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Communication

Resveratrol supplementation improves glycemic control in type 2 diabetes mellitus☆

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ABSTRACT

Resveratrol is a naturally occurring polyphenolic compound. Numerous animal studies have been reported on its wide-ranging beneficial effects in the biological system including diabetes mellitus (DM). We hypothesized, therefore, that oral supplementation of resveratrol would improve the glycemic control and the associated risk factors in patients with type 2 diabetes mellitus (T2DM). The present clinical study was therefore carried out to test the hypothesis. Sixty-two patients with T2DM were enrolled from Government Headquarters Hospital, Ootacamund, India, in a prospective, open-label, randomized, controlled trial. Patients were randomized into control and intervention groups. The control group received only oral hypoglycemic agents, whereas the intervention group received resveratrol (250 mg/d) along with their oral hypoglycemic agents for a period of 3 months. Hemoglobin A_{1c}, lipid profile, urea nitrogen, creatinine, and protein were measured at the baseline and at the end of 3 months. The results reveal that supplementation of resveratrol for 3 months significantly improves the mean hemoglobin A_{1c} (means ± SD, 9.99 ± 1.50 vs 9.65 ± 1.54; $P < .05$), systolic blood pressure (mean ± SD, 139.71 ± 16.10 vs 127.92 ± 15.37; $P < .05$), total cholesterol (mean ± SD, 4.70 ± 0.90 vs 4.33 ± 0.76; $P < .05$), and total protein (mean ± SD, 75.6 ± 4.6 vs 72.3 ± 6.2; $P < .05$) in T2DM. No significant changes in body weight and high-density lipoprotein and low-density lipoprotein cholesterols were observed. Oral supplementation of resveratrol is thus found to be effective in improving glycemic control and may possibly provide a potential adjuvant for the treatment and management of diabetes.

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1. Introduction

Diabetes mellitus (DM) is a common, serious, chronic, and currently incurable metabolic disorder of worldwide significance. India is identified as the diabetes capital of the world, with the current estimated 50.8 million diabetic patients. The worldwide prevalence is 285 million in 2010, and by 2030, the number is expected to increase to 438 million. Most will have type 2 DM (T2DM) [1].

The disease is known to be associated with a high risk of microvascular and macrovascular complications and very often leads to premature death. Despite the availability of

Abbreviations: BMI, body mass index; DM, diabetes mellitus; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus.

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many antidiabetic agents and pharmacotherapies, targeting cardiovascular risk factors, the morbidity, mortality, and economic consequences of DM is still a great burden to patients, society, health care systems, and the economy. Many pharmacologic and nonpharmacologic interventions have been developed based on current understanding of the pathophysiology of T2DM. However, the existing treatments have limitations either because of their side effects, particularly weight gain and hypoglycemia, or contraindications that limit their use. Furthermore, none of the current therapies have a significant impact on the associated risk factors. There is a need, therefore, for new therapies that may improve not only hypoglycemic effect but also the associated problems.

Resveratrol (3,5,4'-trihydroxystilbene) is a naturally occurring phytoalexin. The richest source of this compound is Polygonum cuspidatum Reynoutria japonica, a plant that has been used in oriental folk medicine. Considerable amount of resveratrol is found, among others, in grapevine and peanuts. This compound is available today in various dosage forms and is recommended as a dietary supplement. Although numerous animal studies have been reported on its wide-ranging beneficial effects including DM [2-6], only limited clinical data are available concerning its potential effects [7]. We hypothesized that oral supplementation of resveratrol would improve the glycemic control and the associated risk factors in patients with T2DM. The present study was therefore undertaken to test the hypothesis. The objective of the present study was therefore to investigate the effect of oral supplementation of resveratrol on the glycemic control and the associated risk factors in patients with T2DM in a prospective, open-label, randomized, controlled model. Resveratrol was administered orally to patients with T2DM for a period of 3 months, and the hemoglobin A_{1c} (HbA_{1c}), body weight, body mass index (BMI), systolic and diastolic blood pressures, lipid profile, urea nitrogen, creatinine, and protein measurements were performed at both baseline and after 3-month follow-up.

2. Methods and materials

2.1. Study design and participants

The design was prospective, open-label, randomized, controlled study involving patients with T2DM. A total of 62 patients with T2DM were enrolled after explaining the objectives of the study at the screening visit and verifying the inclusion criteria. The main inclusion criteria were patients with known T2DM, aged between 30 and 70 years, either sex, with or without comorbidities, minimum of 6 months of ongoing oral hypoglycemic treatment (metformin and/or glibenclamide), and 3 years duration of the disease. None of the patients were on antioxidant supplementation. Patients with type 1 diabetes, pregnant women and lactating mothers, voluntary withdrawals, and patients with any significant hepatic and renal dysfunction were excluded.

2.2. Informed consent and ethics committee approval

The experimental protocol was approved by Institutional Human Ethical Committee, JSS College of Pharmacy, Ootacamund, Tamilnadu, India. The trial was also registered with Clinical Trial Registry of India, Government of India (registration no. CTRI/2011/05/001731). Informed, written consent was obtained from each subject. The study was carried out at the outpatient department of secondary care of Government Headquarters Hospital, Ootacamund, The Nilgiris, Tamil Nadu, India, during the period of February 2011 to October 2011.

Enrolled patients were randomized by using computer-assisted randomization procedure and assigned to the control and intervention groups. Patients in the intervention group received 250 mg/Once Daily resveratrol capsule (Biofort; Biotivia Bioceuticals International, New York, NY, USA) supplementation along with oral hypoglycemic agents such as glibenclamide and/or metformin for a period of 3 months, whereas patients in control group received only oral hypoglycemic agents for a period of 3 months.

The primary objective of the study was to assess HbA_{1c}, and the secondary objective was to assess body weight, BMI, systolic and diastolic blood pressures, lipid profile, urea nitrogen, creatinine, and protein. Measurements were performed at both baseline and after 3-month follow-up.

2.3. Procedures

Demographic data and general health characteristics including height, social habit, smoking status, and food habits were collected on a standard structured data collection form during the baseline visit. Height was measured to the nearest 0.5 cm, and the weight, to the nearest 0.1 kg. Body mass index was calculated as weight in kilograms divided by the square of height in centimeters [8]. Blood pressure was measured using a mercury sphygmomanometer according to standard protocol. Subjects were seated at rest for at least 10 minutes, and 3 measurements were taken at 5-minute intervals. The Korotkoff V sound was used to determine diastolic blood pressure.

Fasting (12 hours) venous blood sample (5 mL) was collected from the patients for biochemical estimation at the baseline and after 3 months. Hemoglobin A_{1c} was measured by using A_{1c} Now$^+$ (A_{1c} Now$^+$; Bayer Healthcare LLC, Tarrytown, NY, USA) monitor, and fasting blood sugar was monitored by using Dr Morepen Gluco-One blood glucose monitor system (Plainsboro, NJ, USA). Triglyceride, total cholesterol, and high-density lipoprotein cholesterol (HDL-C) were measured by enzymatic methods of Allain et al [9]. Serum low-density lipoprotein cholesterol (LDL-C) was calculated by Frederickson-Friedwald equation [10]. Urea nitrogen was measured by the method of Murray [11]. Creatinine was estimated by the method of Bower [12]. Total protein was measured by the method of Kjeldahl [13], and albumin was measured by the method of Gendler [14]. All biochemical estimations were carried with commercially available kits using Semi Auto Analyser Merck Microlab 200 (Darmstadt, Germany).

2.4. Statistical analyses

Statistical analyses were performed by using GNU PSPP version 0.7.5-g70514b software (Free Software Foundation, Inc, Boston, MA, USA). Data are presented as means ± SD. $P < .05$ was taken as statistically significant. Patients were randomly allocated to control and intervention groups in a

1:1 ratio. To determine the normality of distribution, the Kolmogrov-Smirnov goodness of fit test was used. Descriptive analyses were used for the baseline characteristics of populations. The Mann-Whitney *U* test and Wilcoxon paired rank test were used for nonparametric distributions. An independent unpaired *t* test and paired *t* test were used for numerical normally distributed data. All statistical tests were 2 sided.

3. Results

Baseline characteristics of the patients enrolled in the study are summarized in Table 1. Of 32 patients in the control group, 2 moved to other places because of job relocation, and 1 discontinued for personal reasons. Of the 30 intervention subjects, 2 were lost during the follow-up. Data obtained for 29 patients in the control group and 28 patients for intervention group were thus used for the analyses at the end of 3 months. In the control group, 3 patients were on metformin; 3, on glibenclamide; and 23, on the combination of these 2 drugs. Among the control group, 18 patients had hypertension comorbidity. In the intervention group, 5 patients were on metformin; 5, on glibenclamide; and 18, on the combination of these 2 drugs. In the intervention group, 17 patients had hypertension comorbidity. Table 2 shows the biochemical and clinical variables at baseline and after 3 months of study in both the groups. Significant differences were observed in the group supplemented with resveratrol with respect to HbA_{1c} ($P < .02$), systolic blood pressure ($P < .0002$), total cholesterol ($P < .004$), and total protein ($P < .04$). The difference was not quite significant in the case of LDL-C ($P = .05$). No significant changes, however, were observed with respect to other variables including weight. Table 3 shows the changes in the variables during the study period in the control and the intervention groups. Significant changes ($P < .0001$) were observed in fasting blood glucose, HbA_{1c}, systolic and diastolic blood pressures, total cholesterol, LDL-C, urea nitrogen, creatinine, and total protein.

4. Discussion

To the best of our knowledge, this is the first clinical study to evaluate the effect of resveratrol as supplement in Indian patients with T2DM. The study clearly reveals that daily oral supplementation of resveratrol in patients with T2DM for a period of 3 months significantly reduces HbA_{1c}, systolic blood pressure, total cholesterol, and total protein. The study also reveals that resveratrol decreases LDL-C, fasting blood glucose, and diastolic blood pressure. However, the latter observations are not statistically significant. The strength of this study is its prospective, randomized, control design that decreases the probability of confounding because the baseline data reveal equal distribution of covariates. Our study has some limitations in that it is an open-label trial that is open to challenge for bias as they do nothing to reduce the placebo effect, and the study is also limited by its relatively small sample size. In addition, we did not include insulin-related parameters. However, this is only a preliminary clinical study to evaluate the effect of resveratrol in patients with T2DM. Furthermore, the study was conducted at the Government Headquarters Hospital, Ootacamund, The Nilgiris, that is situated 2400 m above the sea level, and hence, the climatic conditions, especially the low atmospheric temperature, affect the lifestyle of the residents. Our finding, therefore, may not be generalized to populations of other ethnicities and may need to be confirmed in other independent cohorts with larger sample size and different ethnic groups.

Most of the earlier researchers have reported the hypoglycemic effect of resveratrol [15]. Some researchers, however, have observed a contrary effect [16]. The present study clearly reveals that resveratrol supplementation does decrease HbA_{1c} level significantly. It is also observed that resveratrol decreases fasting blood glucose, although not significantly. The mechanism of hypoglycemic effect of resveratrol is still not clear, although processes such as its binding effect on sulfonylurea receptors and its ability to block the pancreatic adenosine triphosphate–sensitive K^+ channels in β cell and voltage-gated K^+ channels similar to glibenclamide [17,18], which acts as a channel blocker thereby stimulating insulin secretion, have been reported. It has also been reported that resveratrol potentially activates Sirtunin 1 Protein (SIRT1) [19], which is the principle modulator of pathway's downstream of energy restriction that produces beneficial effect on glucose homeostasis and insulin sensitivity [20].

Diabetes is associated with a high risk of microvascular and macrovascular complications with a high risk of

Table 1 – Baseline characteristics of patients

Variables	Control group (n = 29)	Intervention group (n = 28)	Significance
Age	57.75 ± 8.71	56.67 ± 8.91	NS
Sex (Female/male)	20/9	16/12	NS
Education	I, 10; P, 6; M, 6; S, 2; HS, 3; G, 2	I, 4; P, 6; M, 4; S, 5; HS, 5; G, 4	–
Occupation	H, 12, FT, 4, PT, 5, R, 6, D, 2	H, 12,FT, 5, PT, 4, R, 5, D, 2	–
Duration of disease	6.68 ± 4.70	7.57 ± 4.56	NS
Family history of diabetes	9	12	NS
Smoking	6	6	NS
Alcoholic	6	6	NS
Nonvegetarian/vegetarians	28/1	24/4	NS
Comorbidity	18	17	NS

Values are expressed as means ± SD, median and (range), or absolute numbers, as applicable. NS indicates not significant; I, illiterate; P, primary; M, middle; S, secondary; HS, higher secondary; G, graduate; H, house wife; FT, full time; PT, part time; R, retired; D, disable to work.

Table 2 – Biochemical and clinical variables at baseline and after 3 months for the control and intervention groups

Variables	Control group (n = 29)		P	Intervention group (n = 28)		P
	Baseline	After 3 mo		Baseline	After 3 mo	
Body weight, kg	63.10 ± 9.02	63.31 ± 8.92	.45	64.78 ± 9.25	64.94 ± 9.00	.83
BMI, kg/m^2	24.92 ± 3.05	24.86 ± 2.89	.57	24.66 ± 3.57	24.60 ± 3.62	.83
Fasting blood glucose, mmol/L and (mg/dL)	10.11 ± 2.56 (182 ± 46.22)	10.83 ± 2.92 (195.03 ± 52.56)	.05 *	11.82 ± 3.58 (212.82 ± 64.52)	11.02 ± 3.86 (198.43 ± 69.57)	.29
HbA_{1c}, mmol/L [2.4-4.7] and (percentage of total hemoglobin) [3.9-5.1]	11.4 ± −1.9 (8.75 ± 1.56)	11.7 ± −1.7 (8.92 ± 1.65)	.15	13.7 ± −2 (9.99 ± 1.50)	13.1 ± −1.9 (9.65 ± 1.54)	.02 **
Systolic blood pressure, mm Hg	134.51 ± 14.61	142.27 ± 12.99	.0007 ***	139.71 ± 16.10	127.92 ± 15.37	.0002 **
Diastolic blood pressure, mm Hg	78.62 ± 10.86	85.72 ± 9.14	.0001 ***	81.42 ± 9.58	79.28 ± 9.71	.20
Total cholesterol, mmol/L [2.59-6.21] and (mg/dL) [100-240]	4.89 ± 0.89 (191.03 ± 34.91)	5.07 ± 0.90 (197.93 ± 35.22)	.007 **	4.70 ± 0.90 (183.5 ± 35.16)	4.33 ± 0.76 (169.17 ± 29.85)	.004 **
Triglyceride, mmol/L [0.56-1.98] and (mg/dL) [50-175]	1.89 ± 0.59 (168.62 ± 53.21)	1.92 ± 0.56 (171.42 ± 50.25)	.36	1.70 ± 0.63 (151.64 ± 56.92)	1.71 ± 0.74 (152.39 ± 66.51)	.94
LDL-C, mmol/L [<2.6] and (mg/dL) [<100]	2.80 ± 0.80 (108.34 ± 31.01)	2.98 ± 0.79 (115.43 ± 30.66)	.01 **	2.58 ± 0.83 (99.96 ± 32.18)	2.26 ± 0.65 (87.51 ± 25.23)	.05 *
HDL-C, mmol/L [0.90-1.68] and (mg/dL) [35-65]	1.26 ± 0.17 (48.96 ± 6.92)	1.21 ± 0.24 (46.96 ± 9.51)	.21	1.37 ± 0.27 (53.28 ± 10.78)	1.32 ± 0.25 (51.25 ± 9.88)	.42
Urea nitrogen, mmol/L [3.6-17.8] and (mg/dL) [10-50]	10.44 ± 1.42 (29.27 ± 3.99)	10.51 ± 1.33 (29.44 ± 3.73)	.62	11.78 ± 2.11 (33 ± 5.92)	10.60 ± 2.59 (29.71 ± 7.27)	.02 **
Creatinine, mmol/L [44.2-114.9] and (mg/dL) [0.5-1.3]	83.98 ± 9.72 (0.95 ± 0.11)	87.51 ± 7.95 (0.99 ± 0.09)	.02 **	90.16 ± 15.02 (1.02 ± 0.17)	91.93 ± 17.68 (1.04 ± 0.20)	.56
Total protein, g/L [63-84] and (g/dL) [6.3-8.4]	76.5 ± 3.5 (7.65 ± 0.35)	77.3 ± 2.9 7.73 ± 0.29	.72 *	75.6 ± 4.6 7.56 ± 0.46	72.3 ± 6.2 7.23 ± 0.62	.04 **

Figures in square brackets refer to normal reference range in the laboratory. Values are expressed as means ± SD (Student paired t test was used).
* Not quite significant.
** $P < .05$.
*** $P < .001$.

Table 3 – Change in the biochemical and clinical variables during the study period (end of the study minus baseline) for the control and intervention groups

Variables	Control group (n = 29)	Intervention group (n = 28)	P
BMI (kg/m^2)	−0.06 ± 0.16	−0.06 ± 0.05	.99
Fasting blood glucose (mg/dL)	13.07 ± 6.34	- 14.39 ± 5.05	.0001 *
HbA_{1c} (mmol/L) (percentage of total hemoglobin)	0.17 ± 0.10	−0.33 ± 0.04	.0001 *
Systolic blood pressure (mm Hg)	7.76 ± 1.62	−11.78 ± 0.73	.0001 *
Diastolic blood pressure (mm Hg)	7.10 ± 1.72	−2.14 ± 0.13	.0001 *
Total cholesterol (mg/dL)	6.90 ± 0.31	−14.32 ± 5.31	.0001 *
Triglyceride (mg/dL)	2.80 ± 2.96	0.75 ± 9.59	.2768
LDL-C (mg/dL)	7.09 ± 0.35	−12.45 ± 6.95	.0001 *
HDL-C (mg/dL)	−2 ± 2.59	−2.03 ± 0.90	.95
Urea nitrogen (mg/dL)	0.17 ± 0.26	−3.28 ± 1.35	.0001 *
Creatinine (mg/dL)	0.04 ± 0.02	0.01 ± 0.03	.0001 *
Total Protein (g/dL)	0.08 ± 0.06	−0.32 ± 0.16	.0001 *

Values are expressed as means ± SD.
Mean values were significantly different from control group (independent sample t test or Mann-Whitney U test).
* $P < .0001$.

premature death. Indian races and ethnic groups are prone to these complications. Not only hyperglycemia but also disturbances of lipid metabolism are among the major causes of chronic diabetic complications. In the present study, resveratrol supplementation significantly decreases total cholesterol and LDL-C.

During the study period, it was observed that the systolic blood pressure in the control group increased significantly, whereas in the intervention group, it decreased significantly. No significant difference was observed in the weight of control and intervention groups, which may be explained by their normal BMI at the time of enrollment.

In conclusion, the results of the present study support our hypothesis that resveratrol supplementation improves glycemic control and the associated risk factors in patients with T2DM. The study also suggests that resveratrol could be used as an effective adjuvant therapy [21] with a conventional hypoglycemic regimen to treat T2DM.

Our preliminary study provides data about the possible clinical effects of resveratrol supplementation on the glycemic control and cardiovascular risk factors in patients with T2DM and a base for future studies with larger number of patients and longer duration. Further studies on these lines are in progress.

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