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Antihyperglycemic Effect of Ethanol Fraction of *Senna Tora* Leaf on Alloxan Induced- Diabetic Wistar Rats

Emochone Roy Yohanna[1] and Ojochenemi Ejeh Yakubu[1]

[1]Department of Biochemistry, Federal University Wukari, Nigeria
Email: roy.emo94@gmail.com)
(+234) 8067706242
Live DNA: 234.35876

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ABSTRACT

Background and Objective: Plant materials as sources of therapeutic compounds continue to play a crucial role in the maintenance of human health for ages. The present study was designed to evaluate the Antihyperglycemic effect of ethanol fraction of *Senna tora* leaf in alloxan induced-diabetic wistar rats. **Materials and Methods:** A total of twenty five (25) Wistar rats were used, which were randomly distributed into 5 groups of 5 animals each (Group I, II, IV and V). Group I served as a normal control and received only distilled water, Group 2 (negative control), Group III (positive control) and group IV and V received 100mg/kg and 200 mg/kg b.w respectively, and treatment lasted for three weeks, the fasting blood sugar was taken before induction and after, it was taken three times in seven days interval following animal sacrifice. **Results:** There was a significant increase in the blood sugar after induction and significant decreased after treatment. Aspartate aminotransferase (AST) (39.25±5.67), Alkaline phosphatase (ALP) (130.63±5.82), Alanine aminotransferase (ALT) (25.125±1.23), Gamma glutamyl transferase (GGT) (2.12±0.60) decreased significantly between and within the groups administered dose of 200 mg/kg when compared with Normal control. However, the result also revealed that there was significant increase in the concentration of Total protein (10.57±1.33) and albumin (9.33±0.35) treated with 200 mg/kg of the fraction. The result revealed that there was significant decreased in the activity of MDA compared to the control group and significant increase in the activity of SOD and catalase treated with 100 mg/kg compared to the normal control and group treated with 200 mg/kg of the fraction. **Conclusion:** This research showed that at higher concentration (200 mg/kg) *Senna tora* leaf contain antihyperglycaemic, hepatoprotective activity and at lower concentration the plant has antioxidant activity which validates utilization medicinal plants to treat diabetes and liver disease, therefore *Senna tora* leaf should be utilized as an antihyperglycaemic and hepatoprotective plant to treat diabetes and liver disease.

Keywords: Antihyperglycaemic, ethanol, hepatoprotective, alloxan, wister rats

INTRODUCTION

Diabetes mellitus (DM), or simply diabetes, is a group of metabolic disorder in which a person has high blood sugar, either because the body does not synthesize enough insulin, or because cells do not respond to the insulin that is synthesized (Andrali *et al.,* 2008). Diabetes mellitus has been classified into two types i.e. insulin dependent diabetes mellitus (IDDM, Type I) and non-insulindependent diabetes mellitus (NIDDM, Type II). Type I diabetes is an autoimmune disease characterized by abnormally high blood sugar level whereas Type II diabetes is characterized by peripheral insulin resistance and impaired insulin secretion (Arora *et al*., 2009). The global prevalence of DM is increasing at an alarming rate. Recent data indicates that the disease affects over 463 million people globally and the number is likely to rise to 578 million by 2030, and 700 million by 2045 (Saeedi *et al.,* 2019).

The presence of DM shows high risk of several complications such as cardiovascular diseases, peripheral vascular diseases, stroke, neuropathy, renal failure, retinopathy, blindness, amputations, (Jothivel *et al*., 2007). Yakubu *et al*. (2014) reported that Plant obtained products have been utilized for medicinal goals for centuries. At present, it is documented that about 80% of the world population relies on botanical preparations as medicines to meet their health needs (Yakubu *et al*., 2020).

Senna tora is a legume belonging to the family of caesalpiniaceae which grows wild mostly in the tropics and is considered as a weed in many places (Kubmarawa *et al*., 2011). In traditional Chinese Medicine, its usage has been described as an antioxidant, antimicrobial, antihepatotoxic, antidiuretic, antidiarrhoeal and antimutagenic plant (Zhenbao *et al*., 2007; Zhu *et al.*, 2008). The use of the plants, plant fraction and pure compounds isolated from natural sources provided the foundation to modern pharmaceutical compounds. An ethno botanical search on fine species senna shows their importance in the local herbal medicine. In the recent study, screening for hypoglycemic activity of the fraction of *Senna tora* was conducted to yield support for the utilization of this plant as traditional medicine. The discovery of drugs from natural sources particularly plants that has less severe side effects and can

help to remedy the prevalence of disease conditions worldwide is exploited to reduce reliance on synthetic drugs which sometimes comes with side effects and unaffordable for the common man in the society (Patil, 2010).The study focused on the scientific investigation of the effect of ethanol fraction of *Senna tora* leaf and the antihyperglycaemic effect on blood glucose of alloxan induced diabetic wistar rats.

METHODOLOGY

Plant Sample collection and identification

Matured and healthy-looking leaves of *Senna tora* were collected from Wukari, Taraba State, Nigeria. The leaf was thoroughly washed with tap water in order to remove the dust and soil particles. The leaf was air-dried under the shade to prevent ultra-violet rays from inactivating the chemical constituents (Ncube *et al*., 2008; Das *et al.,* 2010). The dried leaf were pounded into fine powder using mortar and pestle, and then stored and labeled in dry containers until use.

Ethanol Extraction

The method of (Yakubu *et al*., 2014) was adopted for this protocol. Four hundred grams (400 g) of pulverized sample each of leaf was weighed into a plastic container and filled with 1200 mL ethanol (1:4 w/v) for 72 hours at room temperature with occasional shaking, after finishing maceration, the sample was sieved with clean white mesh before filtering using Whitman No 1 filter paper. Next, the filtrate was poured into a beaker.

Experimental Animals

Twenty-five (25) wistar albino rats were used for the study. The rats weighing between 150 g – 230 g were purchased from Wukari, Taraba State, Nigeria. All the wistar albino rats were allowed free access to feed and water ad libitum throughout the experimental period.

Induction of Diabetes

Diabetes was induced by intraperitoneal injection of alloxan monohydrate (150 mg/kg body weight), after dissolution of alloxan monohydrate crystals in normal saline (Dash *et al.,* 2001).

Experimental Design

The rats were randomly grouped into five, each of the group containings five rats.

Each rat in every group received the following treatment;

i. Group I: Non-alloxan monohydrate induced rats (Normal control).

ii. Group II: Positive control. (Treated with 5mg/kg b.w of glibenclamide)

iii. Group III: Alloxan monohydrate –induced rats

iv. Group IV: Alloxan monohydrate-induced diabetic rats treated with 100mg/kg body weight of the fraction.

v. Group V: Alloxan monohydrate-induced diabetic rats treated with 200 mg/kg body weight of the fraction.

Animals sacrifies

All animals were sacrificed 24 h following last administration of drug or *Senna tora* leaf fraction. Animals were sacrificed under chloroform anesthesia and whole blood was collected and allowed to stand for two hours for collection of serum. All sera samples were kept in sample tubes and stored at 20°C. The organs were immediately harvested, rapidly rinsed in ice-cold normal saline and stored at -20°C for analysis of malondialdehyde as indicator of lipid peroxidation.

Preparation of Liver Homogenates

One-gram (1g) of the liver and kidney tissues were homogenized in 10ml of ice-cold physiological saline to obtain 10% (w/v) homogenates. The resulting homogenates were centrifuged at 5,000g for 10min and the supernatants obtained were used for determination of superoxide dismutase (SOD), catalase (CAT), MDA, activity in other to ascertain the antioxidant activity of the plant leaf

Determination of Fasting Blood Glucose Level

The fasting blood glucose level of the rats was determined using accu-check active glucometer. The tail vein was punctured and blood from the tail was made to drop on the strip which was then inserted in the glucometer to obtain blood glucose concentration in mg/dl for each rat in all the groups at the following intervals of days: 0, 1, 14and 21 while the feed was withdrawn from the rats a night before checking the blood glucose to obtain fasting blood glucose (Roche accu chek active glucometer user manual).

Assessment of Liver Function Tests

Serum was separated from the clotted blood by centrifugation Refrigerated centrifuge at 4000 rpm at 4°C for 5 minutes. Serum samples were immediately subjected to biochemical estimation of liver function: Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), Gamma-glutamyl transferase (GGT), Total protein (T.P) and Albumin (ALB) using uv/visible Spectrophotometer.

Assessment of Aspartate Aminotransferase (AST) Activity

AST activity was determined by the method described by (Reitman and Frankel, 1957) using Randox reagent kit.

Assessment of Alanine Aminotransferase (ALT) activity

ALT activity was determined by the method described by (Reitman and Frankel, 1957) using Randox reagent kit.

Assessment of Alkaline Phosphatase (ALP) activity

The serum activity of Alkaline Phosphatase (ALP) was determined by the method (Schlebusch, *et al*., 1974) described using Agappe reagent kit.

Calculation

ALP Activity (U/L) =(Δ OD/min.) x 2750.

Assessment of Gamma- glutamyl transferase (GGT)

The serum activity determination of GGT was carried out by the method described by (Szasz, 1976) using Agappe reagent kit.

Calculation

Gamma GT activity (U/L) = (OD/min) x 1158

Determination of Total Protein (T.P)

The total protein concentration was determined using the method described by (Weichselbaum, 1946) using Randox reagent kit.

Calculation

Total protein Conc. = 19 x Asample (g/dL).

Determination of Albumin (ABL)

The serum albumin concentration was determined by the method described by (Doumasa, *et al*., 1971) using Agappe kit.

Calculation

$$\text{Albumin Conc. (g/dL)} = \frac{\text{Absorbance of Sample}}{\text{Absorbance of Standard}} \times 3$$

Estimation of Superoxide Dismutase (SOD) activity

Superoxide dismutase activity was measured using the method described by (Martin *et al*. 1987).

Estimation of Catalase (CAT) activity

Catalase activity was determined using the method described by (Aebi, 1983).

Statistical Analysis

The biochemical results were subjected to statistical analysis using One-Way Analysis of Variance (ANOVA) and further with Duncan Multiple Comparisons with the use of Statistical Package for Social Science (SPSS) version 23. The means were compared for significance at p≤ 0.05 and the group results were presented as mean ± standard deviation.

RESULTS AND DISCUSSION

Table 1: Effect of *Senna tora* leaf on fasting blood sugar levels in normal and Alloxan induced diabetic Wistar rats

Groups	Column	DAY 0(g/dL)	DAY7 (g/dL)	DAY14 (g/dL)	DAY21 (g/dL)
Group I	Normal control	93.60±5.45^{a}	98.00±6.20^{a}	92.60±7.70^{a}	88.00±2.45^{a}
Group II	Alloxan only	109.00±6.34^{b}	225.80±3.34^{b}	200.40±4.45^{ab}	201.00±4.45^{b}
Group III	Alloxan+ Glm	106.20±6.34^{ab}	297.80±7.45^{c}	181.80±5.25^{b}	156.20±8.77^{c}
Group IV	Alloxan+100 mg/kg fraction	102.40±6.34^{ab}	231.00±5.37^{b}	123.20±0.83^{ab}	114.00±5.89^{b}
Group V	Alloxan+200 mg/kg fraction	106.80±4.56^{ab}	300.20±2.17^{c}	106.40±2.32^{a}	100.60±3.33^{a}

Result presented as mean ± Standard deviation. Result within a column with the same superscript indicates no levels of significance while≤ result within the same column with different superscript indicate level of significance (p≤0.05).

Table 2: Effect of *Senna tora* leaf on liver enzymes in Alloxan induced diabetic wistar rats

Parameters	Treatments	AST(IU/L)	ALT (IU/L)	ALP(IU/L)	GGT (IU/L)
GROUP I	Normal control	26.25±5.45^{a}	38.80±6.66^{c}	58.30±7.33^{a}	45.08±4.00^{d}
GROUP II	Alloxan only	42.1875±3.55^{b}	26.25±1.34^{a}	257.13±4.55^{c}	2.32±0.53^{b}
GROUP III	Alloxan+Glm	39.50±4.45^{b}	30.75±2.44^{b}	152.623±6.77^{b}	1.21±0.053^{a}
GROUP IV	Alloxan+100 mg/kg fraction	40.50±6.76^{b}	30.30±1.99^{b}	250.67±5.07^{c}	23.34±2.05^{c}
GROUP V	Alloxan+200 mg/kg fraction	39.375±5.67^{b}	25.125±1.23^{a}	130.63±5.82^{b}	2.12±0.60^{b}

Result presented as mean ± Standard deviation. Results within a column with the same superscript indicate no levels of significance while results within the same column with different superscript indicate level of significances.

Table 3: Effect of *Senna tora* leaf on on total protein and albumin in Alloxan induced diabetic wistar rats

Parameters	Treatments	T.P (g/dL)	ABUMIN (g/dL)
GROUP I	Normal control	19.09±2.55^{d}	3.46±1.12^{a}
GROUP II	Alloxan only	8.50±0.55^{b}	3.07±1.23^{a}
GROUP III	Alloxan +Glm	10.88±1.75^{c}	6.91±1.55^{b}
GROUP IV	Alloxan+ 100 mg/kg fraction	5.31±0.65^{a}	6.59±1.06^{b}
GROUP V	Alloxan+ 200 mg/kg fraction	10.57±1.33^{c}	9.33±0.35^{c}

Result presented as mean ± Standard deviation. Results within a column with the same superscript indicate no levels of significance while results within the same column with different superscript indicate level of significance (p≤. 0.05).

Table 4: Effect of *Senna tora* leaf on antioxidant enzymes

Groups	Treatments	MDA(nmo/mg protein)	SOD (U/mg protein)	CAT(U/mg protein)
GROUP I	Normal control	$42.01{\pm}3.41^{a}$	$85.00{\pm}3.02^{a}$	$6.38{\pm}0.50^{b}$
GROUP II	Alloxan only	$69.05{\pm}0.25^{b}$	$62.91{\pm}0.12^{b}$	$2.76{\pm}0.31^{b}$
GROUP III	Alloxan+ Glm	$45.45{\pm}3.13^{b}$	$89.23{\pm}1.03^{ab}$	$3.42{\pm}0.40^{a}$
GROUP IV	Alloxan+100 mg/kg fraction	$33.62{\pm}0.22^{a}$	$90.45{\pm}4.11^{b}$	$29.35{\pm}0.12^{c}$
GROUP V	Alloxan+100 mg/kg fraction	$32.99{\pm}2.01^{a}$	$96.56{\pm}3.12^{c}$	$4.37{\pm}0.31^{a}$

Result presented as mean ± Standard deviation. Result within a column with the same superscript indicate no levels of significance while result within the same column with different superscript indicate level of significances (p≤0.05)

Discussion and Conclusion

All animals in the trial, with the exception of those in group 1 (Normal Control), received 150 mg/kg of alloxan. The injection of alloxan caused the rats to become hyperglycemic by dramatically raising their blood glucose levels (p 0.05). Alloxan administration to experimental rats produces preferential breakdown of the pancreatic -cell membrane and cytotoxicity after intracellular accumulation, according to Martha *et al*., 2007. In group III (negative control), Induction of alloxan leads to increase in the blood glucose level from 109 mg/dl to 225 mg/dl on the day 7 (Table 1). The administration of the ethanol leaf fraction of *Senna tora* showed a significant decrease in blood glucose levels at the end of 21 days after induction of diabetes. This suggests that ethanol fraction *Senna tora* leaf may have an extra pancreatic antihyperglycemic mechanism of action.

This hypoglycemic effect is similar to the one stated for other plants (Islam, 2011; Sasidharan *et al.,* 2011; Gaamoussi *et al*., 2010). Such effect may be explained in part by either a decrease in the rate of intestinal glucose absorption (Hamden *et al*., 2011; Gupta *et al*., 2012) or increase inperipheral glucose utilization (Porchezhian *et al.,* 2013; Gupta *et al*., 2012).

In table 2, AST showed significant decrease (p≤ 0.05). ALT showed no significant increase (p≥ 0.05) in group II whereas it showed significant decrease (p≤ 0.05) in group V. ALP showed significant increase (p≤ 0.05) in group IV but there was significant decrease (p≤ 0.05) in group V. GGT showed no significant increase. Total protein showed significant increased (p≤ 0.05) in group II (10.88±1.75c) IV (5.31±0.65) with highest increase in group V. Albumin showed significant increase (p≤ 0.05) in group IV (6.59±1.06). Based on the parameters observed, it can be deduced that the administration of high concentration (200 mg/kg) of extract can heal the injuries inflicted on the liver due to oxidative stress. *Senna tora* have the capacity to reduce the reactive oxygen species (ROS) generated by hyperglycaemia that resulted to oxidative damage to the liver because high concentration of blood sugar (hypergycaemia) cause glucose auto-oxidatrion (Widowati, 2008). The state of diabetes will affect the occurrence of cell morphological changes from the liver (Kusuma *et al*., 2014). The increase in the activities of serum AST, ALP and decrease in total protein and albumin indicated that diabetes may have induced hepatic dysfunction. Supporting the finding by (Larcan *et al*., 2014), that liver cells were necrotized in diabetic patient. The serum protein level is a marker of the synthetic function of the liver and a good guide to assess the severity of the damage (Gopal and Rosen, 2000).

When compared to diabetic groups treated with Senna tora leaf fractions, the control group's liver MDA level increased considerably, suggesting an increase in oxidative stress with hyperglycemia (Ayeleso *et al*., 2014; Sankaranarayanan and Kalaivani, 2020). Both the creation of ROS that came along with the established hyperglycemia and the decline in antioxidant activity may have contributed to the rise in MDA in the diabetic rats (Alsenosy *et al*., 2019; Sefidgar *et al*., 2019).

SOD and CAT activity are increased by leaf extracts (Tables 4). The mechanism connected to scavenging activity may be the cause of this action. *Senna tora* leaf's ability to effectively scavenge free radicals, which underlies its antioxidant activity, was demonstrated in a study using albino rats to have a protective effect against diabetes induced by carbon tetrachloride (Rejiya *et al*., 2009).

It follows that important polyphenol with anti-oxidative action is present in Senna tora extracts. According to Scalbert *et al*. (2005), polyphenols may shield cell components from oxidative damage and hence reduce the risk of a number of degenerative disorders linked to oxidative stress.

Using rutin and BHT (butylhydroxytoluene) as standards, Rejiya et al. (2009) examined the nitric oxide scavenging activity of the methanolic leaf fraction of *Senna tora*. Rat liver and brain were used to test the fraction's ability to reduce lipid peroxidation. *Senna tora's* methanolic leaf fraction demonstrated superior nitric oxide scavenging capability to Rutin, suggesting Senna tora can be employed to lessen or delay the harm caused by nitric oxide radicals. *Senna tora's* methanolic leaf fraction has a strong inhibitory effect on lipid peroxidation as well (Rejiya *et al*., 2009).

Based on the findings, Senna tora leaf fraction had less adverse effects when used in low concentrations and had antihyperglycemic, hepatoprotective, and antioxidant activities. This is as a result of its notable decrease in blood glucose levels in the treated mice when compared to the untreated diabetic animals. Additionally, it has the potential to be a useful treatment for diabetes, hepatotoxicity, and lipid peroxidation.

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