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Research Article

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Effect of Curcumin on Liver Enzymes and Liver Proteins in Alloxan-induced Diabetic Wistar Rats

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Abstract Diabetes mellitus is associated with chronic hyperglycemia, impaired liver function, end organ damage among others. Therefore, curcumin may provide a better treatment for this disease. The present study is aimed at investigating the effect of curcumin on liver enzymes and liver proteins of alloxan-induced diabetic Wistar rats. Twenty rats weighing between 100-150g were used for the study. The animals were divided into five (5) groups of four each (n=4). Group I were non-diabeticand received distilled water, group II, III, IV and V were diabetic and received olive oil 1 ml/kg, glibenclamide 2 mg/kg, curcumin 50 mg/kg and curcumin 100mg/kg respectively. Alloxan (150mg/kg) was used to induce diabetes. Diabetes was confirmed 72 hours after induction by glucose oxidase principle. All administrations were done *via* oral gavage for duration of 21 days. On day 21, the animals were sacrificed and the blood samples were collected for biochemical assays. The result obtained from this study showed that there was a significant decrease ($P<0.05$) in the liver enzymes activity (ALT and ALP) when compared with the control group. Also, serum albumin level significantly increases at curcumin 50 mg/kg dose compared to the control group. The findings of this study suggest that curcumin has hepatoprotective effect and improve blood glucose level and may ameliorate diabetes-induced liver disorders.

Keywords curcumin, hyperglycemia, liver enzymes, liver proteins

Introduction

Diabetes mellitus (DM) is a major global public health problem with an escalating incidence and prevalence, particularly in developing and newly industrialised countries [1]. DM is a complex metabolic disorder characterized by persistent hyperglycaemia resulting from defects in insulin secretion, insulin action or both. The two main types of diabetes mellitus are type 1 (formerly known as insulin-dependent diabetes), and type 2 (formerly known as non-insulin-dependent diabetes). Type 1 diabetes is caused by the autoimmune destruction of the β-cells of the pancreatic islets, whereas type 2 diabetes results from both impaired insulin secretion and resistance to the action of insulin [2]. Diabetes mellitus is a metabolic disorder of the endocrine system. It is associated with chronic hyperglycemia, hypercholesterolemia and hypertryglycerideemia, impaired liver function, end organ damage resulting from reduction in insulin secretion or reduced tissue sensitivity to insulin and or both [3]. Diabetes mellitus affected more than 415 million people in 2015 and this is projected to double by the year 2040. Nigeria has a prevalence of 0.8% to 11% involving both rural and urban dwellers [4]. The management of diabetes places an enormous burden on

individuals and government. In 2015, the total global expenditure on diabetes was estimated to be between USD 673 billion to USD 1,197 billion and this is projected to rise to about USD 802 to USD 1,452 billion [5].

Concern regarding this chronic disease is focused on serious DM-related complications which can affect multiple vital organ systems, thereby leading to more severe and irreversible pathological conditions such as nephropathy, retinopathy, vasculopathy, neuropathy and cardiovascular diseases, as well as hepatopathy [6]. Research indicates that DM is associated with a number of liver abnormalities, such as abnormal glycogen deposition, non-alcoholic fatty liver disease (NAFLD), fibrosis, cirrhosis, hepatocellular carcinomas (HCCs), abnormal elevated hepatic enzymes, acute liver disease and viral hepatitis [7,8].

Turmeric (*Curcuma longa*) is an intriguing ingredient with a rich history as a dietary spice and herbal supplement in ancient China and India. This distinctive yellow- colored spice, derived from the rhizome of the plant (*C. longa*), is a member of Zingiberaceae family and is widely cultivated in India and Southeast Asia [9]. Curcumin has been shown to exhibit antioxidant, anti-inflammatory, antimicrobial, and anticarcinogenic activities. It also has hepatoprotective and nephroprotective activities, suppresses thrombosis, protects against myocardial infarction, and has hypoglycemic and antirheumatic properties [10]. The aim of this research work was to evaluate the effect of curcumin on liver enzymes and liver proteins in alloxan-induced diabetic Wistar rats.

Curcumin

Materials and Method

Chemicals and drugs

All chemicals and drugs were of analytical grade. Curcumin was purchased from Arkure Health Center (Haryana, India). Alloxan was purchased from (Sigma chemical Company St. Louis U.S.A.). A digital glucometer (Accu-Chek Advantage, Roche Diagnostic, Germany) was used for the determination of the blood glucose levels of the animals.

Induction of experimental diabetes mellitus

The animals were fasted for 12-16 h with free access to water prior to the induction of diabetes. Diabetes was induced by single intraperitoneal injection of Alloxan monohydrate (Sigma St. Louis, U.S.A.) at a dose of 150 mg/kg b w dissolved in 0.9% cold normal saline. The rats were then kept for the next 24 h on 5% glucose solution bottles in their cages to prevent hypoglycemic [11]. Animals with fasting blood glucose levels of 180 mg/dL and above were considered diabetic [12].

Experimental Design

The animals were randomly divided into five (5) groups of four (4) rats each. All administration was done orally for duration of 21 days as follows

Group I: Normal, received distilled water

Group II: diabetic, olive oil 1 ml/kg

Group III: Diabetic, received glibenclamide (glib) 2 mg/kg

Group IV: Diabetic, received curcumin (cur) 50 mg/kg

Group V: diabetic, received curcumin (cur) 100 mg/kg

Estimation of Blood Glucose

The blood samples were obtained by sequential snipping of the tail. A glucometer was used to measure the blood glucose levels using glucose oxidase principle [13] using the digital glucometer (Accu-Check Advantage, Roche Diagnostic, Germany), and results were obtained as mg/dL [14].

Collection of Blood and Preparation of Serum Samples

After three weeks of treatment, blood samples were obtained from all animals in each group through cardiac puncture for evaluation of serum electrolytes, blood sample from each animal was collected into plain tubes and allowed to clot and centrifuged at 1.957 × g for 10 minutes. The sera was separated and stored at -4 °C for serum liver enzymes analysis.

Determination of serum liver enzymes and liver proteins

The activities of serum liver enzymes (Aspartate Aminotransferase and Alanine Aminotransferase) and liver proteins (Albumin, Globulin and Total proteins) were assayed colorimetrically, using colorimetric assay kits (Randox, Northern Ireland) according to manufacturer's instruction and values were expressed in IU/L and g/dL respectively.

Statistical analysis

Data obtained were expressed as mean ± SEM. The data were statistically analyzed using oneway analysis of variance (ANOVA) with Tukey's multiple comparison post hoc tests to compare the level of significance between control and experimental groups. The values of $P < 0.05$ were considered as significant

Results

Table 1: Effect of Curcumin on Fasting Blood Glucose Levels

Groups	day 0 (mg/dl)	day 7 (mg/dl)	day 14 (mg/dl)	day 21 (mg/dl)
Normal	91.75 ± 4.97^{a}	95.25 ± 2.14^{a}	93.25 ± 2.69^{a}	94.00 ± 2.08^{a}
Control	301.25 ± 9.24^{d}	217.50 ± 6.60^{b}	222.00 ± 13.48^{b}	220.00 ± 7.22^{b}
Glib 2 mg/kg	305.75 ± 6.73^{d}	134.50 ± 3.62^{a}	156.25 ± 5.51^{a}	93.75 ± 3.84^{a}
Cur 50 mg/kg	321.25 ± 6.73^{d}	245.75 ± 4.87^{b}	191.50 ± 5.81^{b}	104.25 ± 3.90^{a}
Cur 100 mg/kg	314.00 ± 9.40^{d}	287.25 ± 5.53^{c}	238.50 ± 1.85^{b}	93.25 ± 4.48^{a}

Values having different superscripts letters are significant ^{a,b,c,d} = $p < 0.05$ significant.

Table 2: Effect of Curcumin on Serum Liver Enzymes and Liver Proteins Levels

Groups	AST (U/L)	ALT (U/L)	ALB	GLOB	TOT Pr
Normal	30.75 ± 1.11	41.38 ± 1.42	5.93 ± 0.55	4.59 ± 0.32	10.52 ± 0.59
Control	35.50 ± 0.25	54.53 ± 0.64	5.30 ± 0.54	4.99 ± 0.31	10.28 ± 0.57
Glib 2 mg/kg	$25.50 \pm 0.65^{*ab}$	$25.33 \pm 0.73^{*ab}$	4.94 ± 0.53	5.74 ± 1.12	10.67 ± 0.37
Cur 50 mg/kg	32.50 ± 1.50^{ab}	$17.93 \pm 1.39^{*ab}$	7.15 ± 0.24*	7.02 ± 0.70*	10.58 ± 0.41
Cur 100 mg/kg	32.25 ± 0.85^{ab}	$21.05 \pm 0.91^{*ab}$	4.50 ± 0.65	6.38 ± 1.07	10.88 ± 0.54

Values having different superscripts letters are significant ($p < 0.05$). *, a and b = compared with normal control, diabetic control and olive oil respectively.

Discussion

Hyperglycemia is reported to be associated with many complications. This include both micro and macrovascular disorders. Curcumin has proved to be beneficial by significantly ($p < 0.05$) decreasing the fasting blood glucose level after 21 days. Comparing the two doses, it is observed that both doses showed a steady decline in the blood glucose level on weekly bases throughout the treatment with no significant ($p < 0.05$) difference. The same is observed for the two doses of curcumin compared to the standard drug. The decrease may be associated with increase tissue uptake of glucose by activating glucose transporters. It is also possible that this effect was as a result of increase plasma sodium concentration and more activation of glucose transporters and glucose uptake by tissues. The effect might also be due to regeneration of the damaged beta cells of the pancreas. This result agree with the

findings of Sharma *et al.* 2014 [15] who also reported decrease in blood glucose level in fluoride induced hyperglycemia in rats.

Hyperglycemia is associated with hepatotoxicity. The serum ALT and AST levels are used in the evaluation of liver damage. Elevation of these enzyme activities is considered as indication for hepatic damage. An increase of these enzyme activities is also associated with fatty liver disease [16]. From the results obtained in this study, I can be observed that the two doses of curcumin reduced the serum level of both ALT and AST compared to the control group. Comparing the two graded doses, the lower dose showed more activity compared to the higher dose even though the difference is not significant ($p < 0.05$). The significant ($p < 0.05$) decreases in the level of these enzymes in the present study suggest that both doses of curcumin possess possible hepatoprotective effect against liver damage induced by hyperglycemia. This might be due to its strong antihyperglycemic effect as seen in table 1 which reduces the formation of advanced glycation end products (AGEs) and glucose shunting into hexosamine pathway [17,18]. This study agree with the findings of Gamal *et al.* 2016 [19] who reported protective effect of curcumin and ginger on liver cirrhosis induced by carbon tetracholoride in rats and that of Tahereh and Saeed, 2016 [20] who reported hepatoprotective effects of curcumin against drugs and toxic agents; an updated review.

Diabetes is characterized by increased levels of plasma glucose, which in turn modify blood plasma proteins by a non-enzymatic reaction called glycation. Protein glycation leads to formation of toxic molecules 'advanced glycation end products' (AGEs). Accumulation of AGEs has been found to be accelerated in diabetes and contribute to pathogenesis of diabetic complications [21]. In diabetes, albumin synthesis and secretion is decreased due to insulin deficiency. From this study, it can be observed that both albumin and globulin levels are increased significantly ($p < 0.05$) in the low dose of curcumin compared to the control group. There was no significant ($p < 0.05$) difference in the standard drug group, curcuma at high dose compared to the control group. There was no significant difference in the total protein across all the groups. The increase in the serum albumin and globulin may indicate increase in the transport capacity of the blood. This might lead to increase in lipid soluble hormones transport such as thyroid hormones and cortisol which increase glucose dynamicity, absorption and metabolism. The findings of this study agree with that of Shatadal *et al.* 2014 [22] who reported protective effect of curcumin streptozotocin-induced diabetic pathophysiology in rats.

Conclusion

The present study suggests that oral administration of curcumin has significant antihyperglycemic effect and possible hepatoprotective effect against hyperglycemia induced liver damage in Wistar rats. This study may justify the use of supplements in the management of diabetes induced liver toxicity.

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