1 activation. This extensive constellation of actions elucidate resveratrol's promise as a pharmacological agent to treat diabetic nephropathy,[14–26] protect against hepatic and renal damage induced by oxidative stress,[27] mediate high-glucose (HG)-induced superoxide production, modulate FOXO3a expression and protect p47phox monocytes against oxidative stress in HG conditions.[28] Resveratrol restores the diminished expression of nephrin in the kidneys of people with diabetes to normal levels and decreases plasma glucose levels, lipid metabolism, β-cell mass lipid content and oxidative stress damage, in addition to promoting SIRT1 expression islets. Resveratrol could thus be a new therapeutic agent for retarding the progression of early diabetic nephropathy.[29] It also shows hepatocyte-protection activity through the attenuation of the markers of hyperglycaemia-mediated oxidative stress without affecting normal cellular function and structural integrity.[30]

Table 2 summarises the clinical studies that have been carried out so far on the benefits of resveratrol in treating diabetes and its accompanying complications, as well as studies in obese patients who are at risk of type 2 diabetes. The data reveal that long-term supplementation with grape extract containing a small quantity of resveratrol has a beneficial immunomodulatory effect on hypertensive patients with type 2 diabetes.[31] Resveratrol supplementation has benefits in type 2 diabetes patients, including lowering of blood glucose, glycated haemoglobin (HbA_{1c}), insulin levels, insulin resistance and the improvement of HDL levels and fasting blood glucose.[32] Resveratrol supplementation has also been shown to reduce body weight, lower systolic blood pressure and to beneficially moderate total cholesterol, HDL:LDL ratios and to lower triglycerides and urea nitrogen. It also significantly increases the levels of endogenous antioxidant enzymes,[33,34] lowers insulin resistance and urinary ortho-tyrosine excretion and increases the platelet ratio of phosphorylated protein kinase B (pAkt) protein to kinase B (Akt) protein (pAkt:Akt). Akt is a serine-threonine kinase that mediates a number of cellular processes including vascular endothelial growth factor (VEGF) expression and insulin sensitivity by improving insulin signalling. Resveratrol is also associated with improvements in glycaemic and lipid parameters in obese individuals.[32–35]

Resveratrol modifies adipokine expression via inhibition of the inflammatory response, thereby reducing insulin resistance by activating SIRT1, which is the principal modulator that produces a beneficial effect on glucose homeostasis and insulin sensitivity.[36] It also restores endogenous antioxidant manganese superoxide dismutase (MnSOD) function independent of sirtuin activation.[12] Resveratrol appears to lower insulin resistance via the inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a redox-sensitive transcription factor and peroxisome proliferator-activated receptor gamma (PPARγ). Resveratrol's inhibition of NF-κB operates to downregulate the pancreatic β-cell apoptotic pathway resulting in improved β-cell survival,[37] and exhibits an antioxidant independent protective effect against diabetic neuropathy.[38]

Resveratrol increases NAD+ levels via upregulation of the NAD+ synthetic enzyme nicotinamide mononucleotide adenyltransferease.[39] Maintaining physiological NAD+ levels is essential for normal cellular

respiratory functions, and may constitute an important mechanism by which resveratrol modulates metabolic homeostasis and supports mitochondrial biogenesis.[40]

At moderate to high concentrations, resveratrol is an inhibitor of the mammalian target of rapamycin complex 1 (mTORC1) also known as FK506 binding protein, 12-rapamycin associated protein 1 and FRAP1.[41] Although the full range of effects of mTORC1 activity on adult metabolic disorders, including type 2 diabetes, is an exceedingly complex matter, it does appear, based on some *in vivo* evidence, that inhibition of mTORC1 plays a constitutive role in the beneficial attenuation of insulin resistance and diabetic nephropathy.[42,43]

Resveratrol and Cardiovascular Protection

Resveratrol, as a component, is believed to be responsible for the 'French Paradox', namely low mortality due to coronary heart disease as a result of moderate consumption of red wine by the French. Both the preclinical and clinical data, shown in *Tables 1* and *2*, as well as a large and growing body of additional *in vitro* and *in vivo* evidence, clearly reinforce this theory and suggest that resveratrol also plays a crucial role in cardiovascular disease (CVD) protection.[44,45] Wine also contains a relatively high level of non-stilbene phytochemicals, which are thought to potentiate the beverage's chemo-preventative properties in terms of CVD and other chronic diseases often associated with ageing and obesity in the general population.

Resveratrol and Diabetic Retinopathy

One of the more devastating pathophysiological sequelae of protracted glycaemic instability is the degradation of vision resulting from acute retinopathy. Retinopathy is one of the leading causes of blindness among adult populations worldwide.[46] The condition is characterised by the propagation of abnormal, profuse microvascularity and concurrent capillary fibrosis, which precipitate occulsion of the retina and optic disc. Overexpression of the angiogenesis regulator, VEGF, has been implicated as a major promoter in the proliferation of these dysfuntional vascular structures. Aberrant angiogenesis and macular oedema are cofactors principally responsible for the progressive loss of visual acuity, which can advance in a relatively brief time to blindness.[47,48] Inflammation also appears to play a significant contributory role in the development of retinal pathologies.[49]

Resveratrol is a non-invasive, multi-modal, chemo-preventative agent with the ability to prevent or impede the onset and development of diabetic retinopathy. Resveratrol attenuates the progression of retinopathy by suppressing angiogenesis,[50,51] inhibiting inflammation[52] and downregulating neuronal apoptosis.[53] In its capacity as a potent small molecule antioxidant, resveratrol counters oxidative stress.[54] Finally, this phytochemical operates to block the vascular lesions as well as the endothelial hyperpermeabiity, which cause capillary leakage and loss of pericytes.[55,56] Resveratrol's inhibition of VEGF appears to be one of the main modalities via which the molecule exerts a potentially therapeutic reduction of a number of the principal initiators and mediators of retinopathy.[57]

Safety and Tolerability of Resveratrol

Resveratrol is well tolerated in both young and older humans, and does not cause any serious adverse effects in subjects on doses of up to 5 g per day. Neither have toxicity or adverse effects been observed at higher doses; however, limited data exist upon which to base any definitive conclusions relative to doses higher than 5 g per day. It is safe as revealed by lack of serious adverse events detected by clinical, biochemical and haematological indices during intervention and a two-week follow up.[58,59] Nearly 90 % of all reported adverse effects can be classified as grades 1 or 2 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), with many being mild and transient.

Conclusion

Resveratrol has been shown to be effective in modulating blood glucose levels, decreasing insulin resistance, inhibiting chronic inflammation, improving blood lipid profiles, attenuating diabetic hypertension and countering odixative stress. Resveratrol may also play a role in the prevention or retardation of diabetes-related comorbidities and complications.

The biological processes, signalling pathways, proteomics and biochemical modalities via which resveratrol operates have been extensively investigated and are relatively well identified and defined. The therapeutic effects of this phytoalexin appear to include a significant improvement of an array of relevant metrics including improvement of insulin sensitivity, modulation of blood glucose levels, cardiovascular protection, attenuation of diabetic hypertension, inhibition of oxidative stress and chronic inflammation, improvement of blood lipid profiles and support of retinal health.

Major challenges remain concerning the safety and efficacy of chronic resveratrol administration as well as optimal doses, due to the well-known hormetic actions of the compound, which demonstrates protective properties at lower doses and detrimental effects at higher doses. Furthermore, although resveratrol administration shows beneficial effects, its molecular mechanisms of action are only partially known. It is well known that resveratrol is rapidly metabolised and conjugated with glucuronic acid and sulphate due to the action of uridine 5'-diphospho-glucuronosyltransferase (UDP-glucuronosyl-transferase) and sulphotransferases and these are the major circulating forms of this molecule, both in humans and experimental models. However, the biological activity of these active metabolites needs to be elucidated fully. Indeed, the majority of *in vitro* available data have been obtained by employing the unconjugated form of resveratrol, at concentrations that largely exceed those that can be reached *in vivo*, at both plasma and tissue levels.

Additional clinical trials are required to better elucidate the optimum dosages, delivery mechanisms and optimally efficacious drug–resveratrol combinations, as well as the qualitative nature of the potential long-term benefits associated with this compound as a nutraceutical adjunct to existing diabetes treatment stratagems.

Given the absence of observed adverse effects attributed to this compound after more than 10 years of investigation, coupled with clinical evidence of its efficacy and safety, the use of resveratrol as a nutritional supplement is well justified in patients with type 2 diabetes. A case now exists to support the enhancement of existing national healthcare systems' diabetes prevention and treatment programmes via augmentation with a resveratrol-based nutraceutical component. Healthcare practitioners should be aware of the potential benefits of resveratrol as an effective adjunct nutraceutical enhancement to patients with diabetes pharmaceutical and lifestyle-focused prevention and treatment stratagems. ■

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