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Antihyperglycemic effect of short term resveratrol supplementation in type II diabetes patients

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ABSTRACT

To study the effectiveness of resveratrol in decreasing blood glucose in the presence of standard antidiabetic therapy in subjects with type 2 diabetes. There was 1 subject dropout from each group in between the trail. At the end of the trail, there were 20 and 20 subjects in control and intervention group, respectively. There were trends towards a decrease, but no notable changes were noticed in triglycerides, cholesterol, and LDL levels with resveratrol supplementation, while a notable increase in LDL levels was noticed in the control group. Metformin, glibenclamide, and insulin are all known to have favorable or no effect on the lipid profiles therefore, other independent factors may have given to the noticed increase in the control group. Subgroup analyses presented that resveratrol may have an added effect when used in union with glibenclamide and metformin. This is a pilot study which study the antidiabetic effects of resveratrol over the short term, and only one dose of resveratrol was tested. There was no followup to check the metabolic parameters of the patients after the resveratrol wash-out period. The study lacks the enquiring of cellular mechanisms underlying the antidiabetic effects of resveratrol. Lage no.of toxicological screening was not done on subjects to confirm the well being of resveratrol administration, and the safety of administering 1 g dose of resveratrol over the long term has not been established. The present trail bear the strong antidiabetic effect of resveratrol documented in numerous animal studies, as well as the effects evaluated in the human studies. It also bears the case for resveratrol supplementation over a short term. Nevertheless, well-designed clinical trials with resveratrol supplementation in a larger T2DM population and over a longer duration are required to recommend the use of resveratrol independently or as an adjunct in diabetic population.

Keywords: Glibenclamide, Metformin, Triglycerides, Resveratrol

INTRODUCTION

Type 2 diabetes maily occurs as a fining of obesity and not enough exercise.[1] Some people are more genetically at threat than others.[2] Type 2 diabetes makes up about 90% of cases of diabetes, with the other 10% due primarily to diabetes mellitus type 1 and gestational diabetes.[1] In diabetes mellitus type 1 there is a complete lack of insulin due to breakdown of islet cells in the pancreas.[3] Diagnosis of diabetes is by blood tests such as fasting plasma glucose, oral glucose tolerance test, or A1C.[4] Type 2 diabetes is partly curable by staying a normal weight, exercising regularly, and eating properly. Therapy includes exercise and dietary changes. [5] If blood sugar levels are not sufficiently lowered, the medication metformin is typically adviced.[6][7] Many people may require insulin injections.[8] In those on insulin, regularly checking blood sugar levels is recomonded; however, this may not be needed in those taking pills.[9] Bariatric surgery often improves diabetes in those who are obese.[10][11]. Rates of type 2 diabetes have increased markedly since 1960 in parallel with obesity.[12] As of 2013 there were approximately 368 million people diagnosed with the disease equated to around 30 million in 1985.[13][14] Typically it starts in middle or older age,[15] although rates of type 2 diabetes are increasing in young people.[16][17] Type 2 diabetes is related with a ten-year-shorter life expectancy.[18] Diabetes was one of the first diseases narrated.[19] The importance of insulin in the disease was resolved in the 1920s.[20]

To study the effectiveness of shorterm use of Resveratrol in patients with Type II Diabetes. To examine the effectiveness of resveratrol in lowering blood glucose in the presence of standard antidiabetic therapy in patients with type 2 diabetes.

MATERIALS AND METHODS

Subjects and Study Design

The trail was accepted by the Medical Ethics Committee. The informed consent was obtained from each patient at the time of allotment and continual as a procedure throughout the examined. Also, the patients had free medical care and consultation during the study period, specifically in the case of any adverse reaction or complications. Seventy individuals with T2DM who continuously visited the Endocrine Clinic were allotted in a randomized placebo-controlled double-blinded single center clinical study. The following in standards were used to hire the patients who had T2DM: (1) age between 20 and 65 years, (2) minimum of 6 months on oral hypoglycemic treatment or dual drug therapy, (3) being not on any antioxidant therapy such as vitamin supplements, and (4) having no allergy to grapes, green tea, and peanuts. subjects with type 1 diabetes, pregnant women, lactating mothers, and patients with severe heart disease, hepatic disease, and renal impairment were eliminated from the present trail. The subjects were randomly assigned to control and intervention groups.

Randomization/blinding procedures

Stratified randomization was used to allotted individuals to the 2 treatment sequences so that equal numbers of men and women will be allotted to each sequence. Thereafter, randomization of the participants into therapy group and placebo group was done by computer generated numbered sequence codes which were given in opaque envelopes to subjects in the first study visit. Both the clinical team and participants were blinded from the time of randomization until analysis was completed.

Compliance

At each visit (once a week during the intervention period), the individuals returned unused capsule bottles. Trail compliance was evaluated by counting the remaining capsules from the bottle every week. Every individual was asked to complete a questionnaire during each visit to monitor the type of food taken during the trail, particularly to confirm that they did not have food products that may contain resveratrol. No other assessments were done during these routine visits.

Treatment regime

The subjects in the intervention group received 500 mg, twice a day (a total of 1 g/day) of resveratrol capsules (99% pure, Biotivia, Bioceuticals) for a period of 45 days. The control group received 500 mg twice daily of placebo capsules supplementation for the same period of time. Since the study was also deliberated to test

the effectiveness of resveratrol when administered in conjunction with existing treatments against T2DM, all patients were allowed to continue their existing antidiabetic medications during the course of the trail. Oral hypoglycemic agents and insulin were not changed during the course of the trail.

Physical measurements

Blood pressure was evaluated twice on the right arm after a 15-minute rest in the sitting position, using a standard mercury sphygmomanometer. Height was calculated using a stadiometer and weight using standard weighing balance. Heavy outer garments and shoes were removed before height and weight were calculated. Body mass index (BMI) was measured as weight in kilograms divided by the square of height in meters using Global Database on BMI (World Health Organization, 2006).

Biochemical measurements

Fasting blood samples (12 hours) were collected at the baseline and after 45 days of therapy. All samples were promptly centrifuged, and plasma and serum were divided and kept frozen at −80°C until used. Analyses for biochemical parameters (blood glucose, triglyceride, and cholesterol levels) were carried out at the Persian Gulf Tropical Medicine Research Center on the day of blood collection using a Selectra 2 autoanalyzer. Glucose levels were calculated with the enzymatic (glucose oxidase) colorimetric method using a commercial kit. Creatinine levels were determined using enzymatic method. Serum total cholesterol and high density lipoprotein (HDL) cholesterol were estimated using cholesterol oxidase phenol aminoantipyrine enzymatic method and triglycerides using the glycerol-3-phosphate oxidase phenol aminoantipyrine enzymatic method. Serum low density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. In order to calculate liver function in the patients, the enzymes serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase (ALP), and gamma-glutamyltransferase (GGT) were measured by enzyme kinetic methods [27]. Intra- and interassay coefficients of variation (CVs) were 2.36%, 2.16%, 3.28%, 1.87%, 1.16%, 1.1%, 1.43%, and 0.9%, respectively. Hemoglobin A1c (HbA1c) in the whole blood sample of patients was calculated using the boronate affinity assay kit. Serum insulin levels were estimated using the electrochemiluminescence immunoassay "ECLIA" kit. The assay sensitivity was 1.76 μIU/mL; the intra- and interassay coefficients of variance were 1.79–2.6% and 2.88–5.99%, respectively. Insulin resistance was evaluated by calculating the homeostasis model of assessment index (HOMA-IR) using the following equation: fasting insulin (μIU/mL) × fasting glucose (mg/dL)/405. Also, the percentage of beta-cell function from fasting serum glucose and insulin concentrations was evaluated by measuring homeostasis model of assessment index (HOMA-β) using the following equation: 360 × fasting insulin (μIU/mL)/fasting glucose (mg/dL) −63.

Statistical analysis

The paired Student's *t*-test was used to compare the means of two variables for a single group. The Mann-Whitney *U* Test was used to relate differences between two nondependent groups when the dependent variable was continuous but not normally distributed. The Wilcoxon signed-rank test was used as an alternative to the paired Student's *t*-test for dependent samples when the variables cannot be accepted to be normally distributed. All statistical analyses were operated using the PASW Statistics GradPack. All data is represented as means ± SD except, the number of subjects in each subgroup was less than enough to use parametric statistics. The Mann-Whitney *U* Test (nonparametric statistics) was used, and the results are documented as Interquartile to have normal distribution among the subjects in different subgroups.

RESULTS AND DISCUSSION

There was 1 subject dropout from each group during the course of the trail. At the end of the trail, there were 20 and 20 subjects in control and intervention group, respectively. A consort diagram is showing the flow of participants through the trail. Shows the general features of the intervention group equated with the controls. At the baseline level, there was notable difference between the two groups regarding age, gender, bodyweight, BMI, systolic and diastolic blood pressure, duration of disease, smoking, history of hypertension, HbA1c, serum triglyceride, insulin, HOMA-β, creatinine,

and HDL-C levels. However, when compared with controls, the intervention group had notably higher fasting blood glucose, HOMA-IR, total cholesterol, and LDL-C levels. The prevalence of diabetes mellitus in the family was higher among the controls than the intervention group ($P < 0.05$, Tables Tables11 and and2).2). None of the participants had a history of alcohol consumption.

Table 1: Baseline clinical characteristics of the intervention and control groups before resveratrol or placebo supplementation.

	Control group	Interventional group	P value
Age	51.81±6.99	52.45±6.18	0.678
Sex(F/M)	11/9	12/8	0.806
Duration of disease	5.39±1.36	5.81±1.53	0.239
Family history of diabetes	15	12	0.024
Smoking	4	6	0.348
History of hypertension	6	8	0.901

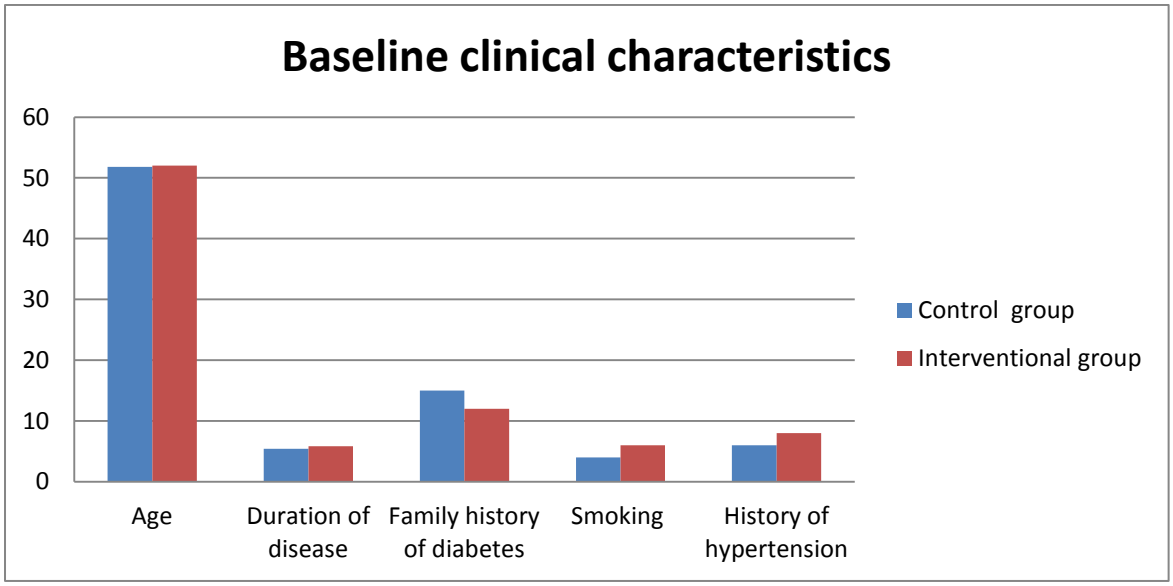

Table 2: Anthropometric, clinical, and biochemical parameters for placebo and resveratrol groups before and after resveratrol supplementation.

	Control/placebo group			Intervention/resveratrol group		
	Baseline	After 45 days	P value	Baseline treatment	After treatment	P value
Body weight (kg)	76.60±14.27	76.60±14.16	0.809	74.26±11.39	74.48±11.34	0.712
BMI (kg/m^2)	27.83±4.21	27.69±4.15	0.332	27.05±3.13	27.16±3.13	0.395
Systolic blood pressure (mmHg)	129.31±15.16	130.68±13.21	0.147	129.03±14.91	121.45±10.26	<0.0001*
Diastolic blood pressure (mmHg)	78.58±15.39	81.55±5.48	0.279	76.93±19.54	78.54±6.35	0.169
Fasting glucose (mg/dL)	151.24±51.52	161.13±53.16	0.002*	175.74±49.63	140.80±39.74	<0.0001*

Insulin (μIU/mL)	9.04±5.35	8.77±4.16	0.642	10.20±4.33	5.37±2.62	<0.0001*
HbA1c	8.30±1.43	8.50±2.46	0.764	8.6±1.390	7.60±1.32	<0.0001*
HOMA-IR	3.20±2.37	3.43±1.83	0.423	4.61±2.77	1.91±1.17	<0.0001*
HOMA-β	36.13±8.45	35.68±7.95	0.039	32.15±5.32	25.80±4.43	0.009*
Triglyceride (mg/dL)	134.69±45.61	123.13±43.27	0.145	160.1±58396	142.28±52.61	0.051
Total cholesterol (mg/dL)	168±41.97	175.34±41.31	0.424	203.61±52.70	192.28±53.13	0.156
HDL-cholesterol (mg/dL)	41.73±9.52	39.69±10.83	0.133	41.40±8.35	46.15±8.40	0.001*
LDL-cholesterol (mg/dL)	107.95±31.67	117.1829.88	0.003*	134.04±36.18	122.71±38.19	0.106
SGOT (IU/L)	24.0±5.4722.61±9.74	25.0±6.71	0.212	26.0±5.87	26.0±7.56	0.837
SGPT (IU/L)	19.44±8.79	21.65±8.67	0.202	21.45±7.91	22.61±9.74	0.365
GGT (IU/L)	30.82±17.79	29.93±17.01	0.545	32.12±15.32	33.38±17.92	0.441
ALP (IU/L)	169.37±52.63	189.41±48.38	0.001*	185.29±59.35	190.64±47.55	0.372
Creatinine (mg/dL)	0.92±0.24	0.97±0.25	0.281	0.96±0.24	0.90±0.21	0.098

Resveratrol and placebo supplementations had no effect on body weight and BMI in the intervention and control groups, respectively. Systolic blood pressure was notably decreased with resveratrol supplementation, while the control groups had no change in systolic blood pressure, when equated to their respective baseline levels. Diastolic blood pressure was unchanged in both groups throughout the trail. Liver function markers (SGOT, SGPT, GGT, and ALP) and a kidney function marker (creatinine) were unchanged with resveratrol therapy for 45 days in T2DM patients. At the end of the trail, ALP was notably elevated in the control group. Glucose levels were notably decreased with resveratrol therapy in T2DM patients in control group showed a small but significant elevated in glucose levels. There was a significant reduce in HbA1c in intervention group when equated to the baseline levels, whereas, there was no change in HbA1c levels in control group. Insulin levels in intervention group were significantly reduced when equated to baseline levels, while control group had no change in insulin levels. Homeostatic model assessment of insulin resistance (HOMA-IR) and beta cell function (HOMA-β) showed that both parameters were significantly reduced in intervention group when equated to the baseline levels; however, HOMA-IR did not change in control group, while, HOMA-β marginally but significantly reduced . When equated with baseline, HDL levels were significantly elevated in the intervention group. Changes in total triglycerides, cholesterol, and LDL levels showed a decreasing trend but were not statistically significant. However, the control group had elevated LDL levels at the end of the study when equated to the baseline levels, while triglycerides, total cholesterol, and HDL were unchanged. A comparison of the changes in the anthropometric, clinical, and biochemical measurements during the trial period between the intervention and control groups. When equated to the controls, a significant decline was observed in systolic blood pressure, HbA1c, HOMA-IR, serum fasting glucose, and insulin, while significant increment was observed in the levels of HDL-C ($P < 0.0001$) in the intervention group. When equated to the control group, no significant changes were found for BMI, body weight, diastolic blood pressure, HOMA-β, levels of total cholesterol, creatinine, and liver enzymes in the subjects supplemented with resveratrol.

Table 3: Comparison of changes in the anthropometric, clinical, and biochemical parameters during the study period between the intervention and control groups.

	Control group	Intervention group	P value
Body weight	0.02±0.64	0.21±0.61	0.22
BMI	-0.01±0.89	0.12±0.43	0.092
Systolic blood pressure	1.37±4.98	-7.58±8.04	<0.0001*
Diastolic blood pressure	2.96±14.48	1.61±6.37	0.638
Fasting glucose	9.89±15.72	-34.93±29.53	<0.0001*
Insulin	-0.27±3.15	-4.82±4.83	<0.0001*
HbA1c	0.01±0.67	-1.20±1.56	<0.0001*
HOMA-IR	0.22±1.50	-2.69±2.79	<0.0001*
HOMA-β	-2.74±2.84	-9.16±12.27	0.549
Triglyceride	-11.56±36.71	-17.81±39.87	0.591
Total cholesterol	6.69±40.68	-11.33±35.24	0.121
HDL-cholesterol	-2.4±6.26	4.75±5.83	0.001*
LDL-cholesterol	9.22±12.88	-11.33±30.65	0.006*
SGOT	-2.34±9.96	0.83±7.90	0.174
SGPT	2.20±9.09	1.16±7.03	0.619
GGT	-0.89±7.88	1.25±8.97	0.329
ALP	20.03±28.15	5.35±32.86	0.069
Creatinine	0.05±0.28	-0.06±0.21	0.062

Table 4: Comparison of changes in the clinical and biochemical parameters during the study period between the intervention and control groups across glibenclamide, metformin, and metformin + glibenclamide treatment subgroups.

	Glibenclamide			Metformin			Glibenclamide + metformin		
	Control group	Intervention group	P value	Control group	Intervention group	P value	Control group	Intervention group	P value
Systolic blood pressure	0.01 (−5.00, 1.25)	−10.00 (−16.25, −3.75)	0.016*	0.01 (−1.25, 10.00)	−10.00 (−10.00, 0.01)	0.043*	0.01 (0.01, 5.00)	−10.00 (−12.50, −2.50)	0.003*
Fasting glucose	13.0 (4.50, 31.50)	−25.00 (−84.50, −5.75)	<0.0001*	2.00 (−3.50, 12.00)	−25.00 (−32.00, −10.00)	0.005*	7 (1.00, 22.00)	−32.00 (−47.50, −22.50)	<0.0001*
Insulin	0.06 (−3.85, 5.39)	−4.42 (−7.85, −2.31)	0.042*	0.73 (0.06, 1.05)	−1.32 (−3.39, −0.04)	0.09	0.37 (0.32, 0.95)	−7.71 (−9.31, −1.96)	0.002*
HbA1c	−0.15	−1.55	0.031*	−0.15	−0.60	0.13	0.05	−1.10	<0.0001

	(−1.04, 0.200)	(−2.22, −0.97)		(−0.70, 0.22)	(−2.00, −0.02)		(−0.10, 0.50)	(−2.05, −0.90)	*
HOMA-IR	0.17 (−1.53, 3.69)	−2.12 (−5.07, −1.16)	0.022*	0.27 (0.15, 0.65)	−0.86 (−1.25, −0.31)	0.043*	0.24 (−0.26, 0.56)	−2.86 (−5.22, −1.12)	<0.0001 *
HDL-cholesterol	−1.65 (−5.77, 1.40)	6.25 (2.82, 11.26)	0.003*	0.10 (−4.07, 2.95)	4.60 (1.40, 12.05)	0.043*	−2.80 (−4.70, 0.60)	6.10 (0.35, 11.20)	<0.0001 *
LDL-cholesterol	8 (5.50, 18.0)	−17.50 (−35.75, −10.50)	0.005*	4.50 (−1.25, 20.75)	−7.0 (−70.00, 2.00)	0.007*	1 (−2.00, 4.00)	−9.00 (−32.00, 1.50)	0.030*

Subgroup analyses were also done to control if resveratrol had any additive effect when merged with metformin and glibenclamide. The seven parameters that showed significant changes were increased in subgroup analyses. Subgroup analyses ended that resveratrol had an additive effect on the metabolic parameters; however, this additive effect was independent of the type of hypoglycemic agents. Only 4 patients were on insulin therapy, two in the intervention group and two in the control group; therefore, the insulin group was not involved in the subgroup analyses. To date, numerous studies testing the effectiveness of resveratrol on cell and animal models have demonstrated the potency of resveratrol against different ailmen depending on the results of currect clinical trials, there is now a sensible amount of scientific confirmation to support the claim that resveratrol is beneficial against chronic diseases. Among the human studies mentioned earlier in the introduction, Bhatt et al. and Brasnyó et al documented that therapy with resveratrol 250 mg/day and 10 mg/day respectively, documented in an development in metabolic parameters in T2DM patients. The report of the present trail showed that resveratrol supplementation at a dose of 1 g/day had a remarkable effect in lowering glucose levels, along with major development in other metabolic variables in humans with T2DM. Given the fact that there is no conclusive data on an effective dosage of resveratrol when used as a supplement, we used a dose that is commonly high (1 g/day) in order to give us a superior chance to observe clinically superficial antidiabetic effects of resveratrol. Throughout the trail, there were no significant changes in the physical features of thepatients in both groups. The drop in systolic blood pressure in resveratrol treated type 2 diabetic patients is consistent with that noticed by Bhatt et al. The small but significant decrease in blood pressure noticed, might be due to the development in insulin resistance and glucose homeostasis. The effectiveness of resveratrol as a blood pressure decreases agent at the present dosage needs to be separately tested on hypertensive subjects. Accordingly, it may be advised that short term supplementation with a avarage to high dose of resveratrol (1 g/day) as used in the present trail may help to markedly lower blood glucose levels. We speculate that, once blood glucose levels are normalized, T2DM patients may be administered a reduced dose (less than the 1 g/day) of resveratrol that in combination with dietary modifications and appropriate exercise regimen may help in maintain reduced blood glucose levels. Whether the use of a lower dose is an effective option in the long term is a question that needs to be tested in an independent clinical trial. A major concern in using elevated doses of resveratrol in humans would be the possibility of toxic effects to major organs in the body. As speculated earlier, use of a lower dose (<1 g) after the 45-day therapy with 1 g resveratrol may eliminate or decrease, if any, resveratrol related toxicity in the long term. On the other hand, it should be stated that the control group which was on standard diabetic therapy alone had elevated in alkaline phosphatase (ALP) levels, when equated to the baseline values. Glycated hemoglobin (HbA1c) levels in blood are another stable marker for blood glucose levels. It must be noted that a reduced by one point in HbA1c levels noticced in the

intervention group is clinically very significant, given that this was gained with 45 days of therapy. This result is comparable to reduce in HbA1c levels in T2DM patients with metformin (a frontline glycemic control drug) administration. Accordingly, this data provides further conformation for the effectiveness of resveratrol supplementation in maintaining the lowered blood glucose levels during the study period. There was also a striking reduced in insulin levels, along with significant reductions in HOMA-IR and HOMA-β in the intervention group, suggesting that addition of resveratrol to standard antidiuretic therapy is beneficial in lowering insulin levels and improving insulin sensitivity and beta cell function in T2DM patients. Our data shows that HDL levels were significantly increased in the intervention group. The increased in HDL levels by 4.75 mg/dL with resveratrol treatment was comparable to that achieved with nicotinic acid. There were trends towards a decrease, but no significant changes were observed in triglycerides, cholesterol, and LDL levels with resveratrol supplementation, while a significant elevated in LDL levels was noticed in the control group. Metformin, glibenclamide, and insulin are all known to have beneficial or no effect on the lipid profiles; therefore, other independent factors may have contributed to the noticed elevated in the control group.

CONSLUSION

The results of this trail clearly indicate that resveratrol supplementation in the presence of standard antidiabetic medication has major benefits in T2DM patients, which involve a pronounced lowering of blood glucose, HbA1c, insulin levels, and insulin resistance, as well as development in HDL levels. Unlike earlier reports which showed mild effects on hyperglycemia and hyperinsulinemia, our trail highlights the marked difference and the potential of resveratrol as an antidiabetic molecule. It is also important to note the favorable effects of resveratrol observed on metabolic parameters, despite the fact that there was no considerable effect on body weight or body composition. Some of the noticed decrease in HbA1c and HDL with resveratrol supplementation are very significant that they can be compared to benefits achieved with front line antidiabetic drugs. Other important observations which stem from this study are that: (a) 1 g/day of resveratrol supplementation for 45 days had no adverse effects in type 2 diabetic patients and (b) resveratrol not only complemented standard antidiabetic medication but also provided added protection (over standard antidiabetic therapy).This is a pilot study which examined the antidiabetic effects of resveratrol over the short term, and only one dose of resveratrol was tested. There was no followup to check the metabolic parameters of the patients after the resveratrol wash-out period. The study lacks the investigation of cellular mechanisms underlying the antidiabetic effects of resveratrol. Extensive toxicological screening was not done on subjects to confirm the safety of resveratrol administration, and the safety of administering 1 g dose of resveratrol over the long term has not been established. In summary, the present study supports the strong antidiabetic effect of resveratrol reported in numerous animal studies, as well as the effects observed in the human studies. It also supports the case for resveratrol supplementation over a short term. Nevertheless, well-designed clinical trials with resveratrol supplementation in a larger T2DM population and over a longer duration are required to recommend the use of resveratrol independently or as an adjunct in diabetic population.

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