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Research Article

Modulatory Role of Resveratrol on Body Weight and Some Liver Enzymes in a Diabetic Nephropathy Rat Model

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Abstract
Diabetic nephropathy is one of the most feared complications of diabetes. An important aspect in the management of diabetic nephropathy is the maintenance of optimal weight, which is difficult with conventional anti-diabetic drugs. Resveratrol, a polyphenolic compound, has been used to prevent/treat several chronic diseases including type-2 diabetes due to its strong antioxidant and other properties. This study aimed to investigate the effect of resveratrol on weight gain and some liver enzymes in hyperglycemia-induced diabetic nephropathy in male Wistar rats. Twenty-five adult male Wistar rats were randomly divided into 5 groups of 5 rats each: normal control, normoglycemic, diabetic untreated, diabetic treated with resveratrol and diabetic treated with lisinopril. Diabetes was induced by feeding the rats high-fat diet and 20% fructose solution as drinking water for 6 weeks followed by a single intraperitoneal streptozotocin injection (35 mg/kg). The resveratrol and lisinopril treatment lasted for 5 weeks after which the rats were humanely sacrificed. The mean body weight of the group treated with resveratrol was increased from the 8th week (180.25 ± 7.73g), when compared to the diabetic control (164.50 ± 2.02g) but markedly decreased compared to the normal control (225.25 ± 11.24g) and these findings were consistent up to the 12th week. There was a significant reduction in alanine transferase level in the group treated with resveratrol compared to the diabetic control group (24.00 ± 0.58 and 38.25± 3.07 IU/L respectively). In conclusion, Resveratrol played a modulatory role on body weight and ameliorated derangement in alanine transferase levels in diabetic nephropathy in Wistar rats.

Key Words: *diabetes nephropathy, liver enzymes, weight gain, resveratrol, lisinopril, Wistar rats*

INTRODUCTION

Diabetic nephropathy (DN) is one of the most important and dreaded complications of diabetes mellitus. It is a chronic progressive renal disease, as a result of poorly controlled hyperglycemia (Sagoo and Gnudi, 2020). Globally, it is the most common cause of end-stage renal disease (Bamanikar *et al*., 2016; Yanowsky-Escatell *et al*., 2020). It is most prevalent among the African-American population (Sagoo and Gnudi, 2020). It can be defined as microalbuminuria (persistent albuminuria >300 mg/day), or creatinine >300 mg/g. DN is associated with deterioration in glomerular filtration rate and an elevation in blood pressure leading to high morbidity and mortality (Dounousi *et al*., 2015). DN affects about 33% of diabetic individuals and occurs 10-30 years of poorly controlled diabetes (Reutens *et al*., 2011). However, those with type 2 diabetes (T2D) are more likely to develop DN earlier than those with type 1 (Gross *et al*., 2005).

Attaining and maintaining a healthy body weight is a key component of achieving glycemic control in managing T2D (Provilus *et al*., 2011), more so in DN. Weight reduction is an effective strategy in improving glucose homeostasis in T2D because it enhances insulin sensitivity and reduces hepatic glucose output (Guilherme *et al*., 2008; Dubé *et al*., 2011; Johnson *et al*., 2016). A modest weight loss of 5-10% of initial body weight can improve insulin sensitivity, glycemic control and blood pressure (Ryan *et al*., 2014). Studies have shown that effective weight loss interventions in obese individuals with glucose intolerance can prevent or delay the progression to T2D (Malin *et al*., 2012; Penn *et al*., 2013; Ibrahim *et al*., 2018). Often people with obesity and T2D have greater difficulty achieving optimal weight compared to people with obesity without diabetes because weight gain is a common side effect of most anti-diabetic medications (Provilus *et al*., 2011).

Liver enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) are major parameters used in assessing liver function (Dasgupta, 2015). Derangement in liver enzymes as seen in non-alcoholic fatty liver disease (NAFLD), which is very common among people with T2D and obesity due to insulin resistance, the common mechanism underlying these conditions (Stefan and Häring, 2011). Hyperglycemia induces hepatic lipogenesis and increases the level of circulating free fatty acids (Stefan and Häring, 2011) thereby contributing to the development of NAFLD. In addition, reports of the use of anti-diabetic medications being associated with marked improvement in liver function as well as histology in some

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studies (Rakoski *et al*., 2010; Kita *et al*., 2012; Eguchi *et al*., 2015; Nguyen *et al*., 2018; Shojaei-Zarghani *et al*., 2018), may suggest the possibility of liver dysfunction in people living with T2D and complications such as DN.

Various drug therapies exist for the treatment of diabetic nephropathy, but most of them are associated with adverse effects. Therefore, the use of safer, more effective and affordable alternative therapies such as resveratrol has become more acceptable in recent years. Resveratrol (3, 5, 4-trihydroxy-trans-stillbene) is a naturally occurring polyphenolic compound present in skin and seeds of several plant species including grapes, berries, peanut and grains (Rege *et al*., 2014). It has been reported that resveratrol can be used to prevent and/or treat several chronic conditions such as T2D due to its antioxidant, anti-inflammatory, cardio-protective, and neuro-protective activities (Darand *et al*., 2021; Seyyedebrahimi *et al*., 2018; Tanko *et al*., 2016). Our previous work on resveratrol revealed a marked reduction in serum creatinine and tumour necrosis factor-alpha levels while boosting antioxidant activity (Abdulazeez *et al*., 2022). But its effects on liver function parameters and body weight in diabetic nephropathy are yet to be explored. Chronic hyperglycemia in the setting of diabetic nephropathy might be associated with liver dysfunction (Stefan and Haring, 2011; Wang *et al*., 2007). Hence, this study was aimed to evaluate the effect of resveratrol on whole body weight and some liver enzymes in diabetic nephropathy in Wistar rats.

MATERIALS AND METHODS

Experimental animals: Twenty-five (25) adult male Wistar rats weighing 120 – 180 g were sourced from the Animal House of the Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria where the experiment was carried out. The rats were housed in metal cages designed with mesh and sawdust for comfort and dryness. The cages also have striped metal coverings onto which their drinking bottles were attached. They were fed standard rat chow with water ad libitum.

Ethical approval: Ethical approval on guidelines for the care and use of laboratory animals in scientific research was obtained from the Ahmadu Bello University Committee on Animal Use and Care (approval number: ABUCAUC/2021/133).

Induction of diabetes and diabetic nephropathy: Diabetes was induced in 3 of the groups by feeding the rats with a high-fat diet (normal feed + Simas margarine [70% of total calorie] in the ratio 10:1) and 20% fructose solution as drinking water for 6 weeks. Rats were fasted overnight after which they were given a single intraperitoneal injection of streptozotocin (STZ) at a low dose of 35 mg/kg diluted in 0.1 M citrate-buffered saline (pH 4.5). This combination was done to effectively mimic human T2D according to a previously described method (Okoduwa *et al*., 2017). Fasting blood glucose (FBG) levels of the rats were checked 3 days post-STZ injection to confirmed and 7 days post-STZ injection (week 7) to validate diabetes. Rats with FBG levels ≥ 200 mg/dL were considered diabetic (Abdulazeez *et al*., 2022). All recordings of blood glucose levels were done after an overnight fasting and at a two-weekly interval.

There was no anti-diabetic intervention given throughout the induction and (throughout the experiment in the diabetic control) to allow for progression to diabetic nephropathy, which was confirmed by measurement of serum creatinine levels. This was according to a recently described method (Ogboli-Nwasor *et al*., 2018).

Animal grouping:

Group I (n=5): Normal control. This group received 1 mL/kg distilled water orally throughout the experiment.

Group II (n=5): Normoglycaemic + carboxymethylcellulose (CMC) orally

Group III (n=5): Diabetic + CMC orally

Group IV (n=5): Diabetic + resveratrol 100 mg/kg orally (Balakumar *et al*., 2010)

Group V (n=5): Diabetic + lisinopril 1 mg/kg orally (Zoja *et al*., 1997). Lisinopril is a standard drug of choice in clinical practice, used for the prevention of nephropathy either from chronic diabetes or long-standing hypertension.

Drug administration: An angiotensin-converting enzyme (ACE) inhibitor and a standard anti-hypertensive drug, was used due to its well-established reno-protective property (Huang *et al*., 2006). It is also widely used in the treatment of diabetic nephropathy. Resveratrol (99% pure trans-resveratrol, from Sigma, USA) was dissolved in the vehicle, CMC and the effects of both were studied separately according to a previously described method (Ogboli Nwasor *et al*., 2018). All treatments began after confirmation of diabetes and lasted for 6 more weeks (at the end of which the animals were humanely sacrificed).

Body weight measurement: Body weights of the rats were measured every 2 weeks from the start of the experiment to the end using a digital weighing balance. The weights were recorded accordingly and analyzed appropriately.

Biochemical analyses: Aspartate aminotransferase (AST) was measured by monitoring the concentration of oxaloacetate hydrazone formed with 2, 4-dinitrophenylhydrazine (Huang *et al*., 2006). Alanine aminotransferase (ALT). was measured by monitoring the concentration of pyruvate hydrazone formed with 2, 4-dinitrophenylhydrazine (Guo *et al*., 2018). Alkaline phosphatase (ALP) was assayed according to the method described by Guo *et al*. (2018).

Statistical Analysis: Data were expressed as mean ± standard error of mean (SEM). Due to the small sample sizes, Shapiro-Wilk test was used to test for the normality of the numerical data. All data were also analyzed using one way analysis of variance (ANOVA) followed by Tukey's post-hoc test to compare the levels of significance between the groups. $P < 0.05$ were considered statistically significant.

RESULTS

The blood glucose levels were comparable across all groups prior to induction (week 0). There was no remarkable difference in the blood glucose levels of all the groups throughout the induction period (from week 0 to week 6). However, two weeks after the induction (i.e. week 8), a markedly elevated blood glucose level (385.00 ± 12.12 mg/dL) was recorded in the diabetic control compared to the

normal control (89.50 ± 2.50 mg/dL), and this persisted till the end of the experiment (Table 1). Treatment with resveratrol produced lower levels of blood glucose which was significant at week 12 (163.75 ± 26.64 mg/dL) compared to the diabetic control (445.00 ± 1.73 mg/dL). Treatment with resveratrol showed lower level of blood glucose (163.75 ± 26.64) comparable to treatment with those recorded with lisinopril (189.25 ± 29.97), and pioglitazone (166.25 ± 29.12 mg/dL) treatments.

Table 1:
Effect of resveratrol on blood glucose levels in high-fat, high-fructose and streptozotocin-induced diabetic nephropathy in Wistar rats (n = 5).

Group	BGL Week 0 (mg/dL)	BGL Week 2 (mg/dL)	BGL Week 4 (mg/dL)	BGL Week 6 (mg/dL)	BGL Week 8 (mg/dL)	BGL Week 10 (mg/dL)	BGL Week 12 (mg/dL)
Normal Control (1 mL/kg DW)	122.75 ± 3.79	122.00 ± 2.45	133.25 ± 7.99	184.00 ± 21.51	89.50 ± 2.50[a]	87.75 ± 0.85[a]	88.50 ± 0.65[a]
Normoglycaemic (1 mL/kg CMC)	133.75 ± 8.59	123.50 ± 5.30	113.75 ± 6.79	114.00 ± 5.45	87.25 ± 1.65[a]	91.00 ± 2.80[a]	93.75 ± 2.50[a]
Diabetic Control (1 mL/kg CMC)	142.50 ± 10.68	124.00 ± 3.46	107.50 ± 6.64	111.50 ± 6.06	385.00 ± 12.12[b]	392.00 ± 10.97[b]	445.00 ± 1.73[b]
Diabetic (100 mg/kg Resveratrol)	141.75 ± 3.20	144.00 ± 13.61	116.75 ± 3.20	128.00 ± 4.80	289.25 ± 39.87	206.75 ± 53.73	163.75 ± 26.64[a]
Diabetic (1 mg/kg Lisinopril)	127.50 ± 5.42	146.75 ± 5.95	162.50 ± 34.83	152.25 ± 27.97	191.75 ± 23.19[c]	241.50 ± 44.17[c]	189.25 ± 29.97
Diabetic (5 mg/kg Pioglitazone)*	125.00 ± 11.97	141.00 ± 4.92	127.00 ± 6.42	121.00 ± 7.15	206.75 ± 42.05[c]	194.00 ± 45.41	166.25 ± 29.12

Values with different superscripts are significantly different at $p<0.05$ (a: compared to diabetic control; b: compared to normal control; c: compared to resveratrol). DW: distilled water; CMC: carboxymethyl cellulose; BGL: blood glucose levels.
* new group introduced for comparison with resveratrol-treated group on blood glucose level, but initially part of the experiment.

Table 2: Effect of resveratrol on blood glucose levels in high-fat, high-fructose and streptozotocin-induced diabetic nephropathy in Wistar rats (n = 5).

Group	BW Week 0 (g)	BW Week 2 (g)	BW Week 4 (g)	BW Week 6 (g)	BW Week 8 (g)	BW Week 10 (g)	BW Week 12 (g)
Normal Control (1 mL/kg DW)	148.25 ± 6.97	168.75 ± 18.29	194.75 ± 24.25	212.00 ± 14.70	225.25 ± 11.24[a]	241.50 ± 13.04[a]	256.50 ± 15.52[a]
Normoglycaemic (1 mL/kg CMC)	123.00 ± 5.02	149.75 ± 6.74	176.75 ± 6.30	191.00 ± 6.04	194.50 ± 7.63[a]	207.25 ± 8.79[a]	216.25 ± 10.53[a]
Diabetic Control (1 mL/kg CMC)	156.00 ± 1.73	175.00 ± 1.73	171.00 ± 2.31	181.50 ± 2.02	164.50 ± 2.02[b]	161.00 ± 2.31[b]	145.50 ± 2.02[b]
Diabetic (100 mg/kg Resveratrol)	156.25 ± 5.68	189.75 ± 4.13	203.50 ± 5.12	209.75 ± 2.14	180.25 ± 7.73[b]	180.25 ± 9.44[b]	178.75 ± 9.01[b]
Diabetic (1 mg/kg Lisinopril)	148.00 ± 10.03	176.75 ± 10.94	187.00 ± 8.90	197.50 ± 12.81	183.50 ± 14.57[a]	195.00 ± 17.97[a]	201.75 ± 22.07[a]

Results presented as mean ± standard error of mean (SEM). The superscripts suggest statistically significant values (a: compared to diabetic control; b: compared to normal control) at $P < 0.05$ (n = 5). DW: distilled water; CMC: carboxymethyl cellulose; BW: body weight.

Table 3:
The effect of resveratrol on lipid profiles of diabetic nephrotic rats (n=5).

Group	TC (mg/dL)	TG (mg/dL)	HDL (mg/dL)	LDL (mg/dL)
Normal Control (1 mL/kg DW)	71.97 ± 6.63[a]	7.70 ± 1.39[a]	22.58 ± 2.63[a]	66.35 ± 11.41[a]
Normoglycaemic (1 mL/kg CMC)	79.50 ± 3.23[a]	17.45 ± 1.17[a]	25.43 ± 1.85[a]	71.20 ± 2.79[a]
Diabetic Control (1 mL/kg CMC)	181.90 ± 3.06[b]	44.75 ± 0.26[b]	5.05 ± 1.18[b]	156.15 ± 7.48[b]
Diabetic (100 mg/kg Resveratrol)	86.28 ± 5.92[a]	19.30 ± 1.19[a]	14.00 ± 2.48[a]	48.52 ± 8.42[a]
Diabetic (1 mg/kg Lisinopril)	78.33 ± 6.23[a]	27.40 ± 4.58	12.33 ± 0.76	39.03 ± 8.52[a]

Values with different superscripts are significantly different (a: compared to diabetic control; b: compared to normal control) at $P<0.05$. DW: distilled water; CMC: carboxymethylcellulose; TC: Total cholesterol; TG: triglyceride; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

At the 8th week of treatment, the resveratrol-treated as well as the lisinopril-treated groups showed higher body weights (180.25 ± 7.73g and 183.50 ± 14.57g respectively), compared to the diabetic control group (table 2).
Similar findings were noted in the subsequent weeks, and the differences in body weights between the resveratrol group and diabetic control were not remarkable throughout the duration of supplementation. The body weights of the resveratrol group were significantly lower from week 8 when compared to the normal control (225.25 ± 11.24g) and normoglycaemic group (194.50 ± 7.63g).

The levels of the total cholesterol (TC), triglycerides (TG) and low-density lipoprotein (LDL) were markedly elevated in the diabetic control (181.90 ± 3.06 mg/dL, 44.75 ± 0.26 mg/dL, 156.15 ± 7.48 mg/dL respectively), compared to the normal control (71.97 ± 6.63, 7.70 ± 1.39, 66.35 ± 11.41 respectively), with a reverse effect on the high-density lipoprotein (HDL) levels (table 3). Treatment with resveratrol showed a

remarkable reduction in the levels of TC (86.28 ± 5.92 mg/dL), TG (19.30 ± 1.19 mg/dL) and LDL (48.52 ± 8.42 mg/dL), compared to the diabetic control, while maintaining the HDL level to some extent (14.00 ± 2.48 mg/dL).

There was a significant decrease in ALT levels in the group treated with resveratrol (24.00 ± 0.58 IU/L), compared to the diabetic control (38.25± 3.07 IU/L) (Table`4). Only treatment with lisinopril caused a significant decrease in AST level (17.25 ± 2.95 IU/L) compared to diabetic (30.50 ± 0.29 IU/L) group. Although resveratrol treatment (10.35 ± 0.38 IU/L) produced no remarkable change in the ALP levels compared to diabetic control (15.15 ± 1.59 IU/L), but compared with lisinopril treatment (20.93 ± 0.52 IU/L), the reduction in ALP level was significant.

Table 4:
The effect of resveratrol on liver enzymes of diabetic Wistar rats (n=5).

Group	ALT (IU/L)	AST (IU/L)	ALP (IU/L)
Normal Control (1 mL/kg DW)	21.75 ± 1.70[a]	6.25 ± 1.44[a]	19.43 ± 1.33[a]
Normoglycaemic (1 mL/kg CMC)	23.25 ± 0.63[a]	12.50 ± 1.19[a]	20.13 ± 1.62[a]
Diabetic Control (1 mL/kg CMC)	38.25± 3.07[b]	30.50 ± 0.29[b]	15.15 ± 1.59[b]
Diabetic (100 mg/kg Resveratrol)	24.00 ± 0.58[a]	29.00 ± 1.22[b]	10.35 ± 0.38[b]
Diabetic (1 mg/kg Lisinopril)	35.25 ± 5.20[b]	17.25 ± 2.95[b]	20.93 ± 0.52[a]

Values with different superscripts are statistically significant (a: compared to diabetic control; b: compared to normal control) at $P<0.05$. ALT: alanine transferase; AST: aspartate transferase; ALP: alkaline phosphatase; DW: distilled water; CMC: carboxymethylcellulose.

The serum creatinine levels of the DN rats showed a significant reduction in the resveratrol-treated group (0.65 ± 0.06 mEq/L) compared to the diabetic control (2.30 ± 0.12 mEq/L). Lisinopril also produced a similar effect (1.13 ± 0.17 mEq/L) (table 5).

Table 5:
The effect of resveratrol on serum creatinine levels of diabetic nephrotic rats (n=5).

Group	**Serum Creatinine (mEq/L)**
Normal Control (1 mL/kg DW)	0.80 ± 0.04
Normoglycaemic (1 mL/kg CMC)	0.65 ± 0.03[a]
Diabetic Control (1 mL/kg CMC)	2.30 ± 0.12[b]
Diabetic (100 mg/kg Resveratrol)	0.65 ± 0.06[a]
Diabetic (1 mg/kg Lisinopril)	1.13 ± 0.17[a]

Values with different superscripts are statistically significant (a: compared to diabetic control; b: compared to normal control) at $P<0.05$. DW: distilled water; CMC: carboxymethylcellulose.

DISCUSSION

This study investigated the modulatory effect of resveratrol on body weight in hyperglycemia-induced diabetic nephropathy in Wistar rats. Resveratrol can reduce blood glucose levels (as depicted in our result above) and protect β-cells and improve other biochemical and clinical parameters in type 1 and type 2 animal models of diabetes (Thazhath *et al*., 2016). Our results showed even a better glycemic outcome at the end of the study, when a new group with a standard antidiabetic agent (pioglitazone) was introduced. This finding was also comparable with the lisinorpril-treated group. It most likely points to the potential efficacy of resveratrol in the management of hyperglycemia in diabetes.

The results obtained from this research showed a slight increase in weight in the groups treated with resveratrol when compared to the diabetic control at weeks 8, 10, and 12. It is worth noting that despite the high-calorie diet given to the diabetic untreated group, their weights were lowest over the last few weeks of the experiment. This was due to the effect of the low-dose STZ administered to the rats to effectively mimic T2D in humans (Okoduwa *et al*., 2017).

In a randomized controlled trial involving 14 diet-controlled T2D patients (Jakubczyk *et al*., 2020), resveratrol showed a non-significant increase in body weight after 5 weeks compared to placebo. A meta-analysis also demonstrated a non-significant change in weight and other anthropometric indices by resveratrol supplementation irrespective of the dose or duration of treatment compared to placebo (Qiao *et al*., 2014). In contrast, few other studies demonstrated reduction in body weight by resveratrol. In a study conducted in mice fed with a high-fat diet (50% of calorie), a high-fat diet with 200 mg resveratrol or a control diet (10% of calories from fat), resveratrol prevented weight gain caused by the high-fat diet (Asghari *et al*., 2018). In addition, a randomized controlled trial demonstrated a significant weight reduction among patients with NAFLD on resveratrol compared to those on placebo (Barber *et al*., 2022). These inconsistent results could be due to the dosage of resveratrol, the animals (rats or mice) used, environmental factors and/or the multiple mechanisms of action of resveratrol which are still not clearly understood (Garcia-Martinez *et al*., 2022; Vijan *et al*., 2015).

This study investigated the modulatory effect of resveratrol on body weight in hyperglycemia-induced diabetic nephropathy in Wistar rats. Resveratrol possesses the ability to not only reduce blood glucose levels and protect β-cells but also improve other biochemical and clinical parameters in both type 1 and type 2 animal models of diabetes (Ozturk *et al*., 2017). The results obtained from this research showed a slight increase in weight in the groups treated with resveratrol when compared to the diabetic control at weeks 8, 10, and 12. It is worth noting that despite the high-calorie diet given to the diabetic untreated group, their weights were lowest over the last few weeks of the experiment. This was due to the effect of the low-dose STZ administered to the rats to effectively mimic T2D in humans (Wang *et al*., 2007).

From a clinical point of view, untreated or uncontrolled T2D especially the one complicated by nephropathy is often associated with weight loss (Komaroff, 2017) due to the

excessive glucosuria and proteinuria and anorexia. However, resveratrol in our study modulated the weights of the rats by slightly increasing the weight of the rats compared to the diabetic control and reducing their weights (from the 8th week) compared to the normal control and normoglycemic group. The resveratrol group maintained a relatively constant weight, from the 8th week of treatment while the other groups produced an upward trend with a downward one only in the diabetic group. Therefore, resveratrol supplementation was able to maintain a balance between the weight loss seen in the diabetic group, and the weight gain recorded in the other groups. This suggests a modulatory role, which is needed for the maintenance of optimal/healthy weight in the management of T2D with or without obesity and diabetic nephropathy. This might be due to its well-established antioxidant and anti-inflammatory properties.

There is a complex relationship between obesity, diet composition and functionality of the gut microbiome (Kim *et al*., 2010). Several studies in mice have suggested that resveratrol can influence this association in several ways, either by directly modulating the gut microbiome to one associated with a healthy weight or by changing the expression and activity of genes involved in weight maintenance, such as fasting-induced adipose factor (Asghari *et al*., 2018; Wei and Yu, 2021). A recent review by Barber *et al*. (2022) described the possible mechanism by which resveratrol maintains optimal weight in the setting of obesity and insulin resistance. It does so via inhibition of the accumulation of triglycerides and lipogenesis through upregulation of sirtuin-1 and peroxisome proliferator-activated receptor gamma genes. This was demonstrated and proven by our results (table 3). The dyslipidemic changes observed in the diabetic control were all corrected or prevented by resveratrol treatment. This further reiterated the anti-dyslipidemic potential of resveratrol. Diabetes mellitus is not only known to be associated with disturbances in glucose metabolism but with also disturbances in lipid metabolism. The results of this study depict the potential benefit of resveratrol in the management of this metabolic disorder.

From our findings, there was a remarkable decrease in ALP levels when treated with resveratrol compared to the diabetic control. This may suggest a hepatoprotective effect but it is contrary to the work of Jacubczyk *et al*. (2014), which recorded a significant increase in ALT levels. A systematic review conducted to evaluate the effectiveness and safety of resveratrol supplementation for improving liver enzymes in adults with non-alcoholic fatty liver disease (NAFLD). The results showed that resveratrol cannot effectively reduce AST and ALT concentrations compared with the normal control. However, subgroup analysis of AST revealed that resveratrol supplementation could significantly reduce AST and ALT levels in the participants (Akbari *et al*., 2020). On the other hand, lisinopril treatment caused a significant elevation in the level of ALT, which could possibly portray a hepatotoxic property.

Again, from our results AST showed no remarkable change when treated with resveratrol compared to the diabetic control but there was statistically significant decrease when compared to normal control and normoglycaemic groups. Asghari *et al*. (Barber *et al*., 2022) also demonstrated no significant changes in the AST levels, which is in line with our results. When treated with lisinopril, there was a great decrease in AST levels compared to diabetic control but a significant elevation compared to normal control.

On the ALP levels, a marked decrease was observed when treated with resveratrol compared to normal control and normoglycaemic groups. Although not significant, ALP levels were reduced in the resveratrol group when compared to the diabetic control, signifying a hepatoprotection. However, there was a marked increase in ALP level in the diabetic control when treated with lisinopril, suggesting some hepatotoxic effect.

Although the only significant reduction recorded in this study was on ALT, resveratrol was able to reduce the level of the other enzymes compared to the diabetic untreated group. Moreover, ALT is more specific to the liver compared to both AST and ALP. So, if resveratrol showed a significant reduction in the ALT levels, it might be deduced that resveratrol possesses some hepato-protective properties.

In a meta-analysis (Darand *et al*., 2021), the pooled analysis failed to show any significant changes in the liver enzymes assayed after supplementation with resveratrol, but subgroup analysis illustrated a greater effect than the overall outcome in the long run (>12 weeks) and among younger subjects (age < 48 weeks). Possible reasons for the lack of effect of resveratrol on liver enzymes were dosage and duration of the supplementation. In another meta-analysis by Jakubczyk *et al*. (2020), resveratrol had been shown to be a safe and potent supplement, especially in NAFLD associated with obesity. However, they concluded that there is no enough evidence to suggest resveratrol as a beneficial supplement in patients with NAFLD, as the level of ALT was significantly elevated but other parameters assessed were only affected slightly.

In a study by Akbari *et al*., 2020 on the effect of resveratrol on lipid profile and liver e`nzymes in patients with metabolic syndrome, the results showed that resveratrol supplementation among patients with metabolic syndrome and other related disorders significantly decrease total cholesterol level, GGT but did not have any effect on ALT and AST. Asghari *et al*. (2018) investigated the effect of resveratrol supplementation at a dose of 600 mg/day for 12 weeks to patients with NAFLD and did not find any changes in liver enzymes. These inconsistent findings could be related to the stage of the disease, type of diseases, the method for measuring the level of liver enzymes and or different dosage of resveratrol.

All of our findings could be traced to the fact that resveratrol exhibited an excellent ability in protecting against diabetic nephropathy (table 5) in the rats. This might be linked to its inherent antioxidant and other properties, some of which have been explored in this study. In addition, it can be deduced from our findings that lisinopril administration caused some derangement in liver enzymes. At such, patients on lisinopril should be assessed periodically with liver function test, to ascertain the levels of liver enzymes and avoid potential hepatotoxic side effects.

CONCLUSION

This study demonstrated the modulatory effect of resveratrol on the body weight of the diabetic nephropathic rats, suggesting its potential in the maintenance of optimal body weight in people living with diabetes and those on anti-diabetic medications. Resveratrol also effectively decreased the levels of liver enzymes (ALT and ALP) in the diabetic Wistar rats. This may signify a potential hepatoprotective effect of resveratrol in diabetes.

Limitations of the study

Insulin resistance is a classical pathogenetic and molecular player in both T2D and obesity, but in this study, we were not able to explore such angle due to shortage of funds. The use of a standard antidiabetic agent in combination with an ACE inhibitor such as lisinopril could be explored in further research and compare them with resveratrol at different dosages.

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