Advanced Pharmaceutical Bulletin, **2011**, 1(2), 81-86
doi: 10.5681/apb.2011.012
http://apb.tbzmed.ac.ir/

Comparison of effect of resveratrol and vanadium on diabetes related dyslipidemia and hyperglycemia in streptozotocin induced diabetic rats

Majid Mohamad Shahi[1], Fatemeh Haidari[1], Mohamad Reza shiri[2*]

[1]*Nutrition Research Center, Ahvaz Jundishapour University of Medical Sciences, Ahvaz, Iran*

[2]*Diabetes Research Center, Ahvaz Jundishapour University of Medical Sciences, Ahvaz, Iran.*

ARTICLE INFO

Article Type:
Research Article

Article History:
Received: 28 July 2011
Accepted: 24 Nov 2011
ePublished: 15 Dec 2011

Keywords:
Resveratrol
Vanadate
Diabetes
Dyslipidemia
Hyperglycemia

ABSTRACT

Purpose: Resveratrol a natural polyphenolicstilbene derivative has wide variety of biological activities. There is also a large body of evidence demonstrating positive effect of resveratrol in treatment of various metabolic complications including metabolic syndrome, obesity, diabetes and dyslipidemia in adults. The purpose of this study was to investigate anti-hyperglycemic and anti-dyslipidemic effects of resveratrol. ***Methods:*** We used 40 diabetic streptozotocinWistar rats. Rats were randomly divided into 5 treatment groups (n=8 in each) including normal control, normal treated with resveratrol, diabetic control, diabetic treated with vanadium , diabetic treated with resveratrol . Resveratrol (25 mg/kgbw) and vanadate (0.2 mg/kgbw) was orally gavaged for 40 days and blood samples were directly collected from heart. ***Results:*** Diabetic rats treated with resveratrol in comparison to control diabetic rats demonstrated a significant (p = 0.001) decline in serum glucose concentration, and high plasma concentrations of total cholesterol and LDL-c were reduced (p = 0.031, p = 0.004 respectively). Furthermore, body weight loss trend that observed in diabetic rats alleviated by resveratrol and vanadate. However triglyceride, VLDL-c and HDL-c levels did not changed significantly. ***Conclusion:*** In conclusion Resveratrol ameliorated dyslipidemia and hyperglycemia in diabetic rats. However further investigations in peculiar human studies are required.

Introduction

Diabetes mellitus, characterized by chronic hyperglycemia and dyslipidemia, is a deleterious metabolic complication and is estimated to afflict 5-7% of the world population.[1]Hyperglycemia and dyslipidemia are the two debilitating concomitants of diabetes which play a key role in creating the secondary disorders such as macro and micro vascular complications.[2]

The Framingham Heart Study found that dyslipidemia was very common in adults with diabetes, characterized by high levels of triglyceride and total cholesterol and low levels of HDL-C.[3] This pattern befalls commonly in both type 1 and type 2 diabetes mellitus, reflecting the basic pathogenic state of insulin secretion insufficiency or lack of effective action due to insulin resistance. Moreover plasma lipoprotein levels reflect increased number not only of LDL, but also of IDL and VLDL particles.[4] This general pattern was shown to be strongly related to the severity of atherosclerosis.[5] A majority of diabetic patients suffer from dyslipidemia that is related to insulin resistance. Dyslipidemia precedes the clinical diagnosis of diabetes by years as a part of diabetic complications and metabolic syndrome and it is so deeply involved in its pathogenesis.[6] Epidemiological investigations demonstrated that increased levels of LDL cholesterol and non-HDL cholesterol, besides decreased level of HDL cholesterol, were strong risk factors for atherosclerosis in diabetic patient.[7-9] Chronic hyperglycemia can also lead to dysfunction and failure of various organs, including the heart, kidneys, eyes, nerves, and blood vessels, and creates a huge economic burden pertaining to the management of diabetic complications.[10]

The current medical nutrition therapy of diabetes mellitus includes diet, exercise, various oral antidiabetic drugs and insulin therapy.[11] The modern oral hypoglycemic agents (such as biguanides, sulphonylureas and α-glucosidase inhibitors), and insulin have characteristic of adverse effects, including hypoglycemia, dyslipidemia, lactic acidosis, hepatotoxicity, hypertension, frequent diarrhea, and hypercoagulability other than economic expenses.[12]

***Corresponding author:** Mohamad Reza Shiri (MS), Tel: +98 (611) 3720299, Fax: +98 (411) 3720299, E-mail: nutshiri@gmail.com

Therefore, concerning the high prevalence of diabetes in the worldwide and mentioned side effects of its current drugs, there is a necessity for novel therapies which are effective with minimal adverse events.[13] Herbal medicines and their active compounds possessed these properties. Resveratrol (3, 5, 4-trihydroxystilbene), which have been getting increasing attention lately, is one of the phytochemicalsfound particularly in grapes and mulberries.[14]Approximately 5-10% of the biomass of grape skins accounts for resveratrol.[15] Resveratrol is also a component of Ko-jo-kon, an oriental folk medicine used to treat lipid disorders.[10] The *in vitro* and *in vivo* studies confirmed the protective properties of resveratrol and its accumulation in red wine had led the scientists to consider that this is the competent substance for the ''French paradox''.[16] Additionally, resveratrol has been reported to involve in numerous cellular responses including cell cycle arrest, apoptosis and differentiation, and has anti-inflammatory, anti-cancer, anti-leukemic, antiviral, and neuroprotective properties.[16-20] Several important human enzymes that are involved in carcinogenesis could be inhibited by resveratrol, including ribonucleotidereductase and cytochrome P450.[21,22] The antioxidant role of resveratrol also has been reported which can reduce the risk of undergoing cardiovascular disease (CVD), likely through its prevention of low density lipoprotein oxidation and modulation of lipid metabolism, as well as inhibition of eicosanoid synthesis and platelet aggregation.[23-25] Since then, it has been investigated as an effective treatment for metabolic complications.[26]
It is also speculated that resveratrol could be effective in controlling of hyperglycemia and dyslipidemia in diabetes. However, no systematic studies exist in the literature on the effect of resveratrol in experimental models of diabetic hyperglycemia and dyslipidemia. Therefore, the present study was aimed to investigate the antihyperglycemic and antihyperlipidemic effects of resveratrol in streptozotocin induced diabetic rats.

Materials and methods

Chemicals

Resveratrol was purchased from Nutrabio Co. (USA) and streptozotocin (STZ) was procured from Sigma-Aldrich Chemical Co. (Steinheim, Germany). All other chemicals used in this study were of the analytical grade, preserved under standard situation and were provided from standard commercial suppliers.

Experimental animals

Male albino rats of Wistar strain weighing 200-220 g and 6 week-old were chosen as animal model for this study, obtained from Physiology Research Center of Ahvaz JundiShapour University of Medical Sciences and maintained in clean, polypropylene cages and fed ad libitum standard chow and water. Before experiment initiation, the rats were quarantined for 2 weeks in order to environmental and trainer handling acclimatization. All animal manipulations were performed in the morning to minimize the effects of circadian rhythm. The animal experimental design was precisely in accordance with the ethical norms approved by Animal Care and Use Committee of Ahvaz JundiShapour University of Medical Sciences, Ahvaz, Iran.

Induction of experimental diabetes

Diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ) (50 mg/kg body weight) dissolved in 0.1 M of cold citrate buffer (pH= 4.5), after rats were 12 h fasted.[27] Due to capability of STZ to induce fatal hypoglycemia as a result of massive pancreatic insulin release, the rats were supported for the next 24 h with 10% glucose solution after STZ administration to hinder hypoglycemia. Neither death nor any other contrary effect was observed. After a week for the evolution and exacerbation of diabetes, rats with fasting blood glucose concentration over than 250 mg/dl were selected for the experimental model of diabetes.

Experimental design

Forty rats were divided randomly into five groups (n=8) and treated as follows:
Group 1: Normal control rats (N); Group 2: Normal rats treated with resveratrol (25 mg/kgbw/d) (N +RV); Group 3: Diabetic rats (DM); Group 4: Diabetic rats treated with resveratrol (25 mg/kg bw/d) (DM + RV); Group 5: Diabetic rats treated with vanadate (0.2 mg/kgbw/d) as positive control (DM + VA). Resveratrol and vanadate was given by oral gavage and the treatments lasted for 40 consecutive days. Food intake and body weight of the animals were monitored twice a week. At the end of the study, the rats were fasted overnight with free access to water, anaesthetized with light ether and sacrificed. Blood samples were directly collected from heart. Serum glucose, triglycerides (TG), total cholesterol (TC) and high density lipoprotein (HDL) levels were determined enzymatically using standard methods to confirm the anti-hyperglycemic and anti-dyslipidemic properties of resveratrol. Low density lipoprotein (LDL) level was calculated by Friedwald formula.

Statistical analysis

The results were expressed as mean ± SD. The statistical significance was evaluated by independent sample t-test and one-way analysis of variance (ANOVA) using the SPSS (version 17.0) program followed by Tuky. Values were considered statistically significant when $p < 0.05$.

Results

Table 1 illustrates the effects of resveratrol on serum glucose levels in experimental groups. As it is shown in the table 1, oral administration of 25 mg/kg resveratrol in normal rats did not change glucose levels

significantly in comparison to the normal control group (p=0.365).

The streptozotocin induced diabetic rats showed a significantly higher serum glucose levels than those of normalcontrol rats, whereas the elevated serum glucose level was significantly reduced in diabetic rats orally administrated with 5 mg/kg resveratrol (p = 0.001). In Vanadate treated diabetic rats (with a dose of 0.2 mg/kgbw/d), reduced glycemia occurred after 40 days of experiment in comparison to STZ induced diabetic control rats (p = 0.000).

The effects of oral administration of resveratrol on serum levels of TG, TC, LDL-C and HDL-C are shown in Figure 1, respectively. As it is obvious in the figure 1, diabetic control group had significantly higher concentrations of triglyceride, total cholesterol and LDL-C, as well as, lower concentration of HDL-C than those of normal control group (p<0.05). The present data also indicated that the serum concentrations of total cholesterol and LDL-C were decreased significantly (p = 0.031, p = 0.004, respectively) after oral administration of resveratrol in diabetic rats but triglyceride and HDL-C levels did not changed significantly when compared to diabetic control group (p> 0.05). In normal group, the effect of resveratrol (25 mg/kg) on lipid profiles was not statistically significant.

In addition no significant change in triglyceride and cholesterol concentration was observed in Vanadate treated rats in comparison to diabetic control group (p>0.05) whereas LDL-c decreased and HDL-c increased significantly (p =0.032 and p=0.041 respectively).

Figure 2 depicts body weight changes in different groups during present study. Diabetes induction in DM group caused deleterious inhibition of normal weight gain trend that was proceeding in N and N + RV groups. Moreover Resveratrol and Vanadate administration ameliorated consequent body weight loss of STZ induced diabetes.

Table 1. Effect of the orally administered resveratroland vanadate on serum glucose levels in experimental groups [a]

Groups	glucose (mg/dl)	P_a	P_b	P_c	P_d
Normal control	122.1±69.9	_	0.365	0.000	0.052
Normal + Resveratrol(25mg/kg)	159.8±42.8	0.365	_	0.000	0.310
Diabetic control	367±154.7	0.000	0.000	_	0.001
Diabetic + Resveratrol(25mg/kg)	202.1±60	0.052	0.310	0.001	_
Diabetic + vanadate(0.2mg/kg)	174.1±28.5	0.215	0.738	0.000	0.500

[a]All values are expressed as mean ± SD (n=8). One way ANOVA test was used for statistical significance assessment.
P_a indicates P value between Normal control and remaining groups.
P_b indicates P value between Normal resveratrol treated and remaining groups.
P_c indicates P value between diabetic control and remaining groups.
P_d indicates P value between diabetic resveratrol treated diabetic and remaining rats.

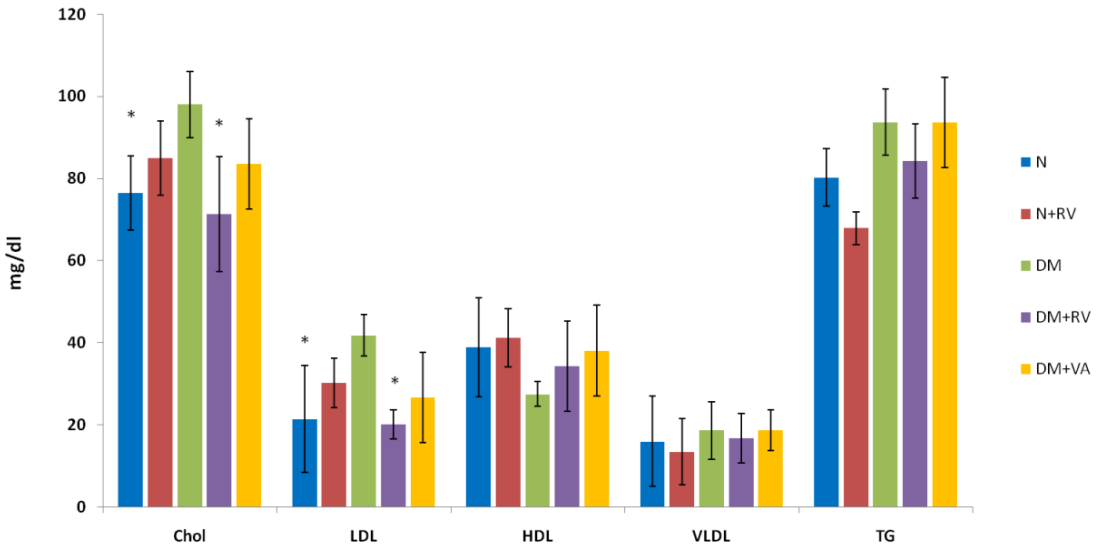

Figure 1. Effect of the orally administered resveratrol and vanadate on serum levels of lipids in experimental groups
Data shown as mean±SD
* means p<0.05 in comparison with diabetic control group

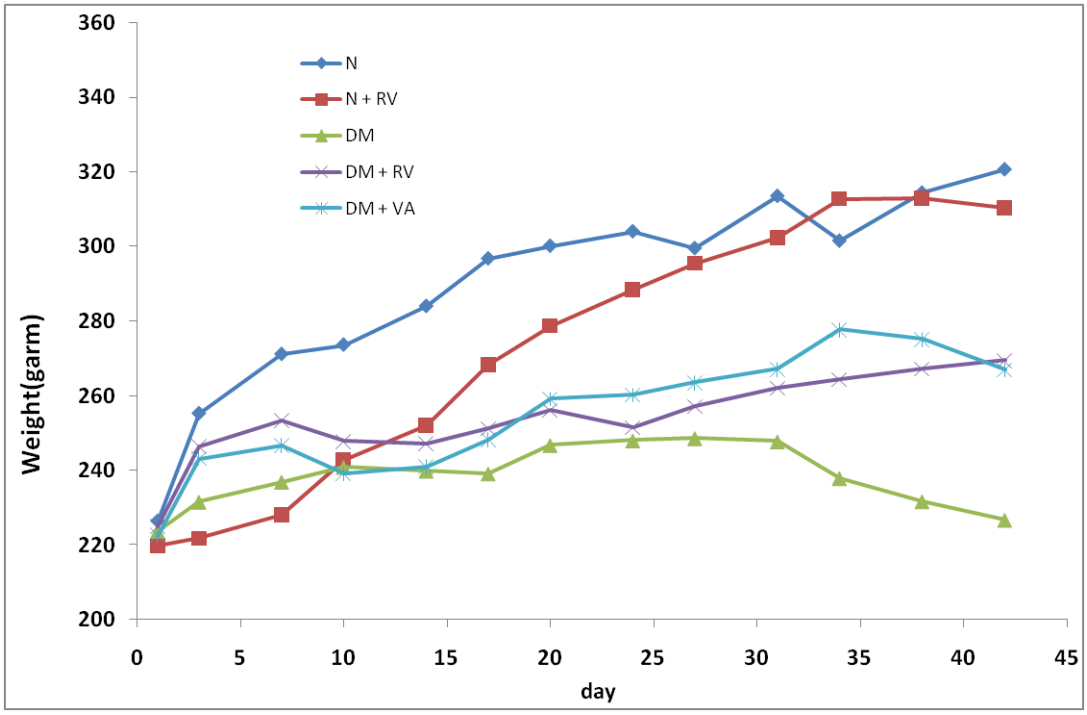

Figure 2. Effect of orally administered resveratrol and vanadate on body weight changes in experimental groups

Discussion

Diabetes mellitus is a metabolic disturbance by a characteristic of hyperglycemia resulting from defects in insulin secretion, insulin action or both[1], and is also concomitant with disorders in glucose and lipid metabolism.[2] Numerous herbal medicines have been reported to have hypoglycemic and hypolipidemic impacts in diabetes. Resveratrol is a substance largely found in the skins of red grapes and it has gained scientists' interest because of having many advantageous effects on promoting health and disease. Therefore, in this study we investigated its potentiality to improve hyperglycemia and hyperlipidemia in STZ-induced diabetic rats.

The elevated blood glucose level in diabetic rats was significantly reduced in resveratrol treated group. These findingshave been corroborated by Miuraet al. research[28], suggesting possible recovery mechanism of resveratrol on the remnant β-cells functionality and partially improved dyslipidemia in experimental diabetic animals.

Diabetes is associated with profound complications of plasma lipid and lipoprotein profile. Many other researchers have reported controversial effect of resveratrol on lipid profile in experimental animals.Rivera et al. reported triglyceride lowering properties of resveratrol with a dosage of 10 mg/kg administered intragastrically, for 8 weeks of study, while this study demonstrated no significant reduction in triglyceride level. It has been proposed that some favourable effects of resveratrol result from phosphorylation/activation of 5′-AMP-activated protein kinase (AMPK). AMPK inhibits acetyl-CoA carboxylase elevating oxidation of fatty acids when activated and suppress their synthesis. A considerable increase in AMPK activity was reported in obese Zucker rats too.[29] In another study Do et al. examined long term effect of resveratrol supplementation on suppression of atherogenic lesion formation and cholesterol synthesis and LDL-C oxidation in apo E-deficient mice. The concentration of LDL-C and total-cholesterol was significantly decreased in the resveratrol treated groups compare to the control group. Besides the plasma HDL-C concentration was significantly augmented.[30] About the mechanism Kim S. and Do G**.**suggested that resveratrol may hinder adipogenesis plausibly through suppression of the galanin-mediated signaling pathway, pro-inflammatory signaling cascades and cytokine production in adipose tissue of mice fed a high fat diet.[31]However in our study HDL-C did not change significantly despite reduction in LDL-C and total-cholesterol levels.

Interestingly, in our studies, in spite of the fact that body weight loss occurred in diabetes induced group, resveratrol alleviated detrimental effects, besides facilitating weight gain. However other studies reported that resveratrol reduce body weight gain in rats[32] and mice[33]fed a high-fat diet (HFD). Lagouge et al. indicated that 0.4% resveratrol supplementation for 15 weeks significantly decreases body weight gain and visceral fat-pad weights in HFD-fed mice.The mechanism by means of that resveratrol exerts positive effects supposedly is related to induction of genes expression for oxidative phosphorylation. Multiple data imply that activation of an NAD^+-dependent protein deacetylase, Sirt1, is pivotal for resveratrol action.[33] Nevertheless, in the other experiments this effect was not observed.[34-35] Resveratrol (10 mg/kg body weight;

administered for 8 weeks) suggested not to be efficient in reducing body weight gain in obese Zucker rats.[29]

At the end our results show that daily chronic administration of 5 mg/kgbw of resveratrol ameliorated dyslipidemia and hyperglycemia in the experimental model diabetic rats. Our results approximately certify the beneficial effects of resveratrol in the treatment of modifications involved in metabolic disturbances including glucose, LDL-C and total cholesterol. [29, 36,37] Nevertheless, there are other investigations suggesting no positive effect of resveratrol on dyslipidemia and hyperglycemia.[38]

In conclusion, since resveratrol possesses significant hypoglycemic potentiality, it may be interceded on the treatment of diabetes. Studies in the last few years infer that resveratrol functions numerous beneficial effects in metabolic disturbances and diabetes, thereby may be beneficial in prevention and treatment of many other diseases. However, further studies are required to distinct discrepancies in the literature. Besides, despite evidences representing promising effects in rodents, human studies are deficient and either therapeutic or preventive values of resveratrol in humans still remain to be elucidated.

Acknowledgement

This paper is issued from the thesis of Mohammad Reza Shiri, and financial support was provided by Diabetes Research Center, Ahvaz Jundishapour University of Medical Sciences.

Conflict of interest

The authors declare no conflict of interests.

References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; 27:1047-1053.
2. Kavey RE, Allada V, Daniels SR, Hayman LL, McCrindle BW, Newburger JW, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation* 2006; 114:2710-2738.
3. Garg A, Grundy SM. Therapeutic perspectives in hyperlipidemic patients with diabetes mellitus. *J Diabet Complications* 1990; 4:72-74.
4. Taskinen MR. Diabetic dyslipidaemia: from basic research to clinical practice. *Diabetologia* 2003; 46:733-749.
5. Tkac I, Kimball BP, Lewis G, Uffelman K, Steiner G. The severity of coronary atherosclerosis in type 2 diabetes mellitus is related to the number of circulating triglyceride-rich lipoprotein particles. *Arterioscler Thromb Vasc Biol* 1997;17:3633-3638.
6. Shafrir E, Raz I. Diabetes: mellitus or lipidus. *Diabetologia* 2003 ; 46:433-440.
7. Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). *BMJ* 1998; 316:823-828.
8. Lehto S, Ronnemaa T, Haffner SM, Pyorala K, Kallio V, Laakso M. Dyslipidemia and hyperglycemia predict coronary heart disease events in middle-aged patients with NIDDM. *Diabetes* 1997; 46:1354-1359.
9. Howard BV, Robbins DC, Sievers ML, Lee ET, Rhoades D, Devereux RB, et al. LDL cholesterol as a strong predictor of coronary heart disease in diabetic individuals with insulin resistance and low LDL: The Strong Heart Study. *Arterioscler Thromb Vasc Biol* 2000; 20:830-835.
10. Schuster DP, Duvuuri V. Diabetes mellitus. *Clin Podiatr Med Surg* 2002;19:79-107.
11. Krentz AJ, Bailey CJ. Oral antidiabetic agents: current role in type 2 diabetes mellitus. *Drugs* 2005; 65:385-411.
12. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: update regarding thiazolidinediones: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2008; 31:173-175.
13. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* 2006; 444:840-846.
14. Brisdelli F, D'Andrea G, Bozzi A. Resveratrol: a natural polyphenol with multiple chemopreventive properties. *Curr Drug Metab* 2009;10:530-546.
15. Stewart JR, Artime MC, O'Brian CA. Resveratrol: a candidate nutritional substance for prostate cancer prevention. *J Nutr* 2003;133:2440S-2443S.
16. Renaud S, de Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. *Lancet* 1992; 339:1523-1526.
17. Joe AK, Liu H, Suzui M, Vural ME, Xiao D, Weinstein IB. Resveratrol induces growth inhibition, S-phase arrest, apoptosis, and changes in biomarker expression in several human cancer cell lines. *Clin Cancer Res* 2002;8:893-903.
18. Bhat KPL, Kosmeder JW 2nd, Pezzuto JM. Biological effects of resveratrol. *Antioxid Redox Signal* 2001;3:1041-1064.
19. Virgili M, Contestabile A. Partial neuroprotection of in vivo excitotoxic brain damage by chronic

administration of the red wine antioxidant agent, trans-resveratrol in rats. *Neurosci Lett* 2000;281:123-126.
20. Gao X, Xu YX, Divine G, Janakiraman N, Chapman RA, Gautam SC. Disparate in vitro and in vivo antileukemic effects of resveratrol, a natural polyphenolic compound found in grapes. *J Nutr* 2002;132:2076-2081.
21. Das DK, Sato M, Ray PS, Maulik G, Engelman RM, Bertelli AA, et al. Cardioprotection of red wine: role of polyphenolic antioxidants. *Drugs Exp Clin Res* 1999;25:115-120.
22. Frankel EN, Waterhouse AL, Kinsella JE. Inhibition of human LDL oxidation by resveratrol. *Lancet* 1993;341:1103-1104.
23. Pace-Asciak CR, Hahn S, Diamandis EP, Soleas G, Goldberg DM. The red wine phenolics trans-resveratrol and quercetin block human platelet aggregation and eicosanoid synthesis: implications for protection against coronary heart disease. *Clin Chim Acta* 1995;235:207-219.
24. Fontecave M, Lepoivre M, Elleingand E, Gerez C, Guittet O. Resveratrol, a remarkable inhibitor of ribonucleotide reductase. *FEBS Lett* 1998;421:277-279.
25. Chun YJ, Kim MY, Guengerich FP. Resveratrol is a selective human cytochrome P450 1A1 inhibitor. Biochem Biophys Res Commun 1999;262:20-24.
26. Thulesen J, Orskov C, Holst JJ, Poulsen SS. Short-term insulin treatment prevents the diabetogenic action of streptozotocin in rats. *Endocrinology* 1997;138:62-68.
27. Rakieten N, Rakieten ML, Nadkarni MV. Studies on the diabetogenic action of streptozotocin (NSC-37917). Cancer Chemother Rep 1963;29:91-98.
28. Miura D, Miura Y, Yagasaki K. Hypolipidemic action of dietary resveratrol, a phytoalexin in grapes and red wine, in hepatoma-bearing rats. *Life Sci* 2003;73:1393-1400.
29. Rivera L, Moron R, Zarzuelo A, Galisteo M. Long-term resveratrol administration reduces metabolic disturbances and lowers blood pressure in obese Zucker rats. *Biochem Pharmacol* 2009;77:1053-1063.
30. Do GM, Kwon EY, Kim HJ, Jeon SM, Ha TY, Park T, et al. Long-term effects of resveratrol supplementation on suppression of atherogenic lesion formation and cholesterol synthesis in apo E-deficient mice. *Biochem Biophys Res Commun* 2008;374:55-59.
31. Kim S, Jin Y, Choi Y, Park T. Resveratrol exerts anti-obesity effects via mechanisms involving down-regulation of adipogenic and inflammatory processes in mice. *Biochem Pharmacol* 2011;81:1343-1351.
32. Aubin MC, Lajoie C, Clement R, Gosselin H, Calderone A, Perrault LP. Female rats fed a high-fat diet were associated with vascular dysfunction and cardiac fibrosis in the absence of overt obesity and hyperlipidemia: therapeutic potential of resveratrol. *J Pharmacol Exp Ther* 2008;325:961-968.
33. Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, et al. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. *Cell* 2006;127:1109-1122.
34. Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, Kalra A, et al. Resveratrol improves health and survival of mice on a high-calorie diet. *Nature* 2006;444:337-342.
35. Rocha KK, Souza GA, Ebaid GX, Seiva FR, Cataneo AC, Novelli EL. Resveratrol toxicity: effects on risk factors for atherosclerosis and hepatic oxidative stress in standard and high-fat diets. *Food Chem Toxicol* 2009;47:1362-1367.
36. Silan C. The effects of chronic resveratrol treatment on vascular responsiveness of streptozotocin-induced diabetic rats. *Biol Pharm Bull* 2008;31:897-902.
37. Palsamy P, Subramanian S. Modulatory effects of resveratrol on attenuating the key enzymes activities of carbohydrate metabolism in streptozotocin-nicotinamide-induced diabetic rats. *Chem Biol Interact* 2009;179:356-362.
38. Schmatz R, Schetinger MR, Spanevello RM, Mazzanti CM, Stefanello N, Maldonado PA, et al. Effects of resveratrol on nucleotide degrading enzymes in streptozotocin-induced diabetic rats. *Life Sci* 2009 ;84:345-350.

