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Research Article

AMELIORATIVE POTENTIAL OF CARISSA SPINARUM LEAF EXTRACT IN DISTORTED CARBOHYDRATE METABOLISM IN ALLOXAN INDUCED DIABETIC MICE

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A R T I C L E I N F O

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A B S T R A C T

Carissa spinarum L. is an evergreen, thorny shrub found in the Himalayan areas of Indo-Pakistan subcontinent. Number of ethno-medicinal applications of this plant has been reported. Pharmacologically this plant has been extensively used for the treatment of asthma and pulmonary diseases, anticancer, diarrhea, hepatoprotective, cardioprotective and reproductive dysfunction. Present study was aimed to study effects of *Carissa spinarum*methanolicleaf extract in alloxan treated mice pancreas. Mice were injected with alloxan monohydrate (150 mg/kg BW) intraperitoneally and selected diabetic mice were divided into four groups with six mice in each group. Diabetic mice were given *Carissa* leaf extract orally to a dose of 600 and 800 mg/kg body weight and glimepiride (2mg/kg body weight) for 28 days daily. The histopathological studies of pancreas of diabetic mice revealed degeneration of pancreatic histoarchitecture, but regenerative changes were observed after treatment with administration of *Carissaspinarum* leaf extract. Significant changes in activities of enzymes involved in carbohydrate metabolism i.e. G6PD, hexokinase and LDH were recorded after extract administration to alloxan induced oxidative stress in diabetic mice.

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INTRODUCTION

Diabetes is a complex multisystemic disorder characterized by a relative or absolute insufficiency of insulin secretion and mainly affects carbohydrate, protein, and lipid metabolism. It is a major degenerative disease in the world today which affects a minimum of 15 million people having complications like hypertension, atherosclerosis, and microcirculatory disorders (Bhalla *et al*., 2013). The progression of diabetes has been increasing globally from 108 million to 463 million up to 2016, with 1.6 million deaths in 2016 worldwide, estimated to rise to 578 million (10.2%) by 2030 and 700 million by 2045 (Pouya*et al*., 2019).In diabetes mellitus, the activity of enzymes involved in glucose metabolism, such as hexokinase, glucose-6-phosphatase, and fructose 1, 6- bisphosphatase, is markedly altered, resulting in hyperglycemia, which leads to the secondary diabetic complications (Sochor *et al.*, 1985). Hexokinase, an important enzyme in the catabolism of glucose, phosphorylates glucose and converts it into glucose-6-phosphate. The end product of mostly dietary carbohydrates in the diet is glucose. The dietary carbohydrates that are actively digested contain glucose, galactose and fructose residues that are released in the intestine.

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Carissa spinarum L.also known as ‘‘conkerberry’’ or ‘‘Bush Plum’’ consists of evergreen shrubs belonging to family Apocyanaceae, native to the subtropical and tropical regions of Asia, Africa, and Oceania (Lindsay *et al*., 2000). The plants are evergreen, shrubs, which grow as a small tree up to 1–5 m in height. The stem is branched, glabrous, greenish, spiny, and rich in white latex. Leaves are in opposite-decussate arrangement, green, simple, ovate or rounded. Flowers begin to bloom between February and April in *C. spinarum*, are small, fragrant, white inside, and pink to red on the outside. *C. spinarum*is traditionally used in India, Ethiopia, and other African countries for the treatment of various respiratory and gastrointestinal infections (Wangteeraprasert *et al*., 2012), fever, jaundice, hepatitis, cardiac diseases, asthma (Feyissa and Melaku, 2016), gonorrhoea, stomach-ache, chickenpox, wound healing, rabies, and also as an antidote to snake bites (Chopra *et al*., 1956). The leaves of *C. spinarum* are also used as a mosquito repellent (Chopra et al., 1956).Considering the various beneficial effects of *Carissa spinarum* the present study was designed to study the effects of *Carissa spinarum*methanolicleaf extract on alloxan induced experimental diabetic mice for 28 days.

MATERIALS AND METHODS

Preparation of extract

Fresh leaves were collected from Joginder Nagar, District Mandi, Himachal Pradesh, India. The leaves were removed from the stems, rinsed in clean water and then dried in shadow

for weeks. After drying, the leaves were ground to powder with the aid of a blender to obtain approximately 1kg. 1 kg powdered plant sample was extracted thrice in a ratio of methanol: water- 80:20 at 25°C for 24 hours each. Whatman No. 1filter paper was used for filtration, then filtrate was concentrated on rotary evaporator under reduced pressure at 50°C and dry extract was stored at 4°C for further investigation.

Animal usage

Healthy pathogen free Swiss albino mice weighing 25-30 g were procured from Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar, India, and protocol of present investigation was approved by Institutional Animals Ethics Committee (IAEC/BIO/1-2013). Mice were kept in polypropylene cages on soft chip bedding and maintained in the animal house of Department of Biosciences under suitable hygienic conditions with suitable light and temperature. Mice were provided with pellet feed (Hindustan Lever Limited, New Delhi, India) and water *ad libitum.*

Administration of alloxan monohydrate

Alloxan monohydrate (Sigma chemicals) was used to induce diabetes in mice. A freshly prepared solution of alloxan monohydrate in normal saline solution was injected to overnight fasted animals intraperitonealy at a dose of 150 mg/kg body weight.

Induction of Diabetes

The animals were fasted overnight and diabetes was induced by a single intraperitoneal injection of a freshly prepared alloxan dissolved in normal saline solution. After injection mice had free access to food and water, and given a 15% glucose solution to drink overnight to counter hypoglycemic shock. The mice were considered as diabetic if their blood glucose values reached above 180 mg/dl on day 3 after alloxan injection. The blood glucose levels were measured by using one touch glucometer (Gluco one). After diabetes confirmation, mice were allowed for 7 days to acclimatize to the diabetic condition, and mice with hyperglycemia (blood glucose above 180 mg/dl) were chosen for further study. Treatment with extractstarted on day 8 after alloxan injection which was also considered as the first day oftreatment and continued further until end of the study period.

Grouping of Animals

Mice of the same age group (3 months old) were divided into sixgroups. Six micein each group.

- Group I: Control animals, received only distilled water.
- Group II: Received methanolic leaf extract of *Carissa spinarum*(800 mg/kg BW) daily for 28 days.
- Group III: Injected with alloxan intraperitonealy at a dose of 150 mg/kg BW.
- Group IV: Diabetic mice received *Carissa spinarum* methanolic leaf extract (600 mg/kg BW) daily for 28 days.
- Group V: Diabetic mice received *Carissa spinarum* methanolic leaf extract (800 mg/kg BW) daily for 28 days.
- Group VI: Diabetic mice received glimepiride (2mg/kg BW) daily for 28 days acted as standard. This group was maintained for better comparison of the protective effect of *Carissa spinarum* methanolic leaf extract against diabetes induced complications.

All the chemicals used in the study were of analytical grade and obtained from SD fine chemicals (Mumbai, India) and HIMEDIA (Mumbai, India).

Tissue harvesting

Animals were sacrificed at 7, 14, 21, 28 days of experiment by cervical dislocation. Pancreas was immediately dissected out, cleaned in normal saline quickly blotted and weighed.

Histopathological studies

The tissues after excision were fixed in Bouin's fixative for 24 hours. After thorough washing in running tap water excess of fixative was removed from the tissues. Tissues were dehydrated finally in different grades of alcohol (30%, 50%, 90%, 100%) and embedded in paraffin wax (58-60^{0}c). Thin 5-6 µm sections were cut on a Spencer type rotary microtome and employed for haematoxylin eosin staining.

Biochemical studies

Spectrophotometric assays were performed on Hitachi VSU-double beam spectrophotometer and Bausch and Lomb spectronic-20.Blood glucose levels were measured using glucometer every time on 7, 14, 21, 28 days of experiment and was expressed in mg/dl. Hepatic hexokinase enzyme activity was measured by method of Brandstrup *et al*. (1957). The hexokinase activity was recorded as units/min/mg of protein. Method of Balinsky and Bernstein (1963) was adopted for G6PD assay. Lactate dehydrogenase activity was estimated as per method of Bergmeyer and Burnt (1974).

Statistical analysis

The results were obtained as mean ± SEM. Statistical significance was determined by one wayAnova with post-hoc Tukey HSD to find out mean differences between groups. The differences were considered significant at $^{**}p<0.01$.

RESULTS

Effects of Carissa spinarum on histopathology of pancreas

Microscopic examination of normal pancreas of mice after haematoxylin eosin staining showed that it was divided into lobules by connective tissue septa. Lobules were composed largely of grape like clusters of exocrine cells called acini. Interlobular ducts were smaller in size and with regular round outline. Islets of Langerhans of pancreas in normal mice were scattered throughout the pancreas as irregular, spheroidal masses with rich vascular supply and were embedded within the pancreatic exocrine tissue forming the endocrine component of the pancreas (Fig.A).

Severe damage to mice pancreas was witnessed at 28 days stage of alloxan administration. Deformed acinar cells were seen. Nuclear pleomorphism was noticed in shape and size of the nuclei of acinar cells and dark hyperchromatic nuclei were also observed. Depletion of cytoplasmic zymogen granules was also witnessed with reduction in formation of acinar cells.Whereas in alloxan administered mice pancreas sections islet cells had ill defined boundaries with elongated size and were not compactly arranged with acinar cells. Number of beta cells were also reduced and islets were occupied by eosinophilic material and few atrophic cells (Fig. B,C).

Diabetic mice supplemented with CS extract for 28 days showed reformation of pancreatic architecture. Histological appearance of nuclei was almost near to normal with rounded outline and no karyolysis. The nuclei were less damaged, cells become organized and the intercellular spacing was very less. The acinar cells tried to regain their normal pyramidal structure. Pink coloured lumen contained the zymogen granules in the cytoplasm. Hypertrophied nuclei were also seen scattered in the section. Number of beta cells were also regained after supplementing CS extract for 28 days of treatment. Few pycnotic nuclei were noticed with few acinar cells having vacuoles (Fig. D,E).

Glimepiride treated diabetic mice showed less dilated intercellular and interlobular septum as compared to the alloxan administered diabetic mice. Collagen fibres deposition was also reduced in the intercellular space. Vacuolation and degranulation of acinar cells was noticed. Irregular cell outlines of acinar cells were also noticed at some areas however there was decrease in degenerating acinar cells (Fig.F).

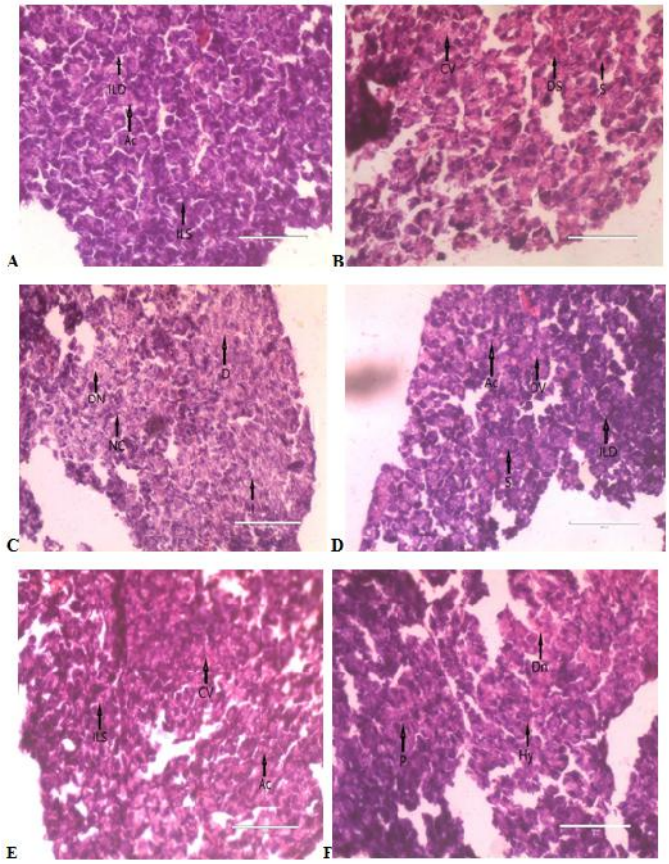

Fig. A: T. S. of normal mice pancreasrevealing pyramidal shaped acinar cells (Ac), intralobular ducts (ILD), narrow interlobular spaces (ILS). **Fig. B:** Alloxan administered mice pancreas depicting cytoplasmic vacuolation (CV) indicating focal acinar damage, distorted structure (DS) of acinar cells compared to pyramidal shaped normal cells, narrowing septum of acinar cells (S). **Fig. C:** Alloxan administered mice pancreas revealing degenerative (DN) and necrotic changes (NC) in acinar cells, nuclei of some acinar cells become irregular (I) or hyperchromatic, deformed (D) pancreatic architecture.**Fig. D:**ALX+ CS extract (800 mg/kg) treated mice pancreas showing closely arranged pancreatic acini (Ac) as compared to distorted cells in diabetic mice,decline in vacuolization of nuclei (DV), reformation of intralobular ducts (ILD), shrinkage of acinar cells (S). **Fig. E:** ALX+CS extract (800 mg/kg) treated mice pancreasdemonstrating reformed pyramidal shape of acinar cells (Ac),with decreased cytoplasmic vacuolation (CV) and shrinkage of intralobular septum (ILS), however normal acinar architecture is almost regained. **Fig. F:** ALX+ glimepiride treated mice pancreas revealing closely packed pancreatic cells (P) with normal shape, some acinar cells were in degenerated (Dn) state with few hypertrophied nuclei (Hy).

Effects of C. spinarumextract on biochemical parameters

Changes in fasting blood glucose concentration after administration of *C. spinarum* leaves extracts are summarized in Table I. Daily oral administration of *C. spinarum* leaves methanolic extract at dose 800 mg/kg BW to normal mice led to decrease in fasting blood glucose at the end of study. As for the positive controls, administration of glimepiride (2 mg/kg BW) and *C. spinarum*leaf extract (600 and 800 mg/kg BW) had significantly showed 65.7%, 61.7% and 67.7% reduction in fasting blood glucose, respectively.

Enzyme activity of G6PD in alloxan induced diabetic mice showed a reduction of 46.4%as compared to control mice whereas extract treatment to diabetic mice for 28 days led to significant increase in enzyme activity of G6PD up to 82.2% as compared to diabetic mice. Diabetic mice showed reduction of 58.7% in hexokinase activity as compared to control mice. Enzyme activity of hexokinase also showed a significant increase of 127.7% as compared to diabetic mice after supplementation of CS extract to diabetic mice for 28 days. LDH is a marker of tissue injury. LDH levels in alloxan induced mice showed an increase of 24.6% as compared to control. CS extract treatment to diabetic mice for 28 days led to decrease in LDH levels by 17.0% as compared to diabetic mice (Table I).

Table I The effects of *Carissa spinarum*on blood glucose and carbohydrate metabolizing enzymes of alloxan induced mice after 28 days of extract treatment

Groups	Blood Glucose	G6PD	Hexokinase	LDH
	(mg/dl)	(U/mg protein/min)	(U/mg protein/min)	
Control	92.4±0.23	0.168±0.010	0.218±0.040	0.327±0.06
CSE	84.3±0.17	0.180±0.06**	0.234±0.040	0.294±0.03
ALX	322.7±1.43	0.090±0.060	0.09±0.02**	0.410±0.03
ALX+E1	123.4±1.50**	0.161±0.03**	0.154±0.09	0.353±0.03
ALX+E2	104.1±2.16**	0.164±0.02**	0.205±0.02**	0.340±0.03**
ALX+G1	10.5±1.12	0.149±0.060	0.193±0.01**	0.347±0.03

Each value is mean±S.D. for six mice in each group. The data for various biochemical parameters were analysed using one wayAnova post hoc Tukey's test. Values were considered statically significant at $p^{**}<0.01$. G6PD: Glucose-6-phosphate dehydrogenase, LDH: Lactate dehydrogenase. CSE: Carissa spinarum extract, ALX: Alloxan, E1: CSE (600 mg/kg BW), E2: CSE (800 mg/kg BW), G: Glimepiride (2mg/kg BW).

DISCUSSION

Diabetes mellitus is the most common endocrine disorder with impairment of glucose homeostasis resulting in severe diabetic complications and causing neurological disorders due to impaired glucose utilization (Anusooriya *et al.*, 2014). Alloxan is a hydrophilic and unstable chemical compound used to induce diabetes in experimental models and resembles shape of glucose, which is responsible for its selective uptake and accumulation by the pancreatic beta cell. Similarity in the shape with glucose allows it to transport into the cytosol by the glucose transporter (GLUT2) in the plasma membrane of beta cells (Elsner *et al.*, 2002). The biosynthesis of insulin is also suppressed by alloxan through the same mechanism. Alloxan supresses many cellular functions at higher concentrations such as the ability to oxidize thiol groups of many functionally important enzymes like hexokinase, phosphofructokinase, calmodulin-dependent protein kinase, aconitase and other proteins (Lenzen, 2008). Hence, it is evident that the inhibition of glucose induced insulin secretion by alloxan is because of the thiol reactivity of the glucokinase. Another biological

effect of alloxan is pancreatic beta cell toxicity and diabetogenicity that may be attributed to alloxan-induced redox cycling and ROS generation.

The study aimed to evaluate the effects of *Carissa spinarum*methanolic leaf extract in diabetic patients uncontrolled with their hypoglycemic medications. Administration of *Carissa spinarum* leaf extract daily for 28 days concurrently with oral hypoglycemic drugs resulted in significant decrease of the fasting glucose level. The decrease in blood glucose level was significant and sustained throughout the study for 28 days. These results are corelated with other reports which confirm the hypoglycemic effect of *C. spinarum* extract in experimental animals.

The hypoglycemic effect of the extract may have been produced by the flavonoids, saponins and tannins present in the leaves. The flavonoids, saponins and tannins are families of compounds with established hypoglycemic activity (Hegde *et al*., 2010; Pereira *et al*., 2009; Fatima *et al*., 2013). *Carissa* species have shown the presence of phytoconstituents such as alkaloids, flavonoids, glycosides, reducing sugar, steroids, terpenoids, tannins, and saponins, which mostly attributed for the pharmacological activity of the plant (Mishra *et al*., 2013). Similar findings were reported by study in aqueous leaf extract of *Carissa carandas* on alloxan induced and normoglycemic Wister rats, and it was found that the doses of 500 and 1000 mg/kg of the drug significantly reduced the blood glucose level of alloxan induced diabetic rats at 4, 8 and 24 hours (Gaurav *et al*., 2010; Fartyal and Kumar, 2017).

Alloxan has a destructive effect on the beta cells of the pancreas. Alloxan induces diabetes by destroying the insulin-producing beta cells of the pancreas. In vitro studies have shown that alloxan induces cell death due to its poisonous effect on pancreatic beta cells (Jorns *et al*., 1997). Alloxan induces diabetes by pancreatic cell damage mediated through generation of oxygen free radicals. The primary target of these radicals is the DNA of pancreatic cells causing DNA fragmentation (Shankar *et al*., 2007). The histopathological study clearly revealed that in alloxan induced diabetic mice, endocrine region of pancreas showed the presence of shrinkage, necrosis and damaged β-cells. The histopathological examination of pancreas of alloxan induced diabetic mice has revealed destruction of beta cells and reticular changes of islets as evidence of fibrosis.

Treatment of diabetic mice with CS leaf extract resulted in improvement in the beta cell granulation of islets as compared with diabetic mice. Among two doses of extracts, CS leaf extract at 800mg/kg exhibited maximum effect which was almost comparable to the standard drug treated animals. The restoration ability may be due to protection of beta cells from oxidative stress and reduced inflammation may be due to combined effect of phytoconstituents supported by reducing the lipase enzyme level in blood. The islets were apparently normal in the architecture of the nucleus, which revealed that administration of CS extract prevented the b-cells damage compared to diabetic mice. Treatments with CS leaf extract and glimepiride to diabetic mice for 28 days resulted in partial improvement in pancreatic tissue integrity. The number of infiltrated and degranulated islet cells were reduced as compared to diabetic control group. The results of current study were in agreement with findings of Ahmed *et al*. (2015) who reported the protective effect of extract of *Euryale ferox salisb*. on the liver, pancreas and kidney in STZ induced diabetic rats when administered for 45 days.

One of the major enzymes in the catabolism of glucose is hexokinase, which phosphorylates glucose and converts it into glucose-6-phosphate (Li *et al*., 2020). The increased activity of hexokinase by the administration of CS leaf extract can enhance utilization of glucose for energy production. Furthermore, the decline in the concentration of blood glucose of diabetic mice treated with the *C. spinarum*leaf extract from current study suggests enhanced glycolysis as evident in the increased liver hexokinase activity in the present study. The administration of *Carissa spinarum* leaf extract significantly improves G6PD enzyme activity in hepatic tissue notifying another possible way of antidiabetogenic activity of the extract.

Lactate dehydrogenase (LDH) controls the conversion of pyruvate to lactate, which is eventually converted to glucose in gluconeogenic flux and is a functional enzyme in anaerobic glycolysis. *Carissa spinarum* leaf extract treatment tried to reverse the effect of alloxan administration by decreasing the enzyme activity in liver, kidney and pancreas. Diabetic mice treated with CS leaf extract had significantly restored LDH activity, probably as a result of the stimulation of the oxidation of NADH. Normal LDH activity is indicative of improved channelling of (pyruvate) glucose for mitochondrial oxidation. The results of our study are in accordance with the study conducted on flower and root extracts of *Aervalanata* which regulate the carbohydrate metabolic enzymes activities in alloxan induced diabetic rats. The extracts of flower and root of *A. lanata* significantly maintained the levels of carbohydrate metabolic enzymes such as aerobic and anaerobic glycolytic key enzymes, HMP shunt, gluconeogenic key enzymes and glycogen metabolic enzymes which were restored to near normal levels in liver and kidney (Vidhya, 2018).

CONCLUSION

Thus from above findings it can be concluded that CS leaf extract has a potential to revert the effects caused in diabetic mice and was also effective in restoring activities of carbohydrate metabolizing enzymes proving it to be a great supplement to replace synthetic antidiabetic drugs.

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Conflict of Interest

None of the authors show any conflict of interest.

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