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RESEARCH ARTICLE

ANTIDIABETIC AND ANTIHYPERTENSIVE EFFECT OF DEHYDROZINGERONE IN MODEL OF STREPTOZOTOCIN INDUCED DIABETIC AND NΩ- NITRO-L ARGININE METHYL ESTER HYDROCHLORIDE (L-NAME) HYPERTENSIVE RATS

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ABSTRACT

Diabetic hypertension continues to be the leading health problem around the globe. The goal of this study was to examine the effect of dehydrozingerone (DZ), (4-(4-hydroxy-3-methoxyphenyl)-3-buten-2-one) on type 2 diabetes and hypertension induced in male Wistar rats. Type 2 Diabetes mellitus was induced by a single intraperitoneal injection (40 mg/kg bw) of streptozotocin (STZ) and hypertension was induced by daily oral administration of N^{ω}-Nitro-L-arginine methyl ester (L-NAME) 40 mg/kg bw dissolved in drinking water for 4 weeks. Effects of DZ against diabetic hypertension were assessed by measuring systolic and diastolic blood pressure, and biochemical parameters such as plasma glucose, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltranspeptidase (GGT), in serum and urea, uric acid and creatinine in plasma. Intraperitoneal injection of DZ (50, 100 and 200 mg/kg bw) to diabetic hypertensive induced rats significantly reduced plasma glucose levels and systolic and diastolic blood pressure. The hepatic and renal functional markers are also significantly decreased. Our histopathological examination confirmed the biochemical findings. Among the three doses used, DZ at a dose of 100 mg/kg was effective compared to other two doses. Our results suggested that DZ has the potential to reduce diabetic and hypertension in STZ and L-NAME induced diabetic hypertensive rats.

INTRODUCTION

The presence of hypertension is about twice often in diabetic patients compared to the general population, and diabetic hypertension is associated with increased morbidity and mortality (Contreras *et al*., 2000; Marry and McLay, 1998). Hypertension aggravates the complications of diabetes. Indeed, the co-existence of these two conditions is a powerful promoter of cardiovascular disease (CVD) by accelerating micro and macrovascular complications and greatly increasing possibility of stroke and end stage renal disease risk (Kubra *et al*., 2013). During the last few years, efforts have been made to increase the number of synthetic antihypertensive drugs, but their use is often limited because of their adverse effects. In recent years, dietary agents such as increased consumption of fruits, vegetables, whole grains, and fish have been shown to be important in the control of CVD including hypertension (Retelny *et al*., 2008). Ginger (*Zingiber officinale* Roscoe; family Zingiberaceae) is one of the most common spices with an array of applications in traditional Indian, Ayurvedic and Unani-Tibb medicines. It possesses various pharmacological activities including cardiovascular protection, anti-oxidant, anti-inflammatory and anti-cancer activities (Shukla and Singh, 2007).The health-promoting effects of ginger are due to its rich phytochemical constituents (Rosenthal and Younis, 2010). One of the phytochemicals isolated from ginger rhizomes is DZ. It is an unsaturated derivative of the natural product zingerone (Rajkumar and Rao, 1993) Figure: 1.

Fig. 1. Structure of dehydrozingerone (DZ)

Dehydrozingerone (DZ) (Fig.1) is an unsaturated derivative of the natural product zingerone and also a metabolic product of curcumin. It is a phenolic derivative with anortho-hydroxyl substituted compound. It possesses many structural similarities with curcumin (Rajakumar and Rao, 1994). It possesses various pharmacological activities including cardiovascular

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protection, antioxidant, anti-inflammatory, anti-cancer activities, and so on (Shukla and Singh 2007). Extensive literature survey has shown that to sufficient work has been dose to study its antidiabetic and antihypertensive effects. Through this study we evaluate the diabetic hypertensive in STZ, L-NAME induced rats.

MATERIALS AND METHODS

Experimental animals

Male albino Wistar rats were obtained from the Central Animal House, Department of Experimental Medicine, Rajah Muthiah Medical College and Hospital, Annamalai University, Tamilnadu, India. They were housed in polypropylene cages with husk and pellet diet (Kamadhenu Agencies, Bangalore, India). The whole experiment was carried out according to the guidelines of the committee for the purpose of control and supervision of experiments on animals, New Delhi, India and approved by the animal ethical committee of Annamalai University.

Drugs and chemicals

Dehydrozingerone (DZ), Streptozotocin (STZ) and N-Nitro-L-arginine methyl ester (L-NAME) were purchased from Sigma-Aldrich Company (St. Louis, Missouri, USA). All other chemicals used were of analytical grade obtained from E. Merck, Mumbai and HIMEDIA, Mumbai, India.

Preparation and mode of administration of DZ

Three different doses of DZ (50, 100 and 200 mg) for intraperitoneal injection were prepared by dissolving it in 1% Carboxy Methyl Cellulose (CMC) freshly before use (Parihara *et al*., 2007).

Experimental protocol

The rats were randomly divided into seven groups each consisting of six rats

Group 1: Control rats
Group 2: STZ treated diabetic control rats
Group 3: L-NAME induced hypertensive control rats
Group 4: STZ + L-NAME treated diabetic hypertensive control rats
Group 5: Diabetic hypertensive rats with DZ (50mg/kg bw)
Group 6: Diabetic hypertensive rats with DZ (100mg/kg bw)
Group 7: Diabetic hypertensive rats with DZ (200mg/kg bw)
After four weeks, all the rats were sacrificed by cervical dislocation. Blood samples were collected from all the rats for the estimation of various biochemical parameters.

Measurement of blood pressure by non-invasive method

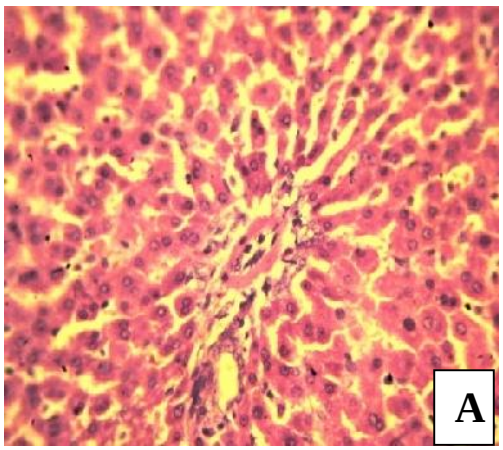
Systolic and diastolic blood pressure values were recorded every week during the entire period of the study by tail cuff method (IITC, model 31, Woodland Hills, CA, USA). The rats were placed in a heated chamber at an ambient temperature (30-34ºC) for 15 minutes and from each rat, 1-9 blood pressure values were recorded. The lowest three readings were averaged to obtain a mean blood pressure. All the data recorded were analysed using a computerized data acquisition system and software.

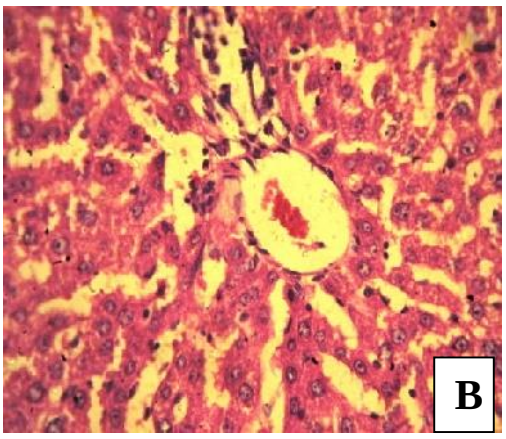
Biochemical estimations

Glucose was estimated by the method of Trinder (Trinder, 1969) using a reagent kit. The activities of serum AST, ALT, ALP and GGT were assayed by the method of Reitman and Frankel (1957), Kind and King (1954), Rosalki and Rau (1972), respectively. The levels of urea, uric acid and creatinine in plasma were estimated by diagnostics kit (Qualigens Diagnostics, Mumbai, India) based on the method of Fawcett and Scott (1960), Caraway (1955) and Tietz (1987).

Histopathological examination of hepatic and renal tissues

The hepatic and renal tissues obtained from all experimental groups were washed immediately with saline and then stored in 10% buffered neutral formalin. The tissues were processed by embedding in paraffin wax. The tissues were then, sectioned (3-5 µm) and stained with haematoxylin and eosin (H&E) dye and examined under a high power microscope (Nikon ELWD 0.3/OD75; Japan). Microscopic photomicrographs of hepatic tissues and renal tissues are presented in Figure 2 and 3.





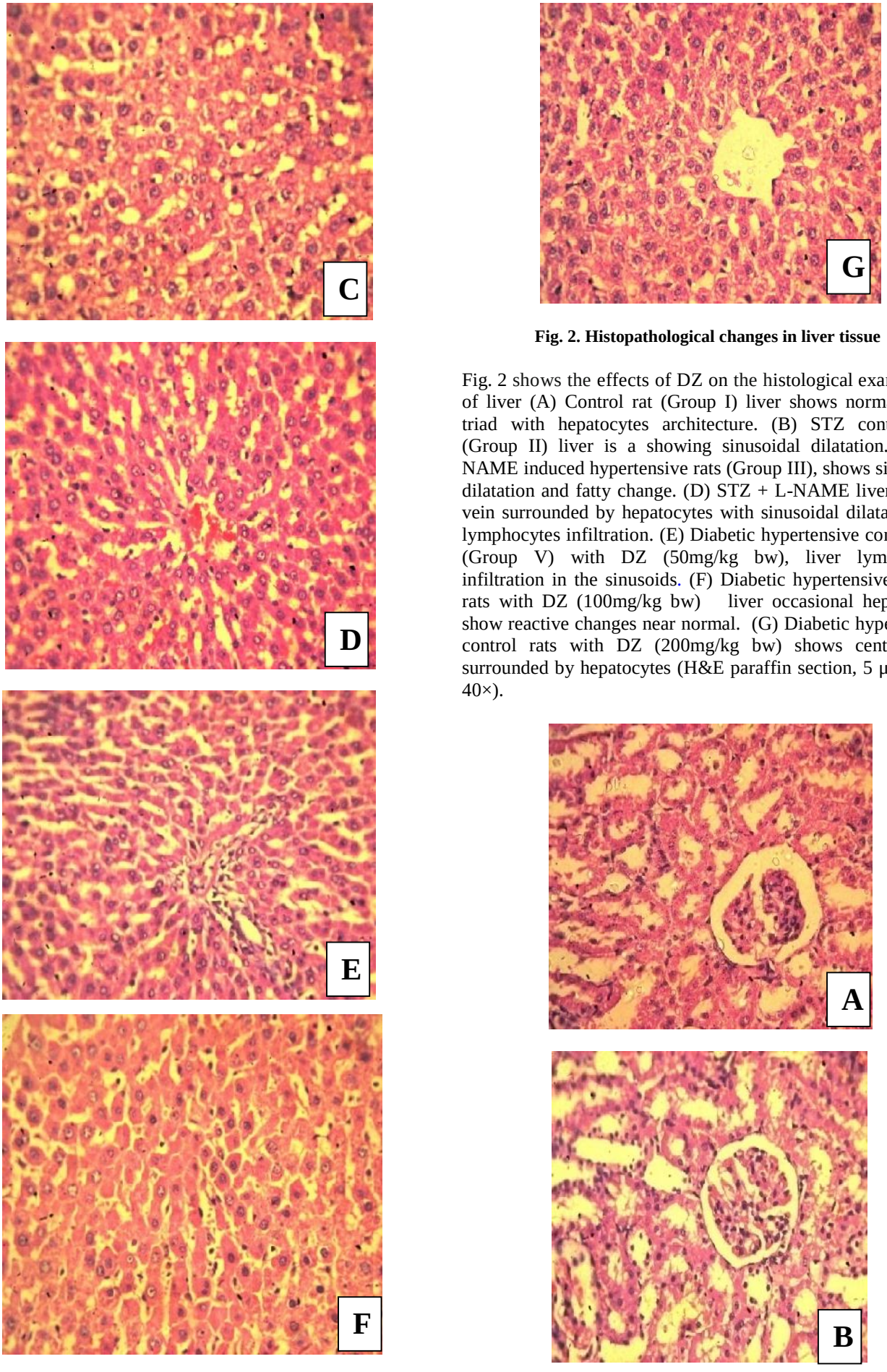


Fig. 2. Histopathological changes in liver tissue

Fig. 2 shows the effects of DZ on the histological examination of liver (A) Control rat (Group I) liver shows normal portal triad with hepatocytes architecture. (B) STZ control rats (Group II) liver is a showing sinusoidal dilatation. (C) L-NAME induced hypertensive rats (Group III), shows sinusoidal dilatation and fatty change. (D) STZ + L-NAME liver cubical vein surrounded by hepatocytes with sinusoidal dilatation and lymphocytes infiltration. (E) Diabetic hypertensive control rats (Group V) with DZ (50mg/kg bw), liver lymphocytic infiltration in the sinusoids. (F) Diabetic hypertensive control rats with DZ (100mg/kg bw) liver occasional hepatocytes show reactive changes near normal. (G) Diabetic hypertensive control rats with DZ (200mg/kg bw) shows central vein surrounded by hepatocytes (H&E paraffin section, 5 µm thick, 40×).

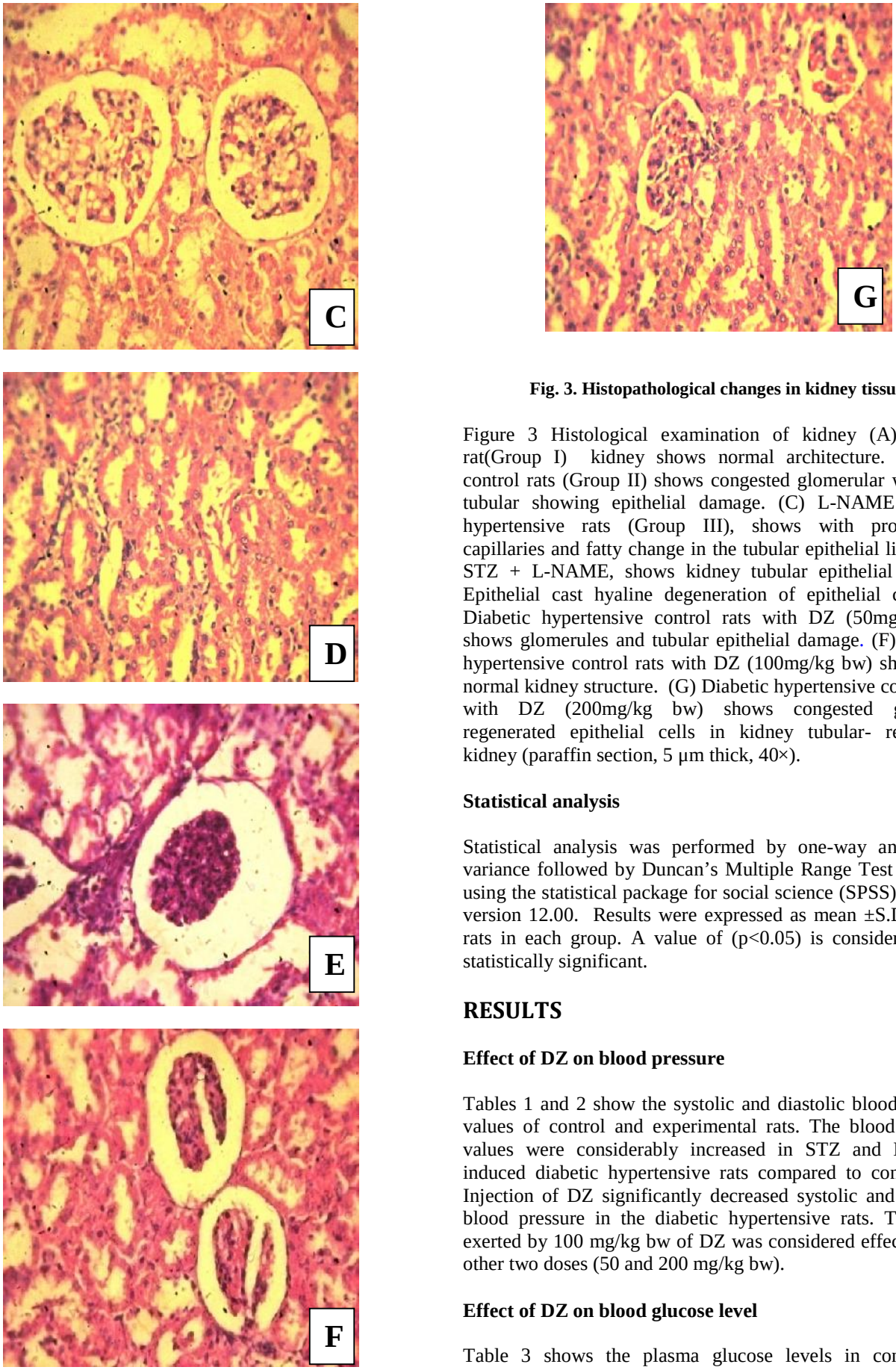


Fig. 3. Histopathological changes in kidney tissue

Figure 3 Histological examination of kidney (A) Control rat(Group I) kidney shows normal architecture. (B) STZ control rats (Group II) shows congested glomerular with little tubular showing epithelial damage. (C) L-NAME induced hypertensive rats (Group III), shows with proliferating capillaries and fatty change in the tubular epithelial lining. (D) STZ + L-NAME, shows kidney tubular epithelial damage, Epithelial cast hyaline degeneration of epithelial cells. (E) Diabetic hypertensive control rats with DZ (50mg/kg bw), shows glomerules and tubular epithelial damage. (F) Diabetic hypertensive control rats with DZ (100mg/kg bw) shows near normal kidney structure. (G) Diabetic hypertensive control rats with DZ (200mg/kg bw) shows congested glomeruli regenerated epithelial cells in kidney tubular- recovering kidney (paraffin section, 5 µm thick, 40×).

Statistical analysis

Statistical analysis was performed by one-way analysis of variance followed by Duncan's Multiple Range Test (DMRT) using the statistical package for social science (SPSS) software version 12.00. Results were expressed as mean ±S.D. for six rats in each group. A value of ($p<0.05$) is considered to be statistically significant.

RESULTS

Effect of DZ on blood pressure

Tables 1 and 2 show the systolic and diastolic blood pressure values of control and experimental rats. The blood pressure values were considerably increased in STZ and L-NAME induced diabetic hypertensive rats compared to control rats. Injection of DZ significantly decreased systolic and diastolic blood pressure in the diabetic hypertensive rats. The effect exerted by 100 mg/kg bw of DZ was considered effective than other two doses (50 and 200 mg/kg bw).

Effect of DZ on blood glucose level

Table 3 shows the plasma glucose levels in control and experimental rats. The levels were considerably increased in the diabetic hypertensive rats compared to control rats.

Intraperitonial injection of DZ considerably decreased the plasma glucose levels. The values were near to normal on dose of 100 mg/kg bw of DZ compared to other two doses making it a better dosage.

Effect of DZ on the activities of hepatic marker enzymes

The activities of AST, ALT, ALP and GGT in the serum of control and experimental rats were depicted in Table 4. STZ and L-NAME induced diabetic hypertensive rats exhibited a

Table 1. Effect of Dehydrozingerone on SYSTOLIC BLOOD PRESSURE in L-NAME induced hypertension in diabetic rats

GROUP	0 day (mm/Hg)	1 week (mm/Hg)	2 week (mm/Hg)	3 week mm/Hg)	4 week (mm/Hg)
CONTROL	107.64±8.30	105.32±8.21^{a}	108.31±7.20^{a}	110.36±9.53^{a}	112.64±7.70^{a}
STZ CONTROL	114.24±9.36	121.02±9.61^{c}	142.11±12.17^{d}	157.06±13.60^{d}	168.12±12.24^{c}
L-NAME CONTROL	104.73±9.43	127.20±9.40^{c}	154.45±11.06^{e}	163.07±14.35^{e}	177.89±13.40^{d}
STZ+L-NAME+CONTROL	115.36±9.6	142.10±12.70^{e}	159.62±11.60^{f}	174.67±14.78^{f}	182.80±14.70^{e}
STZ+L-NAME+DZ(50mg)	106.28±7.61	132.71±11.54^{d}	159.62±9.20^{c}	128.51±10.50^{c}	136.73±11.48^{b}
STZ+L-NAME+DZ(100mg)	110.21±8.2	108.70±8.18^{a}	159.62±8.54^{a}	112.09±9.80^{a}	117.64±8.30^{a}
STZ+L-NAME+DZ(200mg)	107.96±10.3	112.21±9.29^{b}	114.30±12.84^{b}	118.31±7.20^{b}	120.07±9.42^{a}

Values are means ± S.D. for six rats in each group
Values not sharing a common superscript differ significantly at p<0.05. Multiple Range Test (DMRT)

Table 2. Effect of Dehydrozingerone on DIASTOLIC BLOOD PRESSURE in L-NAME induced hypertension in diabetic rats

GROUP	0 day (mm/Hg)	1 week (mm/Hg)	2week (mm/Hg)	3 week (mm/Hg)	4 week (mm/Hg)
CONTROL	78.32±4.40	79.36±5.20^{a}	77.10±4.67^{a}	76.70±4.21^{a}	73.36±4.20^{a}
STZ CONTROL	82.32±5.30	89.61±6.45^{c}	88.89±5.25^{c}	97.75±7.48^{b}	102.82±8.40^{c}
L-NAME CONTROL	80.67±7.70	92.80±7.40^{d}	97.09±7.64^{d}	101.34±8.56^{c}	113.18±7.6^{d}
STZ+L-NAME+CONTROL	86.24±8.75	96.12±8.75^{e}	107.04±9.38^{e}	111.77±9.22^{d}	124.03±10.1^{e}
STZ+L-NAME+DZ(50mg)	85.00±5.37	88.32±5.59^{c}	95.68±6.21^{d}	96.98±7.65^{b}	92.26±6.36^{c}
STZ+L-NAME+DZ(100mg)	81.84±4.23	83.42±4.48^{a}	83.12±6.07^{a}	81.28±4.80^{a}	76.42±4.22^{a}
STZ+L-NAME+DZ(200mg)	83.21±5.62	85.60±6.78^{b}	84.61±7.35^{a}	82.14±5.30^{a}	79.30±5.77^{b}

Values are means ± S.D. for six rats in each group
Values not sharing a common superscript differ significantly at p<0.05. Multiple Range Test (DMRT)

Table 3. Effect of Dehydrozingerone on GLUCOSE LEVELS in L-NAME induced hypertension in diabetic rats

GROUP	Glucose initial (mg/dL)	Glucose final (mg/dL)
CONTROL	87.05±4.10^{a}	90.53±7.28^{a}
STZ CONTROL	343.28±22.4^{d}	370.02±21.40^{d}
L-NAME CONTROL	164.35±12.5^{c}	192.24±17.20^{c}
STZ+L-NAME+CONTROL	407.61±27.21^{e}	442.98±32.08^{e}
STZ+L-NAME+DZ(50mg)	324.58±20.25^{d}	388.16±25.47^{d}
STZ+L-NAME+DZ(100mg)	115.80±9.24^{b}	118.67±6.61^{b}
STZ+L-NAME+DZ(200mg)	118.13±9.32^{b}	120.54±10.19^{b}

Values are means ± S.D. for six rats in each group
Values not sharing a common superscript differ significantly at p<0.05. Multiple Range Test (DMRT)

Table 4. Effect of Dehydrozingerone on HEPATIC MARKERS in L-NAME induced hypertension in diabetic rats

GROUP	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	GGT(IU/L)
CONTROL	28.31±1.65^{a}	71.28±5.06^{a}	76.28±5.43^{a}	16.63±0.42^{a}
STZ CONTROL	70.47±4.98^{c}	112.0±8.15^{c}	132.1±9.56^{c}	29.84±1.88^{c}
L-NAME CONTROL	74.63±5.52^{c}	117.2±9.24^{c}	139.4±8.82^{c}	32.09±1.57^{c}
STZ+L-NAME+CONTROL	86.28±4.64^{e}	120.5±7.42^{d}	148.6±9.74^{d}	35.37±1.25^{d}
STZ+L-NAME+DZ(50mg)	80.42±4.36^{d}	118.2±5.22^{c}	145.3±6.14^{d}	32.30±1.40^{c}
STZ+L-NAME+DZ(100mg)	45.51±3.86^{b}	85.72±6.59^{b}	99.07±7.62^{b}	19.75±0.33^{a}
STZ+L-NAME+DZ(200mg)	48.65±2.25^{b}	87.06±6.48^{b}	102.5±5.47^{b}	21.64±0.78^{b}

Values are means ± S.D. for six rats in each group
Values not sharing a common superscript differ significantly at p<0.05. Multiple Range Test (DMRT)

Table 5. Effect of Dehydrozingerone on RENAL FUNCTION MARKERS in L-name induced hypertension in diabetic rats

GROUP	UREA (mg/dL)	URIC ACID (mg/dL)	CREATININE (mg/dL)
CONTROL	20.97±1.76^{a}	2.67±0.25^{a}	0.94±0.04^{a}
STZ CONTROL	46.47±3.98^{d}	3.71±0.36^{c}	2.45±0.25^{c}
L-NAME CONTROL	47.58±3.52^{d}	4.02±0.38^{d}	2.68±0.12^{c}
STZ+L-NAME+CONTROL	54.28±2.64^{e}	5.08±0.28^{e}	4.47±0.39^{e}
STZ+L-NAME+DZ(50mg)	42.51±2.86^{c}	3.10±0.74^{b}	3.31±0.24^{d}
STZ+L-NAME+DZ(100mg)	25.51±1.86^{b}	2.60±0.47^{a}	1.08±0.11^{b}
STZ+L-NAME+DZ(200mg)	26.40±0.76^{b}	2.64±0.08^{a}	1.12±0.17^{b}

Values are means ± S.D. for six rats in each group
Values not sharing a common superscript differ significantly at p<0.05. Multiple Range Test (DMRT)

considerable ($p<0.05$) increase in the activities of these marker enzymes compared to control rats. DZ (50, 100 and 200 mg/kg bw) significantly ($p<0.05$) reduced the activities of these enzymes in the diabetic hypertensive rats.

Effect of DZ on renal function markers

The values of renal function markers such as urea, uric acid and creatinine in plasma are presented in Table 5. The levels of plasma urea, uric acid and creatinine were considerably ($p<0.05$) increased in the diabetic hypertensive rats compared to control rats. Intraperitonially injection of DZ decreased the levels of these markers in plasma.

Histopathology of liver

Fig. 2 shows the effects of DZ on the histological examination of liver (A) Control rat (Group I) liver shows normal portal triad with hepatocytes architecture. (B) STZ control rats (Group II) liver is a showing sinusoidal dilatation. (C) L-NAME induced hypertensive rats (Group III), shows sinusoidal dilatation and fatty change. (D) STZ + L-NAME liver cubical vein surrounded by hepatocytes with sinusoidal dilatation and lymphocytes infiltration. (E) Diabetic hypertensive control rats (Group V) with DZ (50mg/kg bw), liver lymphocytic infiltration in the sinusoids. (F) Diabetic hypertensive control rats with DZ (100mg/kg bw) liver occasional hepatocytes show reactive changes near normal. (G) Diabetic hypertensive control rats with DZ (200mg/kg bw) shows central vein surrounded by hepatocytes (H&E paraffin section, 5 µm thick, 40×).

Histopathology of kidney

Figure 3 Histological examination of kidney (A) Control rat (Group I) kidney shows normal architecture. (B) STZ control rats (Group II) shows congested glomerular with little tubular showing epithelial damage. (C) L-NAME induced hypertensive rats (Group III), shows with proliferating capillaries and fatty change in the tubular epithelial lining. (D) STZ + L-NAME, shows kidney tubular epithelial damage, Epithelial cast hyaline degeneration of epithelial cells. (E) Diabetic hypertensive control rats with DZ (50mg/kg bw), shows glomerules and tubular epithelial damage. (F) Diabetic hypertensive control rats with DZ (100mg/kg bw) shows near normal kidney structure. (G) Diabetic hypertensive control rats with DZ (200mg/kg bw) shows congested glomeruli regenerated epithelial cells in kidney tubular- recovering kidney (paraffin section, 5 µm thick, 40×).

DISCUSSION

Diabetes, hypertension, dyslipidemia and obesity were independent risk factors for the development of cardiovascular disease, with hypertension being the most common risk factor (Andersson and Svardsudd 1995, Laakso 1996, Lehto *et al* 1997 and Lehto *et al* 1996). Importantly, in diabetic patients a clustering of risk factors commonly occurs which markedly increases the risk for the development of cardiovascular pathology. In view of the need for effective medication to supplement lifestyle changes to control these disease states, utilizations of plant-based therapies were currently advocated (Tuso *et al*., 2013) Such therapies offer potentially cost-effective management but need scientific validation of their effects.

In the present study, the antidiabetic and antihypertensive effect of DZ was studied in the model of STZ induced diabetic and L-NAME hypertensive rats. Diabetes mellitus is a disease due to abnormalities of carbohydrate metabolism, STZ, which was a specific cytotoxic agent for pancreatic b-cells, has been confirmed to have a diabetogenic action and the intensity of the damage were graded according to the dosage used (Mythili *et al*., 2004). The mechanism by which STZ brings about its diabetic state includes impaired glucose tolerance and loss of b-cell sensitivity to glucose (Arulmozhi *et al*., 2004), which make cells less active and lead to poor glucose utilization by tissues (Junod *et al*., 1969; Elsner *et al*., 2000). Chronic inhibition of NO synthase by administration of L-NAME was associated with induction of hypertension, hypertrophy, cardiac remodeling (Baylis *et al*., 1992; Ulker *et al*., 2003), and renal functional alterations (Sharifi *et al*., 2005; Pereira *et al*., 2004). Our study STZ and L-NAME-treated rats reflected by glycosuria, hyperglycemia, hypoinsulinaemia, polyphagia, and polydypsia and also significantly increased blood pressure when compared to normal rats. Treatment with DZ significantly reduced the plasma glucose level and blood pressure in STZ and L-NAME induced diabetic hypertensive rats. It was already reported that the phenolic compounds reduces blood pressure and prevent target organ damage in hypertensive rats (Jalilietal.2006). DZ was a phenol acting as an antioxidant by scavenging both chain initiating and chain propagating free radicals. This effect directly indicates that part of the antihyperglycemic and antihypertensive activity. DZ possesses various pharmacological activities including cardiovascular protection, antioxidant, anti-inflammatory, anti-cancer activities, and so on (Shukla and Singh 2007). It is evident that DZ supplementation significantly decreased blood pressure in STZ and L-NAME treated groups.

Liver injury due to STZ and L-NAME intoxication could be assessed by measuring the activities of hepatic marker enzymes which were the biochemical hallmarks of hepatic damage (Raza *et al*., 2003). The transaminase enzymes, such as AST, ALT were regarded as the most reliable markers of hepatic injury (Chenoweth and Hake, 1962) might be very useful in studying the oxidative stress related issues. In the present study, the increased activities of AST, ALT, ALP and GGT levels after STZ and L-NAME treatment reflect the destructive effect of the cell membrane, which causes outflow of these enzymes from hepatocytes as a result of membrane breakage, showing a clear evidence for liver damage (Murali and Saravanan, 2012; Prahalathan *et al*., 2012). This could be due to necrotic and oxidative action on hepatic tissues. Treatment with DZ considerably reduced these enzymes activity. It was believed that DZ aids in parenchymal cell regeneration in liver, thus protecting membrane reliability. Histopathological examination of hepatic tissues confirmed our biochemical findings. Administration of DZ to the diabetic hypertensive rats showing a remarkable recovery in liver as evidenced microscopically. The findings suggest the therapeutic potential use of the DZ for liver ailments for ameliorating

hepatotoxicity. The kidney plays a key role in the regulation of solidity of the body wastages, and in sodium homeostasis (George *et al*., 2008). Elevation of the serum urea and creatinine, as significant markers are related to renal dysfunction in diabetic hyperglycemia (Almdal and Vilstrup, 1988).Our results revealed that renal functional markers such as urea, uric acid and creatinine has been considerably increased in the plasma of the diabetic hypertensive rats and this could be due to renal damage caused by increased formation of superoxide ions (Chua and Bakris, 2004). Administration of DZ significantly decreased these markers such as urea, uric acid and creatinine. It has been suggested that renal and cardiac injury can be avoided or minimized by reducing oxidative stress through increased intake of antioxidants (Indira Priyadarsini *et al*., 1999; Parihar *et al*., 2007; Kuo *et al*., 2005). These findings were correlated well with histological examination. Administration of DZ to the diabetic hypertensive rats considerably reduced the fatty change in the tubular epithelial lining, an evidenced microscopically. This effect could be due to its antioxidant property. These results indicated that renal damage can remarkably be recovered by the treatment of DZ.

Conclusion

Our results clearly proved that DZ possesses anti-diabetic and anti-hypertensive effects against the diabetic hypertensive rats, which were evidenced by a considerable decrease in blood pressure, blood glucose level, hepatic and renal functional markers. DZ at a dose of 100 mg/kg/bw elicited better effects than its other two doses.

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