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Original Research Article

Effect of resveratrol on diabetic neuropathy in wistar albino rats

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ABSTRACT

Background: Type 2 diabetes mellitus (DM) is a common chronic disease with increasing prevalence worldwide. Prolonged uncontrolled hyperglycemia, dyslipidemia are major risk factor for its complication like neuropathy. Since there is no definite treatment for diabetic neuropathy, this study aims to evaluate the effect of resveratrol on diabetic neuropathy in high fat diet with low dose streptozotocin induced type-2 DM model in wistar albino rats.
Methods: First type 2 diabetic rat model was established. Wistar albino rats, fed with high-fat diet (HFD) rendered diabetic with streptozotocin, were divided into 6 groups, disease control (DC) treated with vehicle, standard control (SC) which received metformin, test groups treated with 5, 10, and 20 mg/kg b.w. of resveratrol and combination of half dose of metformin and resveratrol (10 mg/kg) (TC). A group of six normal animals served as normal control (NC), another six as HFD control. Fasting plasma glucose, lipid profile were measured one week after induction of diabetes. The animals were then treated orally for 2 weeks after which the same parameters were repeated. Behavioral biomarkers for neuropathy are measured in 4 weeks and 6 weeks of treatment. The *in-vivo* results were analyzed by one way ANOVA followed by Tukey's multiple comparison test for biochemical parameters and Kruskal Wallis test followed by Dun's multiple comparison test for behavioral biomarkers.
Results: Increase in fasting plasma glucose (FPG), deranged lipid profile, increased neuropathy in DC compared to NC, HFD control while a significant decrease in FBG, improved pain behavior with SC, test groups ($p<0.05$) as compared to the DC group.
Conclusions: Resveratrol prevents diabetic neuropathy.

Keywords: Diabetes, Resveratrol, Diabetic neuropathy

INTRODUCTION

International Diabetes Federation has estimated that 415 million people have been diagnosed with diabetes mellitus (DM) worldwide and a rise of up to 640 million by 2040 being anticipated.[1] Diabetic neuropathy (DN) is one of the important complications of diabetes mellitus resulting in a great deal of morbidity, increased mortality and impaired quality of life. The prevalence of diabetic neuropathy is increasing up to 30% in Indian population.[2]

In US, DN is the leading cause of diabetes related hospital admissions and non-traumatic amputations.[3] Peripheral diabetic neuropathy, untreated for a longer period, may lead to loss of neuronal reflexes and deformities that may progress to gangrene. In about 80% cases of DN amputations follow a foot ulcer or injury.[4]

Diabetic neuropathy is characterized by complex changes in functional and sensorimotor parameters. There is no definitive treatment for DN at present. Only few

nonspecific drugs like tricyclic antidepressants, SNRIs, anticonvulsants, opioids and topical capsaicin have been tried in the management of painful neuropathy. Out of which duloxetine and pregabalin have been approved by the US FDA.[5] But the cost and side effects of these drugs limit their use. Epalrestat, the only aldose reductase inhibitor, is approved and marketed in Japan. As free radicals play an important role in pathophysiology of DN, the drugs with antihyperglycemic and antioxidant properties will be more beneficial in this condition.[6] Though there are various approaches are available to treat diabetes and prevent its secondary complications, herbal medications may be used as an alternative therapy as these are well tolerated.

Resveratrol is a plant-derived polyphenolic phytoalexin from grape skin and seeds of groundnuts, peanuts and several other plants that is produced by certain enzyme when under attack by infectious agents. Grape skin provides a relatively high concentration of resveratrol.[7] Resveratrol has inhibitory effects on free radicals accounting for antioxidant properties, also blood sugar lowering effect, anti-inflammatory, cardio protective effect in experimental animal models.[8]

Aims and objectives

In this context, the present study was undertaken to evaluate the effect of resveratrol on diabetic neuropathy in high fat diet with low dose streptozotocin induced type-2 DM model in wistar albino rats.

METHODS

Wistar albino rats of either sex weighing between 100-150 g were procured from National Institute of Nutrition, Hyderabad, India. They were housed in clean polypropylene cages (four rats per cage), maintained under controlled room temperature (25±1ºC) and with relative humidity of 45-55% under 12:12 hr light and dark cycle in the central animal house. They were provided with standard lab diet and water ad libitum and kept for 1 week to acclimatize with the laboratory condition before starting the experiment. Prior to the study, the study protocol was approved by I.A.E.C, M.K.C.G. Medical College, Berhampur. The study was carried out as per CPCSEA guidelines.

Study design

54 wistar albino rats were grouped randomly into 9 groups and distributed 6 in each as follows:

Control groups

Gr-I: Normal pellet diet and distilled water PO.
Gr-II: Normal pellet diet and dimethyl sulfoxide (DMSO) PO.
Gr-III: High fat diet (HFD) and DMSO PO.

Disease control

Gr–IV: HFD and oral DMSO after induction of diabetes.

Test groups

Gr-V-VII: Resveratrol in 5, 10, 20 mg/kg orally for 2 weeks, after induction of diabetes.

Standard group

Gr-VIII: Metformin (0.5 gm/kg) orally for 2 weeks after induction of diabetes

Combination of test and standard

Gr-IX: Minimum effective dose of resveratrol (10 mg/kg) and half dose of metformin (250 mg/kg) orally for 2 weeks after induction of diabetes.

Procedure

The test drug resveratrol was obtained from InvivoGen, streptozotocin from Himedia Lab. and high fat diet was prepared in the laboratory.[9] The doses of standard and test drugs were selected from published literature.[10] The test drug resveratrol was dissolved with DMSO before administration whereas distilled water served as vehicle for standard drug metformin.

Preparation of HFD: High fat diet was prepared by adding excess of coconut oil to normal diet so as to provide 42% of total calories from the fat source.[9]

Preparation of stock solution resveratrol: To obtain a 20 mg/ml stock solution, 250 µl DMSO was added to 5 mg resveratrol powder. Solution was then vortexed until complete solubilization, aliquoted and stored at 4^0C. Required dose was obtained by dilution with distilled water as per the instruction given by the product manufacturer.

Induction of diabetes

Diabetes was induced in HFD fed wistar albino rats fasted overnight by I.P injection of single dose of freshly prepared solution of streptozotocin (40 mg/kg) which was made by dissolving with 0.1 M citrate buffer solution (pH 4.5) containing 0.9% NaCl after 2 weeks of high fat diet.[11] To avoid an early fatal hypoglycemia 5% glucose solution was fed on 1st day of streptozotocin administration to all rats. The rats having fasting glucose level ≥200 mg/dl after 48 hrs of administration of streptozotocin (STZ) and persistent after 7^{th} day after administration of STZ were considered diabetic and included in the study groups.[12] Diabetic neuropathy developed after 4 weeks of induction of diabetes.

Estimation of biochemical parameters

After 12 hour fasting, about 3 ml of blood was collected in a sterilized test tube containing ethylenediamine-tetra acetic acid through retro-orbital puncture under light ether anesthesia. Assay of fasting plasma glucose (FPG) by glucose oxidase or peroxidase method, plasma cholesterol by cholesterol oxidase or phenol and aminophenazone (PAP) method, triglyceride by glycerol-3-phosphate oxidase or PAP method and high-density lipoproteins (HDL) by Peg precipitation method were estimated by using commercially available kits. The low-density lipoproteins (LDL) cholesterol was calculated from the formula of Friedwald et al as given below:[13]

LDL-C = Total cholesterol - [HDL+VLDL]
Where VLDL = Triglyceride/5

Evaluation of biomarkers of neuropathy

Behavioral biomarker: Assessment of neuropathic pain was done by thermal method which include tail flick test (tail immersion test) for hot allodynia and acetone induced cold allodynia and chemical method by formalin test.[14-16]

Functional biomarkers: Gastroparesis assessed by charcoal meal test.[17]

Statistical analysis

The data obtained from parametric tests of this study like FPG, lipid profile were analyzed by one way ANOVA followed by Tukey's multiple comparison test and Kruskal wallis test followed by Dun's multiple comparison test for behavioral biomarkers.

The p values less than 0.05 was considered statistically significant. SPSS was used for data analysis in a personal computer.

RESULTS

The mean FPG level and lipid profile in HFD or streptozotocin induced diabetic rats treated with resveratrol at doses 10 mg/kg and 20 mg/kg were significantly decreased in comparison to that of disease control (DC) which is comparable to standard treated groups. But 5 mg/kg dose of resveratrol does not produce any significant effect on hyperglycemia. Minimum effective dose of resveratrol (10 mg/kg) with half dose of metformin (250 mg/kg) produced significant decrease in FPG and improvement in lipid profile compared with that of disease control.

Behavioural biomarkers

Assessment of neuropathic pain

In Table 1 it is observed that tail flick latency (TFL) is significantly decreased in disease control at 4 weeks i.e. 2.21±0.13 sec in comparison with normal control (2.95±0.09 sec) showing development of hyperalgesia. Groups that received resveratrol 10 mg/kg and 20 mg/kg produced significant increase in TFL i.e 2.99±0.16 and 3.33±0.13 sec respectively at 4 weeks which are similar to metformin treated group (2.96±0.05) and not significantly different from normal control. But at 6 weeks interval the TFL (4.97±0.20 sec) which is significantly increased in disease control in comparison to control received DMSO due to development of hypoalgesia, a feature of neuropathy. Resveratrol treated groups at 10 and 20 mg/kg doses significantly decreased the TFL i.e. 3.7±0.14 and 3±0.07 sec, respectively compared with that of control group at 6 weeks which is similar with metformin treated group i.e. (3.2±0.1 sec) The combined effect of resveratrol and metformin also produced significant reversal of TFL and is not significantly different from metformin alone at both the time points.

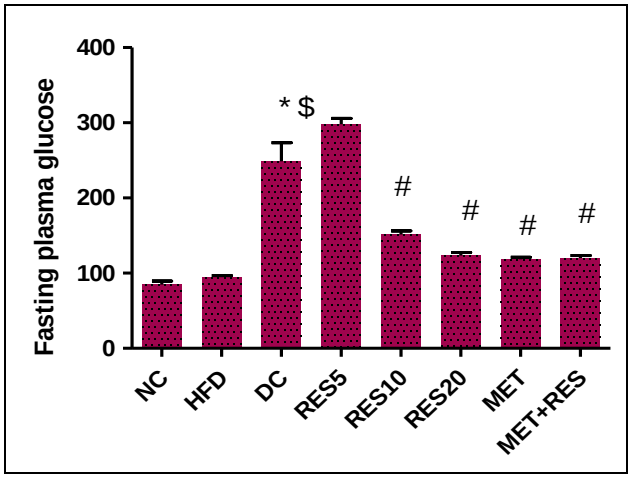

Figure 1: Effect of resveratrol on FPG concentrations in HFD and STZ induced diabetic rats (n=6).
Data expressed as Mean±SE, Resv-resveratrol, Met- metformin, *p<0.05(NC vs. DC), $ p<0.05 (HFD vs. DC), #p<0.05(DC vs. treatment groups).

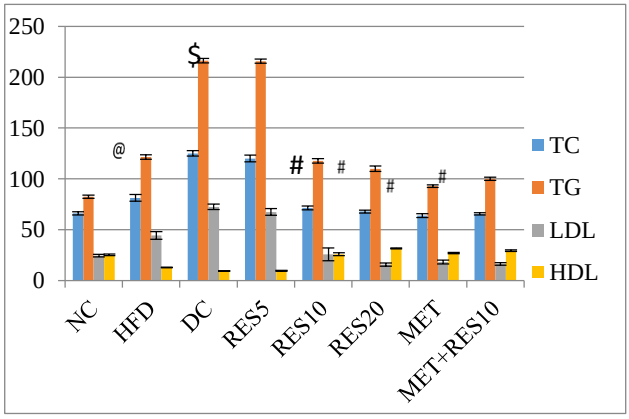

Figure 2: Effect of resveratrol on plasma lipid profile in HFD and STZ induced diabetic rats (n=6).
Data are expressed as Mean±SEM, Resv-resveratrol, Met-metformin, @ (p<0.05) (NC vs. HFD), *(p<0.001) (NC vs. DC), $p<0.05 (HFD vs. DC), #(p<0.05) (DC vs. treatment groups).

Table 1: Effect of drugs on TFL in tail immersion test in diabetic rats at 4 weeks and 6 weeks interval (n=6).

Groups		TFL (in sec)	
		4 weeks	6 weeks
Gr-II	Control (DMSO)	2.95± 0.09	2.96± 0.07
Gr-III	HFD control+ DMSO	3.37± 0.15	3.23± 0.14
Gr-IV	DC (HFD+STZ-40 mg/kg)+DMSO	2.21± 0.13*	4.97± 0.20*
Gr-V	Diabetic+Resv (5 mg/kg)	2.23± 0.14	4.8± 0.16
Gr-VI	Diabetic+Resv (10 mg/kg)	2.99± 0.16 @	3.73± 0.14@
Gr-VII	Diabetic+Resv (20 mg/kg)	3.33± 0.13 @	3± 0.07@
Gr-VIII	Diabetic+Met (500 mg/kg)	2.96± 0.05@	3.2± 0.1@
Gr-IX	Diabetic+(Resv 10 mg/kg +Met 250 mg/kg)	3.0± 0.06@	2.9± 0.08@

Data expressed as Mean±SEM, Resv-resveratrol, Met-metformin, *p<0.05 (control vs. diabetic group),@p<0.05 (diabetic group vs. treatment group).

Assessment of acetone induced cold allodynia

It was observed from Table 2, that cumulative score is significantly increased in disease control i.e. 11.17±0.40 in comparison with normal control received DMSO i.e. 0.67±0.21. Groups received resveratrol 5 mg/kg and 10 mg/kg produced decrease in cumulative score i.e. 9.67±0.21 and 5.17±0.48 respectively in comparison to disease control but it is significantly more than that of normal control, but with 20 mg /kg dose, significantly decreased i.e. 2.33±0.42 in comparison to disease control which is similar to metformin treated group and not significantly different from normal control.

It is observed from the Table 3, that cumulative score is not significantly different in disease control i.e. 0.5±0.21 in comparison with normal control i.e. 0.67±0.21. Groups received drugs also did not produced significant change in cumulative score than that of disease control.

Table 2: Effect of drugs on mean score of paw acetone test at 4 week interval (hyperalgesia) (n=6).

Groups		Mean scores				Cumulative score
		RT PAW		LT PAW		
		0 min	5 min	0 min	5 min	
Gr-II	Control (DMSO)	0.17	0.17	0.17	0.17	0.67±0.21
Gr-III	HFD control+DMSO	0.17	0.17	0.17	0.17	0.67±0.21
Gr-IV	DC(HFD+STZ- 40 mg/kg)+ DMSO	3	2.6	2.6	2.8	11.17±0.40*
Gr-V	Diabetic+Resv (5 mg/kg)	2.5	2.3	2.5	1.17	9.67±0.21
Gr-VI	Diabetic+Resv (10 mg/kg)	1.67	1.17	1.3	1	5.17±0.48#
Gr-VII	Diabetic+Resv (20 mg/kg)	0.67	0.5	0.5	0.67	2.33±0.42#
Gr-VIII	Diabetic+Met (500 mg/kg)	0.67	0.5	0.33	0.33	1.83±0.30#
Gr-IX	Diabetic+(Resv 10 mg/kg+Met 250 mg/kg)	0.3	0.3	0.3	0.67	1.67±0.21#

Data expressed as Mean±SEM, Resv-resveratrol, Met- metformin, *p<0.05 (control vs. diabetic group), #p<0.05 (diabetic group vs. treatment groups).

Table 3: Effect of drugs on mean score of paw acetone test at 6 weeks interval (hypoalgesia) (n=6).

Groups		Mean scores				Cumulative score
		RT paw		LT paw		
		0 min	5 min	0 min	5 min	
Gr-II	Control (DMSO)	0.17	0.17	0.17	0.17	0.67±0.21
Gr-III	HFD control + DMSO	0.17	0.17	0.17	0.17	0.67±0.21
Gr-IV	DC (HFD+STZ- 40 mg/kg)+ DMSO	0	0.16	0.16	0.16	0.5±0.21
Gr-V	Diabetic+Resv (5 mg/kg)	0.16	0.16	0.16	0.33	0.83±0.16
Gr-VI	Diabetic+Resv (10 mg/kg)	0.33	0.33	0.33	0.33	1.33±0.21
Gr-VII	Diabetic+Resv (20 mg/kg)	0.33	0.33	0.16	0.33	1.16±0.16
Gr-VIII	Diabetic+Met (500 mg/kg)	0.16	0.16	0.16	0.16	0.66±0.21
Gr-IX	Diabetic+(Resv10 mg/kg+Met 250 mg/kg)	0	0.16	0.16	0.16	0.50±0.22

Resv-resveratrol, Met- metformin.

To assess chemical allodynia

Table 4 showed that mean score is significantly increased in disease control (2.8±0.17, 1.83±0.17) in comparison to HFD control (0.33±0.21) as well as normal control (0.17±0.17) at both the time interval of 30 and 60 minutes. Group that received resveratrol 20 mg/kg produced significant decrease in mean score (0.5±0.21)

which is similar with metformin (0.16±0.17) treated group and not significantly different from normal control at 30 min interval in comparison to disease control. But at 60 min interval only metformin treated group (0.17±0.17) produced significant decrease in mean score whereas resveratrol 10 and 20 produced decrease in the mean score but is not statistically significant in comparison to disease control.

Table 4: Effect of drugs on mean score in formalin test in diabetic rats at 4 weeks (n=6).

Groups		Mean score	
		30 min	60 min
Gr-II	Control (DMSO)	0.17±0.17	0.17±0.17
Gr-III	HFD control+DMSO	0.33±0.21	0.33±0.21
Gr-IV	DC (HFD+STZ-40 mg/kg)+ DMSO	2.8±0.17$^{*\$}$	1.83±0.17$^{*\$}$
Gr-V	Diabetic+Resv (5 mg/kg)	2.3±0.21	1.67±0.21
Gr-VI	Diabetic+Resv (10 mg/kg)	1.16±0.17	1±0.26
Gr-VII	Diabetic+Resv (20 mg/kg)	0.5±0.21$^{\#}$	0.33±0.21
Gr-VIII	Diabetic+Met (500 mg/kg)	0.16±0.17$^{\#}$	0.17±0.17$^{\#}$
Gr-IX	Diabetic+(Resv 10 mg/kg+ Met 250 mg/kg)	0.33±0.21$^{\#}$	0.17±0.17$^{\#}$

Data expressed as mean±SEM, Resv-resveratrol, Met-metformin, *p<0.05 (control vs. diabetic group), $p<0.05 (HFD vs. DC), $^{\#}$p<0.05 (diabetic group vs. treatment groups).

Table 5: Effect of drugs on charcoal meal test in diabetic rats.

	Groups	Gastrointestinal transit (%)
Gr-II	Control (DMSO)	61.03±0.47
Gr-III	HFD control + DMSO	61.28±0.65
Gr-IV	DC (HFD+STZ-40 mg/kg)	28.17±0.98$^{*\$}$
Gr-V	Diabetic+Resv (5 mg/kg)	27.58±0.99
Gr-VI	Diabetic+Resv (10 mg/kg)	41.63±0.81#
Gr-VII	Diabetic+Resv (20 mg/kg)	52.17±0.37#
Gr-VIII	Diabetic+Met (500 mg/kg)	60.15±1.37#
Gr-IX	Diabetic +(Resv 10 mg/kg +Met 250 mg/kg)	55.40±1.79#
	F value	191.3

Data expressed as mean±SEM, Resv-resveratrol, Met-metformin, *p<0.05 (control vs. diabetic group), $ p<0.05 (HFD vs DC), $^{\#}$p<0.05 (diabetic group vs. treatment groups).

Functional biomarkers

It was observed from Table 5, that gastrointestinal transit (%) is significantly decreased in disease control (28.17±0.98%) in comparison with normal control (61.03±0.47%) as well as in HFD (61.28±0.65%). Groups received resveratrol at a dose of 10 and 20 mg/kg produced significant increase in the gastrointestinal (GI) transit percentage (41.63±0.81 and 52.17±0.37%) which is similar to metformin (60.15±1.37%) and not significantly different from normal control.

DISCUSSION

This study has been undertaken to evaluate the effect of resveratrol on diabetic neuropathy in HFD and low dose STZ (40 mg/kg) model of type 2 DM in wistar albino rats. The effect resveratrol in different doses like 5, 10 and 20 mg/kg, were studied by estimating biochemical parameters (FPG, lipid profile) in plasma, behavioral biomarkers of neuropathy (tail flick latency using tail immersion test, acetone induced cold allodynia, chemical allodynia using formalin test) and functional biomarker of autonomic neuropathy using charcoal meal test. The results were compared with that of standard drug (metformin). Wistar albino rats are selected for the study as they are standardized experimental animals and streptozotocin induces diabetes in experimental animals showing significantly higher FPG and lipid abnormalities.[18]

To mimic type 2 DM, a single low dose of STZ at 40 mg/kg body weight was injected after 2 weeks of HFD feeding. High doses of STZ (>40 mg/kg body weight) is well known to be taken by pancreatic β-cells via GLUT2 and to induce severe damages of pancreatic β-cells, mimicking type 1 DM.[19] But the combination of HFD and low doses of STZ resulted in characteristic of type 2 DM where insulin resistance plays a major role in pathophysiology leading to various metabolic alterations like increased blood glucose level, hyperinsulinemia, and dyslipidemia.[20] So in this present study HFD or low dose STZ model was selected. This model was also based on the principle that an increased level of blood sugar, dyslipidemia, derangement of oxidative stress parameter in a diabetic rat lead to development of neuropathy. This condition is characterized by altered pain threshold (hyperalgesia, hypoalgesia and allodynia) due to the hyperactivity / inactivation of nociceptive 'C' fibers and other mechanisms and gastroparesis due to autonomic neuropathy. These characteristics were assessed by observing behavioral and functional biomarkers of DN in this model.[21]

Early treatment with antidiabetic dugs and lifestyle modification are often recommended for prevention and control of diabetes and its complications. Though there are a good number of drugs available to control the disease but most of them are not free from lethal unwanted effects. Thus, there has been a growing interest

in pharmaceutical products with the least side effects and the maximal preventive outcome.[22] Resveratrol which is used as nutritional supplements has been reported in several studies to possess antihyperglycemic, beneficial effect on lipid profile.[8] It also prevents development of various complications. So the present study was undertaken to evaluate the effects of resveratrol to know whether it has got any beneficial effects on type 2 DM and can prevent development of diabetic neuropathy or not.

In this study vehicles used like distilled water and DMSO didn't produce any change in biochemical parameters.

Effect on FPG level

DC group received HFD or STZ produced significant increase in plasma glucose level in this present study.[20] Resveratrol treated groups in doses 10 and 20 mg/kg for a period of 14 days produced significant decrease in FPG in comparison to disease control which was consistent with Jung et al study.[20] This effect is similar to standard drug metformin. The combined effect of resveratrol with metformin showed significant decrease in plasma glucose level which is comparable with normal control group.[23]

Effect on lipid profile

Resveratrol in doses 10 and 20 mg/kg produced significant decrease in TC, TG and LDL level with increase in HDL level in a dose dependent manner in comparison to disease DC which showed beneficial effect on dyslipidemia due to diabetes. Result of the present study corroborates with observations made by Shahi et al.[24] Also metformin alone as well as in combination with resveratrol showed significant improvement in plasma lipid profile in diabetic rats, comparable with normal control.

Effect on neuropathic pain

Effect on thermal test

At 4 weeks of induction of diabetes, the DC group showed significant decrease in pain threshold to hot (tail flick latency) and cold form of nociception (acetone induced cold allodynia) as indicated by tail immersion test and acetone paw test respectively. The pain produced, is due to hyperalgesia in tail immersion test (hot) whereas allodynia occured in case of acetone paw test. These characteristics are may be due to altered sensory processing is developed in case of diabetic neuropathy to mild nocifensive responses (hyperalgesia) and to normally non-painful stimuli (allodynia).[25] Pretreatment with resveratrol in doses (10 and 20 mg/kg) produced significant increase in pain threshold in comparison to DC which corroborates with Sharma et al.[26] Result showed resveratrol's protective effect against DN.

Metformin alone as well as in combination with resveratrol showed significant protection against pain behavior.

At 6 weeks after induction of diabetes, hypoalgesia developed leading to significant increase in TFL. This development of hypoalgesia may be the result of nerve damage due to DM. Resveratrol at dose of 20 mg/kg showed significant change in TFL in comparison to diabetic group and is comparable to that of normal control.[27] In paw acetone test similarly due to hypoalgesia cumulative score is not significantly different in disease control compared with normal control. Groups received standard and test drugs also did not produced any significant change in cumulative score than that of disease control. This effect is similar to that of normal control.

Effect on chemical test

This study was conducted once only considering persistent nature of tissue damage by formalin. At 4 weeks of induction of diabetes, the disease control group showed significant decrease in pain threshold at both the time intervals (30 and 60 mins) of late tonic phase (15-60 mins) which may be due to role of neurotransmitters such as spinal prostaglandin in tonic phase in diabetic neuropathy.[25] Pretreatment with resveratrol in doses (10 and 20 mg/kg) produced increase in pain threshold in comparison to disease control. Metformin alone as well as combination with resveratrol showed significant protection against pain behaviour in comparison to disease control which is comparable with normal control group.

Effect on autonomic neuropathy

At 8 weeks, it is observed that gastrointestinal transit (%) is significantly decreased in DC in comparison with normal control which showed the development of gastroparesis due to autonomic neuropathy associated with prolonged untreated type 2 DM.[28] Resveratrol pretreated group at 10 and 20 mg/kg doses produced significant increase in GI transit percentage compared with that of DC which is similar to metformin treated group and not significantly different from normal control showing prevention of autonomic neuropathy.

So results show the prevention of behavioral and functional biomarkers of neuropathy, corroborates with Kumar et al.[23]

CONCLUSION

Predisposing factors for development of DN in type 2 DM are hyperglycemia, insulin resistance, dyslipidemia and oxidative stresses. Resveratrol at a dose of 10 and 20 mg/kg and combination with metformin produced significant protection against development of neuropathy in this study due to its better control over the predisposing factors. Basing on this evidence it can be concluded that

test drug (resveratrol) itself and its combination with other antidiabetic drug can be evaluated to control blood glucose in type 2 DM and for preventive therapy in patient at risk of developing complications like DN. By this the dose of antidiabetic agent can be reduced and may limit the incidence of adverse drug reaction because of particular drug. Therefore it can be suggested to consider test drug for more and more animal studies and further clinical trials to establish its clinical use in future.

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