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Nutrient and Anti-diabetic Activity of *Azadirecta indica* and *Corriandrum sativum* Leaf Extract on Allaxon Induced Diabetic Rat

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Azadirecta indica (Meliaceae) is a medicinal plant, commonly known as 'Neem' and distributed randomly in the whole of India. *Corriandrum sativum* belongs to the family of Apiaceae was considered to be native from Asia and Africa and known locally in Sudan as Kazbra. *Azadirecta indica* and *Corriandrum sativum* extract have been studied for therapeutic possessions. The nutrient parameters and gas chromatography mass spectroscopy (GC-MS) analysis in the leaves of *Azadirecta indica and Corriandrum sativum* were studied and also the antihyperglycemic activity of hydro alcoholic extract. An acute oral toxicity study was carried out in healthy male Wister rats (100 g). Diabetic rats were orally and daily administrated of hydro alcoholic leaf extract of *A. indica* and *C. sativum* at the different doses (200-400 mg/kg. b.w) with anti-diabetic reference drug (metformin). After 21st days of treatment, level of blood glucose, as well as Albumin, Protein, Creatinine, Urea and Uric acid were significantly decreased when compared with the diabetic control. These plant fruit extract will be subjected for further extensive studies to isolate and identify their active constituents which are useful for against antidiabetic. Ethanol leaf extract of *Azadirecta indica* effect was confirmed minerals such as sodium (Na), copper (Cu), magnesium (Mg), manganese (Mn), Cobalt (Co) and iorn (Fe) were decreases of the respect of *Corriandrum sativum*. The results was indicated that the hydro alcoholic extract from leaves of *Azadirecta indica* and

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Corriandrum sativum showed the reduced blood glucose and other biochemical parameters level were observed in diabetic rats treated with both doses of ethanol extract of *Azadirecta indica* and *Corriandrum sativum leaf* compared to diabetic control rats. These observed strongly suggest that hydro alcoholic extract could act as a source of functional compounds for the control of diabetes mellitus.

Keywords: Alloxan; antidiabetic; Azadirecta indica; Corriandrum sativum; metformin.

1. INTRODUCTION

Diabetes mellitus (DM) is a metabolic syndrome categorized by changes the blood glucose levels and insufficient insulin secretion. Diabetes mellitus (DM) is measured one of the main threats to human fitness in the 21st century. In developing countries, the incidence of diabetes is increasing very fast [1]. Action of diabetes efforts are curing of glucose or lipid metabolism [2]. Develop of diabetic complication is a serious issue which affected millions of people worldwide. More than 10% of the population is affected all over the world. WHO the prevalence of diabetes has increased by leaps and bond and is expected to reach 439 million by 2030 [3]. The development of oxidative stress (OS) in diabetes is major complication [4]; increased oxidative stress is caused to cell damage and destruction of the cells [5]. There are several studies reported that the increased generation of reactive oxygen species (ROS) causes damage to cells, tissues like pancreas, kidney and liver contributed to diabetic complications [6]. On the other hand dyslipidaemia is a present in insulin resistance and alter insulin secretion that affect enzymes and pathways of lipid metabolism , Which is a major risk factor for cardiovascular diseases and that is currently leading to cause of morbidity and mortality worldwide. Major metabolic derangements which result from insulin deficiency in diabetes mellitus are increased blood glucose levels, lipid and protein metabolism [7, 8]. The two types of diabetes are referred to as type 1 and type 2. Former names for these conditions were insulin-dependent and non-insulin-dependent diabetes, or juvenile onset and adult onset diabetes. DM is a chronic disorder in humans and responsible for different complications and also causes mortality and morbidity [9]. There are several hypoglycaemic drugs for the treatment of diabetes mellitus, have side effects [10]. Hence, there is need of scientific investigation to find alternative therapeutic approaches for the treatment of diabetes has become inescapable. The plants extract has been used in diabetes management and large number of medicinal plant has been documented for effective role in the curing of diabetes management [11], under hyperglycaemic condition various risk factor such as alter insulin secretion, hyperlipidemia and oxidative stress were causing major complication such as diabetes retinopathy, neuropathy and cardiovascular diseases [12]. In recent years, there is upward signal that phytochemical compounds like as polyphenols potent ability to reduced dyslipidaemia and diabetes [13], a part of this beneficial effects largely attributed to phenolic compounds, including flavonoids, phenolic acids, lignans and stilbenes on metabolic disorders and complications induced by diabetes [14]. The Indian Council of Medical Research India Diabetes Study (ICMR- INDIAB) presented that India had 62.4 million people with diabetes in 2011. These numbers are projected to increase to 101.2 million by 2030. ICMR- INDIAB homework exposed that the no of diabetic cases of type- 2 DM, insulin- like growth factor, and impaired glucose tolerance (IGT) in north India are increased, in this region such as Chandigarh is which state among the selected region where the more incidence. In therapeutic practice, an inspiring number of natural products have been presented for lead and model molecules for structure optimization and the expansion of more potent and/or better- tolerated remedies [15]. Numerous plants have been rummage-sale as dietary adjuvant and in treating the number of diseases even without any information on their proper purposes and ingredients.

2. MATERIALS AND METHODS

2.1 Plant Material and Sample Collection

The leaves of *Azadirecta indica* and *Corriandrum sativum* were collected from the Prayagraj district, U.P., India and identification from CSIR-National Botanical Research Institute Lucknow. The specimen number of the plant is EBH No.: 6166 and 5241 store in Herbarium Division.

2.2 Chemicals

All chemicals were obtained from ethanolic alcohol (boiling range 65-80ºC) (S.D. Fine

chemicals Ltd., India); $Na_2HPO_4.2H_2O$ (Rankem), $K_2HPO_4.2H_2O$ (Rankem), Trichloroacetic acid (Bio-Rad), EDTA (Ranbaxy), Nitro blue tetrazolium salt (Rankem), H_2O_2 (Ranbaxy), Guiacol (Rankem), CaSO4 (Ranbaxy), Thiobarbituric acid (Rankem), Poly Vinyl Polypyrrolidone (Rankem) whereas Alloxan was purchased from the Lobachemie, Mumbai, India. Commercially available kits for biochemical analyses such as glucose, metformin were done using commercial diagnostic kits following manufacturer's instructions. All reagents used in study were of analytical grade.

2.3 Acute Oral Toxicity Studies

Azadirecta indica and Corriandrum sativum at the dose range of 200–400 mg/kg body weight were administered by oral gavage method on different group of mice comprised of 6 mice in each group. Animals were kept under close observation for 4 hours after administering the fraction for behavior, neurological, and autonomic profile and then observed for any change in the general behavior and/or physical activities; mortality was recorded within 72 hours.

2.4 Sample Preparation and Maintenance of Animals and Approval of Protocol

The oven dried leaves of *Azadirecta indica* and *Corriandrum sativum* were subjected to pulverization to get coarse powder. Hydro-alcoholic (20:80) extract was made by Soxhlet methods for 15h. The extracts were filtered through Whatmann No. 1 filter paper and stored at 4 ^{0}C used for further experiments. The dose was finally made to 200 mg/kg and 400 mg/kg body weight for oral administration after the LD_{50} estimation. After the 21st days, animals were sacrificed and blood was collected by the orbital sinus puncture method. Biochemical parameters are LFT (SGOT, SGPT, ALP and Bilirubin) KFT (urea, Uric acid, protein, albumin, and Creatinine) and serum glucose levels were estimated according to the protocol of the manual of diagnostic kits.

The animals were acclimatized to laboratory condition for one week prior to experiment. Standard pellets were used as a basal diet during the experimental period. The control and experimental animals were provided with purified drinking water *ad libitum*. The animals were maintained in accordance with the"CPCSEA guidelines for laboratory animal facility" (Committee for the Purpose of Control and Supervision on Experiments on Animals) and the approval number is CPCSEA Registration Number 1451/PO/Re/CPCSEA, dated 16/06/2017.

2.5 Experimental Induction Alloxan Diabetes and Treatment with *Azadirecta indica* and *Corriandrum sativum* Leaf Extract

Diabetes was induced by IP administration of alloxan monohydrate 150 mg/kg body weight after an overnight fasting for 16 hours (had access only to water), to make them more susceptible to develop diabetes. Alloxan monohydrate was dissolved in 0.9% NaCl solution and administrated to experimental rat. After 3 days of alloxan monohydrate induction, glucose level was monitored. The rat was having blood glucose level > 200 mg/dl for the present study.

The groups were treated as follows:

Group I [CN] consisted of normal rats, orally given water and feed.

Group II [DM] consisted of diabetic rats were received Alloxan (150 mg/ kg b.w.) by intraperitoneal injection.

Group III [DM+AIA200] consisted of diabetic rats orally given *Azadirecta indica* leaf extract by gavages (mg/kg b.w.) once daily for 28 days.

Group IV [DM+CSA400] consisted of diabetic rats orally given *Corriandrum sativum* leaf extract by gavages (400 mg/kg b.w.) once daily for 28 days.

Group V [DM+MET200] consisted of diabetic rats orally given standard drug Metformin (200 mg/kg b.w.) once daily for 28 days.

2.6 Changes in Gas Chromatography Mass Spectroscopy Metabolic Analysis

TMS derivative was prepared of the different extracts. Approximately 5 mg of the sample was suspended in 40 µl of the solution of methoxylamine hydrochloride in pyridine (20 mg/ml). The mixture was shaken for 2 h at 37°C before adding 70 µl of the 2, 2, 2-trifluoro-N-methyl-N-trimethylsilylacetamide (MSTFA). Shaking was continued for another 30 min. Resulting derivatized mixture of metabolites was subjected to analysis on Gas Chromatography-Mass Spectrometry (GC-EIMS) on a Thermo

Fisher TRACE GC ULTRA coupled with DSQ II Mass Spectrometer instrument using a TR 50MS column (30m x 0.25mm ID x 0.25 µm, film thickness). Constant flow at 1 ml/min of carrier gas (Helium) was used for the analysis. The injector temperature of the instrument was 230°C and oven temperature was started from 70°C, (hold time 5.0 min) to 290°C with ramp of 5°C/min (hold time 5 minutes). Sample was injected in split mode (1:50) with injection volume of 1µl. The ion source temperature was set at 220°C and transfer line temperature was at 300°C. The ionization of the sample was performed in electron impact mode at an ionization voltage of -70 eV. Mass range was used from *m/z* 50 to 650 amu. Identification of individual compounds was carried out by comparison of their mass spectra with those of the internal reference mass spectra library (NIST/Wiley).

2.7 Metal Analysis

The collected samples were oven dried at 70-80ºC for 24h. Dried petals powder (0.5 g) were digested in H_2SO_4 and $HClO_4$ in 5:2 ratio upto 20 ml, using Digestion System (Kelplus- Classic DX) after that we makeup in 100 ml volumetric flask from distil water (DW). Heavy metals content was estimated by HPLC-ICP-MS, model 7500cx. The results obtained were expressed as mg kg^{-1} of dry matter (DM).

2.8 Statistical Analysis

The obtained data were subjected to statistical analysis for the determination of significance using analysis of variance. The analysed data were presented as mean ± standard deviation (n=4). A statistical analysis was analysed by one way analysis variance (ANOVA). At significant value is $p<0.05$.

3. RESULTS

3.1 Body and Organs Weight

The body and organ weight of control and experimental group were having given Table 1. The total body weight decreased as well as kidney weight during diabetes, when compared with control mice ($P < 0.001$). Oral administration of aqueous extract (200 mg/kg body weight and 400 mg/kg body weight) significantly improved.

Table 1. Effect of *D. pentagyna* on body weight and organ/kidney weight in alloxan induced diabetic rat

Treatments	Body weight (gm)		Kidney weight (gm)
	Initial	Final	
CN	41.03±1.65	42.14±1.86	1.40±0.15
DM	39.20±1.55	38.85±1.56	0.96±0.09
DM+200	40.03±1.65	41.14±1.86	1.20±0.15
DM+400	40.43±1.65	41.31±1.86	0.85±0.15

*The value represented as means ±S.D for six mice per group. p<0.001 as compare to normal group and *p<0.001 as compare to diabetic group*

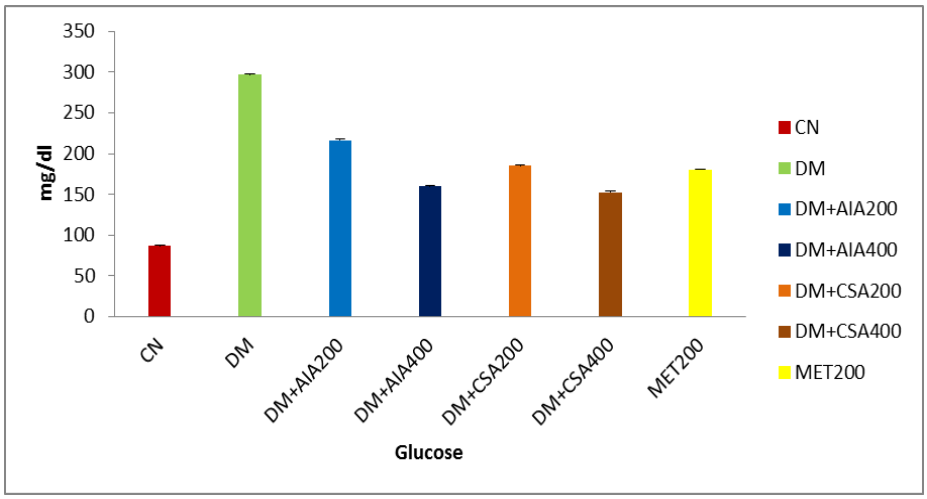

Fig. 1. Effect of *A. indica* and *C. sativum* serum glucose level in alloxan induced diabetic model
Values are statistically significant at p<0.05

3.2 Effect on Serum Glucose

Alloxan (150 mg/kg b.w.) administration resulted in significant elevation of glucose level. The administration of *A. indica* and *C. sativum* at a dose of 200 and 400 mg/kg b.w. administered for 21st day were able to correct this aberration significantly ($P < 0.001$). The results of all the formulations tested i.e. after induction of diabetes by alloxan, diabetes was confirmed by the presence of hyperglycemia in animals and the mean level of glucose in the control group of rat was evaluated to be 85.67 ± 12.03 mg/dl (range 60–95) whereas it was 298.5 ± 25.64 mg/dl (range 190–300, $P = 0.0001$) in alloxanized group. After the treatment of rat with the leaves extract of *A. indica* (200 mg/kg b.w.) and *A. indica* (400 mg/kg b.w.) the glucose level decreased down to 216 ± 8.52 mg/dl ($P = 0.0001$) having a range of 160–216 mg/dl and more potent effect at the dose of 400 mg/kg b.w. of extract the level of glucose also significantly decreased to 134.3 ± 6.04 mg/dl ($P = 0.0003$) having range of 100–140 mg/dl. Farther more, the leaves extract of *C. sativum* (200 mg/kg b.w.) and *C. sativum* (400 mg/kg b.w.) the glucose level decreased down to 185 ± 5.52 mg/dl ($P = 0.0001$) having a range of 152–185 mg/dl and more potent effect at the dose of 400 mg/kg b.w. of extract the level of glucose also significantly decreased to 152.3 ± 5.04 mg/dl ($P = 0.0003$) having range of 100–140 mg/dl. The significant increase in glucose concentration in the diabetic animals than that of the control mice is evident on alloxanization. However, the oral administration of hydro alcoholic extract of *A. indica* and *C. sativum* significantly reduced the glucose level in serum when compared with alloxan- induced diabetic rat.

3.3 Liver Function Level

The level of serum SGPT, SGOT, ALP and bilirubin were presented in Figs. 2-5. Significantly increased ($p<0.05$) were in alloxan induced diabetic rats, compared to normal group. On the other hand daily oral administration of extract at the dose of 200 and 400 mg/kg body weight on diabetic group showed significantly reduced comparison with alloxan induced groups. Both the dose of *A. indica* and *C. sativum* and Metformin treatment significantly reduced.

3.4 Kidney Function Level

The level of uric acid, serum albumin and protein were presented in Fig. 6-8 significantly reduction in albumin and protein level ($p<0.05$) were in alloxan induced diabetic rats, compared to normal group. On the other way oral administration of extract on diabetic group, significantly increased. The level of urea, uric acid and creatinine were seen significantly ($p<0.05$) increased comparison with alloxan induced groups. Both the dose of *A. indica* and *C. sativum* and Metformin treatment significantly reduced.

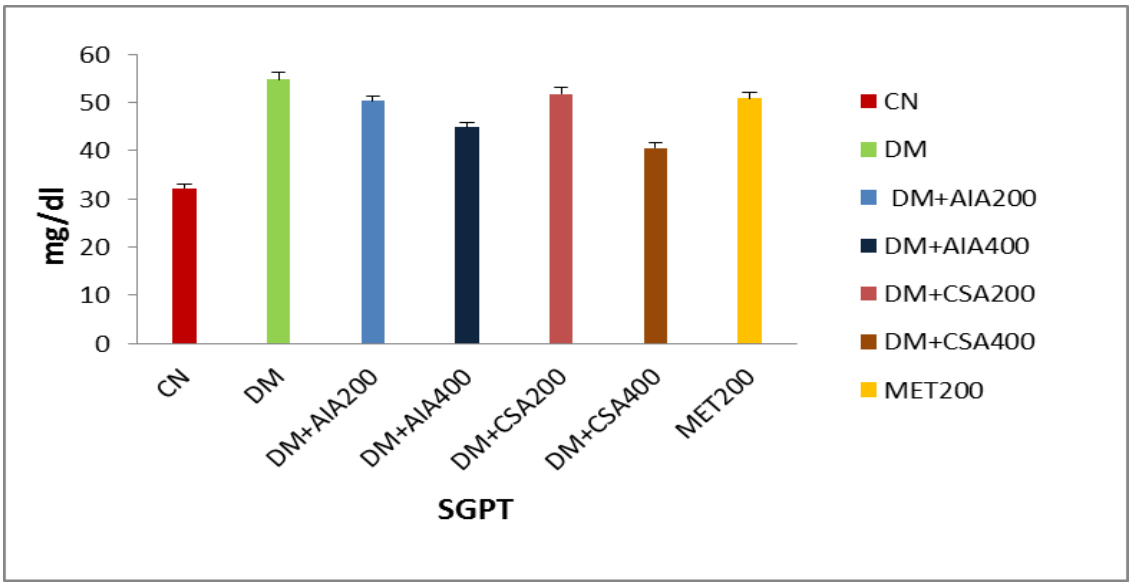

Fig. 2. Effect of *A. indica* and *C. sativum* on serum SGPT level in alloxan induced diabetic model

Values are statistically significant at p<0.05

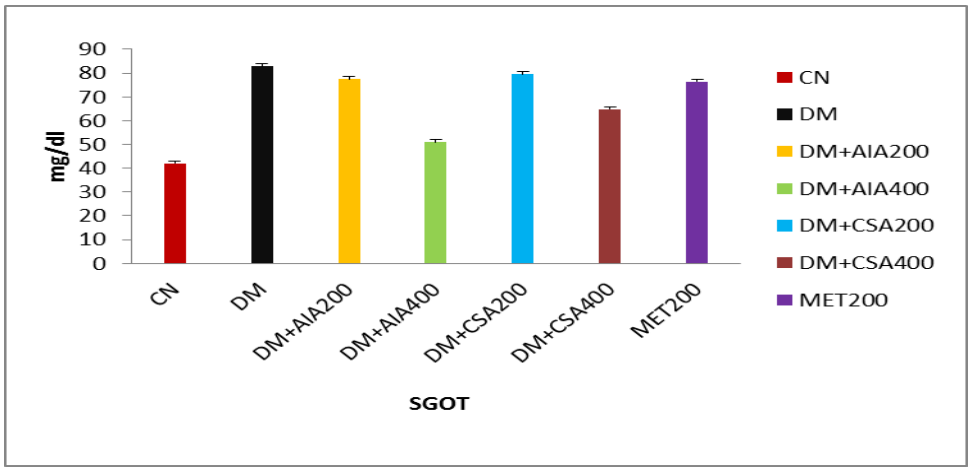

Fig. 3. Effect of *A. indica* and *C. sativum* on serum SGOT level in Alloxan induced diabetic model

Values are statistically significant at p<0.05

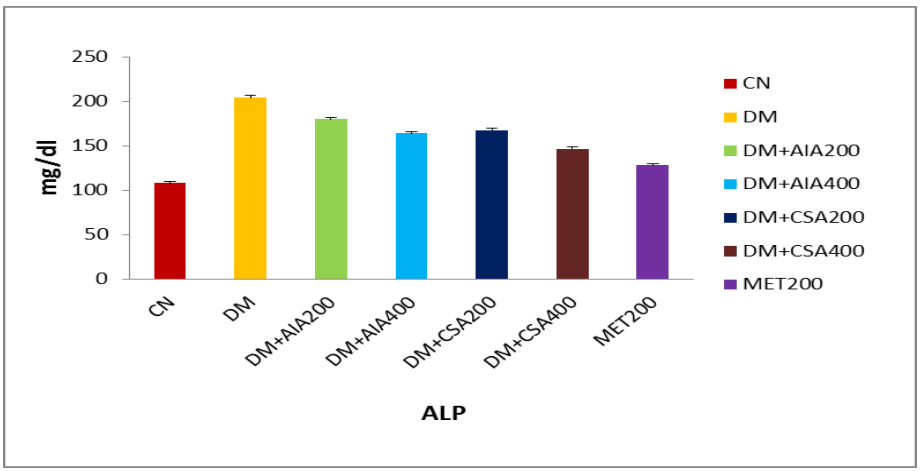

Fig. 4. Effect of *A. indica* and *C. sativum* on serum ALP level in alloxan induced diabetic model

Values are statistically significant at p<0.05

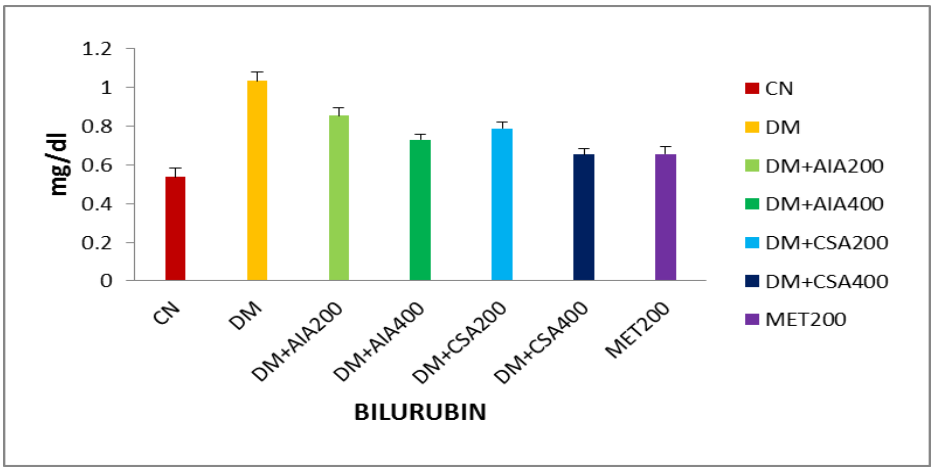

Fig. 5. Effect of *A. indica* and *C. sativum* on serum Bilirubin level in Alloxan induced diabetic model

Values are statistically significant at p<0.05

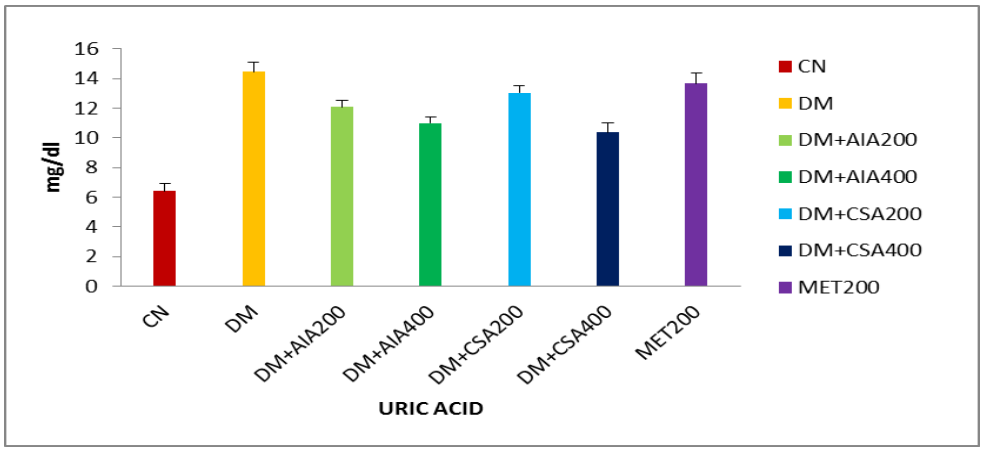

Fig. 6. Effect of *A. indica* and *C. sativum* on serum Uric acid level in Alloxan induced diabetic model

Values are statistically significant at p<0.05

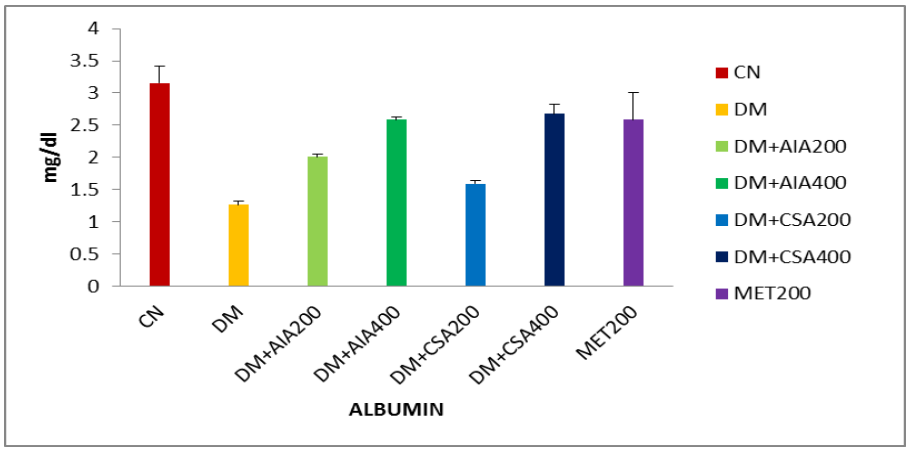

Fig. 7. Effect of *A. indica* and *C. sativum* on serum Albumin level in alloxan induced diabetic model

Values are statistically significant at p<0.05

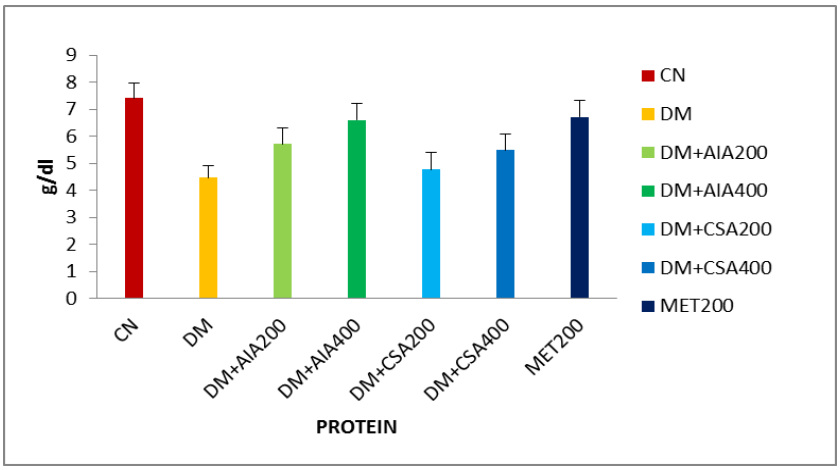

Fig. 8. Effect of *A. indica* and *C. sativum* on serum Protein level in Alloxan induced diabetic model

Values are statistically significant at p<0.05

3.5 Mineral Analysis by ICP-MS

The mineral analysis was carried out from *A. indica* and *C. sativum* leaves were found Sodium (0.35g/100g to 0.56g/100g) Magnesium (0.81g/100g to 0.98g/100g), Copper (0.95g/100g to 1.12g/100g), Manganese (0.87g/100g to 1.02g/100g), Zinc (0.92g/100g to 1.14g/100g), and Iron (1.25g/100g to 1.60g/100g) detail showed in Table 2. Level of micronutrients *i.e.* manganese (Mn), iron (Fe), zinc (Zn), copper (Cu) and magnesium (Mg) were more in *C. sativum* in compression of the *A. indica* leaf. Human bodies daily need more than 100 mg of major minerals (N, P, K, Ca, Mg, and Na) and less than 100 mg of minor minerals such as Cu, Fe, Zn, Mn, Co, Si [16].

3.6 Biochemical Marker of *A. indica* and *C. sativum* Leaves Extract by GC-MS

The extract of leaf samples of *A. indica* and *C. sativum* were injected for screening of metabolic compounds in GC-MS. GC-MS chromatogram compound of the hydro alcoholic extract of leaves showed in Table 3 and Table 4. GCMS data indicate that the leaf of *A. indica* leaves have 9, 12-octadecadienoic acid (Z, Z) (6.85%), Hexadecanoic acid (6.42%), Methyl stearate (6.09%), Oleic acid (3.16%), Docosanoic acid (3.60%) while *C. sativum* have major compounds like 9, 12-octadecadienoic acid (Z, Z) (42.35) Hexadecanoic acid (1.45%), Squalene (5.50%), Oleic acid (3.2%) and Benzenesulfonyl chloride (2.25). Oshiobugie et al. 2017 [17] reported that Caryophhyllane oxide, 3-Octadecenoic acid, methyl ester, Methyl stearate, Phosphorothoic acid 0-0diethyl 0- (3, 5, 6-Trichloro- 2 pridinyl) ester, Phytol, 2-Hydroxy-3-[(9E)-9-octadecenoyloxy] propyl (9)- 9- Octadecenoate, methylnonadecanoate different compounds were determined.

4. DISCUSSION

Medicinal plants being the probable sources of bioactive agents are ahead acceptability worldwide. A number of educations on ethno medicinal plants and herbal medicines have been conducted in the past and plants have been testified for being used for medicinal purpose by tribals in several countries. The ethno botanical survey can bring out many different clues for the development of drugs to treat human diseases like diabetes. Safe, effective, and inexpensive indigenous remedies are gaining popularity equally among the people of both the urban and rural areas, particularly in evolving countries like India [18]. Allaxon was widely used for making of diabetic model in animal in the present study 150 mg/kg body weight alloxan used for making model. Alloxan is well known for destruction pancreatic islets beta cell, Alloxan causes time and concentration dependent degradation lesions of the pancreatic beta cells leading to hyperglycaemia. A standard antidiabetic drug metformin is widely used in alloxan induced diabetic treatment to compare the efficacy of variety of hypoglycaemic agents [19, 20]. Findings of our study showed that ethanolic extract of *Mangifera indica* produced a marked decrease in blood glucose level in diabetic rats after 4 weeks of treatment. The antidiabetic effect may be due to release of insulin from existing pancreatic beta cells. In alloxan induced diabetic animal's alteration in the activity of serum liver marker enzymes is associated to changed metabolism and increased liver marker enzymes such as SGOT, SGPT and ALP in diabetic animals are reported

Table 2. The changes of mineral content in *A. indica and C. sativum*. All values are introduced as g/100g DW

Nutrients		*Azadirecta indica* (g/100g)	*Corriandrum sativum* (g/100g)
Macro Nutrients	Sodium (Na)	0.35	0.56
	Potassium (K)	0.65	0.73
	Calcium (Ca)	0.42	0.68
	Magnesium (Mg)	0.81	0.98
Micro Nutrients	Copper (Cu)	0.95	1.12
	Manganese (Mn)	0.87	1.02
	Zinc (Zn)	0.92	1.14
	Iron (Fe)	1.25	1.60
	Nickel (Ni)	0.56	0.72

Table 3. Biochemical markers identified in the hydro alcoholic leaves extract of *A. indica* A. Juss analysed by GC-MS

S.No.	R.T.	Chemical compounds	Composition %
1.	10.64	Caryophyllene oxide	1.54
2.	30.21	9,12-octadecadienoic acid (Z, Z)	6.85
3.	11.05	Hexadecanoic acid	6.42
4.	6.50	Methyl stearate	6.90
5.	13.52	Oleic acid	3.16
6.	24.80	Docosanoic acid	3.60
7.	11.50	Lenoleic acid	1.52
8.	8.50	Lenolenic acid	1.80

Table 4. Biochemical markers identified in the hydro alcoholic leaves extract of *C. sativum* analysed by GC-MS

S.No.	R.T.	Chemical compounds	Composition %
1.	10.64	Cyclotetradecane	1.24
2.	30.21	9,12-octadecadienoic acid (Z, Z)	42.35
3.	16.80	Benzenesulfonyl chloride	2.25
4.	11.05	Hexadecanoic acid	1.45
5.	6.50	Squalene	5.50
6.	13.52	Oleic acid	3.2
7.	13.80	Palmitoyl chloride	1.20
8.	11.50	Lenoleic acid	1.52

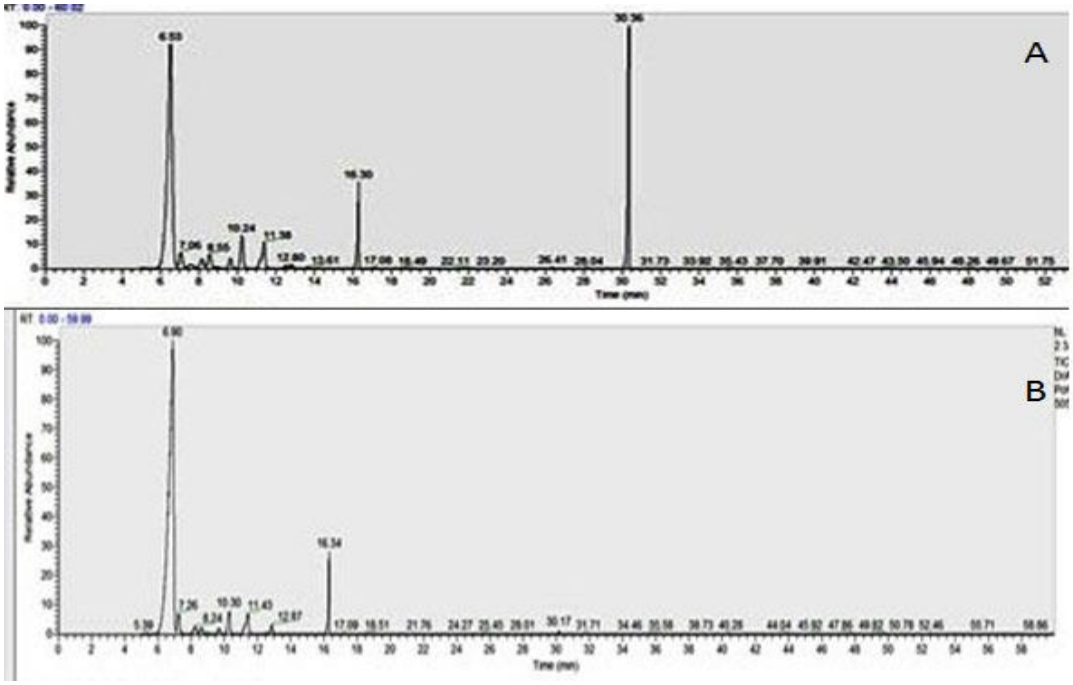

Fig. 9. GC-MS chromatogram images of *C. sativum* extract (A) and *A. indica* (B)

by many researchers. Increased liver marker enzymes level due to attenuated insulin secretion and increased amino acid activity in hyperglycaemic condition are responsible for ketogenesis and gluconeogenesis [21]. The present study represents increased activities of serum AST; ALT and ALP level indicated that hepatic dysfunction in alloxan induced diabetic animals due to hyperglycaemia. Treatment with medicinal extract showed remarkable reduction in alloxan diabetic group as well as standard drug. Results similar was Najafi,

2011 [22] reported that the extract has a potent ability to restore the normal functional status and also to protect liver against alloxan induced toxicity. Moreover, in another study it was documented that by improving the diabetic diet helps to prevent diabetic complications [23]. In this experiment kidney function test (urea, creatinine, uric acid) values were increased and albumin, protein had decreased in the diabetic groups. The formation of urea from ammonia in the liver and that is an end product of protein catabolism, urine constitute about half of the total urinary solids [24]). Urea is formed in a cyclic pathway that is known as the urea cycle. In this cycle, amino groups donated by ammonia and L-aspartate are converted to urea [25]. Though, treatment with ethanolic extract showed significant role in these parameters.

5. CONCLUSION

Data from the present study clearly indicate that the aqueous extract of the fruit at 400 mg/kg body weight dose exhibited significant antihyperglycemic than at low dose (150 mg/kg body weight) in the induced diabetic Rat, various biochemical parameters like KFT as well as regeneration of kidney tissues. Therefore, further investigation is necessary to determine the exact phytoconstituents responsible for antidiabetic effect. In conclusion, Leaf extract of *Azadirecta indica* and *Mangifera indica has* a potential ability to attenuate blood glucose level as well as kidney function test and liver function test in alloxan-induced diabetes mellitus through its phytochemical constituents. A major factor preventing the development of the medicinal plant based industries in developing countries has been the lack of information on the social and economic benefits that could be derived from the industrial utilization of medicinal plants. As a result, determining the biological properties of plants used in traditional medicine would be helpful to the rural communities and informal resolutions.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author (s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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