ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 01, 2021

EXPLORATION OF ANTI-HYPERGLYCEMIC POTENTIAL OF *AERVA SANGUINOLENTA (L.) BLUME ON* STZ INDUCED DIABETIC RATS.

Nilanjan Sarkar[1-2],
Department of Pharmaceutical Technology, NSHM Knowledge Campus, Kolkata - Group of Institutions&Department of Pharmaceutical Technology, Jadavpur University, Kolkata, West Bengal, India

Debankini Dasgupta[1],
Department of Pharmaceutical Technology, NSHM Knowledge Campus, Kolkata - Group of Institutions. Kolkata, West Bengal, India

Mainak Chakraborty[1],
Department of Pharmaceutical Technology, NSHM Knowledge Campus, Kolkata - Group of Institutions. Kolkata, West Bengal, India

Shwetlana Bandyopadhyay[1],
Department of Pharmaceutical Technology, NSHM Knowledge Campus, Kolkata - Group of Institutions. Kolkata, West Bengal, India

Sandipan Jana[2],
Department of Pharmaceutical Technology, Jadavpur University, Kolkata, West Bengal, India

PallabKantiHaldar[*2],
Department of Pharmaceutical Technology, Jadavpur University, Kolkata, West Bengal, India

[*]Corresponding Author:
Dr.PallabKantiHaldar
Department of Pharmaceutical Technology, Jadavpur University, Kolkata-700032.
Email- pallab_haldar@rediffmail.com

ABSTRACT:

BACKGROUND: Aervasanguinolenta (L) (Amaranthaceae), commonly known as Blume in India and its native place. **Objective:** To evaluate the hypoglycemic activity of methanol extract of *A.sanguinolenta*i.e MEAS leaves in streptozotocin (STZ)-induced diabetic Wistar rats. **Materials and Methods**: In rats fed with HFD for 4 weeks, hyperglycemia was induced by single intraperitoneal injection of STZ (50 mg/kg body weight). Three days after STZ induction, the hyperglycemic rats were treated with MEAS orally at the doses of 100 and 200 mg/kg b.w. daily for 14 days. Glibenclamide (0.5 mg/kg, orally) was used as reference drug. The fasting blood glucose levels were measured on every 3, 7, 10 and 14th day during the 15 days of treatment. Serum and hepatorenal biochemical parameters were estimated.

RESULTS: MEAS at the doses of 100 and 200 mg/kg orally significantly and dose dependently reduced and normalized blood glucose levels as compared to that of STZ control group. Serum and hepatorenal parameters were significantly restored toward normal levels in MEAS-treated rats as compared to STZ control animals. **Conclusion:** The present study

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concludes that A.sanguinolenta leaves demonstrated promising hypoglycemicaction in STZ-induced diabetic rats.

KEY WORDS: Diabetes, *Aervasanguinolenta*, Flavonoids, Poly phenol, Antioxidant. Tannins.

INTRODUCTION:

Diabetes Mellitus (DM) is a chronic metabolic disorder characterized by a high blood glucose concentration or hyperglycemia (fasting plasma glucose > 7.0 mmol//l, or plasma glucose > 11.1 mmol/l 2hr after a meal) caused by insulin deficiency, often combined with insulin resistance [1].

It is associated with reduced life expectancy, significant morbidity due to specific diabetes-related microvascular complications, increased risk of macrovascular complications (ischemic heart disease, stroke, and peripheral vascular disease), and diminished quality of life.

Hyperglycaemia occurs because of uncontrolled hepatic glucose output and reduced uptake of glucose by skeletal muscle with reduced glycogen synthesis. When the renal threshold for glucose reabsorption is exceeded, glucose comes into the urine (glycosuria) and causes an osmotic diuresis (polyuria), which, in turn, results in dehydration, thirst, and increased drinking (polydipsia). Insulin deficiency causes wasting through increased breakdown and reduced synthesis of proteins. Diabetic ketoacidosis is an acute emergency. It develops in the absence of insulin because of the accelerated breakdown of fat to Acetyl-CoA, which, in the absence of aerobic carbohydrate metabolism, is converted to acetoacetate and β-hydroxybutyrate (which cause acidosis) and acetone -a ketone [2].

Plant medicines are the most widely used medicines in the world today. Plant and extracts have been used in Ayurveda, Siddha, and Unani for treating different types of diseases from ancient times [3].

More than 80% population from develop-ing countries depends upon the traditional medicines mainly plant drugs used for their primary health care reported by World Health Organization (WHO). Medicinal plants exhibit lower side effects compared to synthetic drugs. Because of this, the use of medicinal plants is growing worldwide [4].

Medicinal Significance of *Aervasanguinolenta* as a folk medication, the leaves and the flowers of the plant were used as wound healing and as an anti-inflammatory for injuries, rheumatic arthritis, and pain in muscles. [5] The whole plant is being used as a diuretic and demulcent.[6] Tender of shoot of the plant is used as decoction form for galactagogue to mother [7] and decoction of the plant is taken two times a day to throw out intestinal worms.[8] Leaves and roots have been used for body ache or pain and the paste of the leaves and roots is applied to the affected area they can also be used in diabetes.[9] The plant extract showed significant wound healing properties.[10]

MATERIAL AND METHOD:

PLANT MATERIAL:

The leaf of the *Aervasanguinolenta (L.)* plant was collected from the Diamond harbour. region of WestBengal, India in the month August. The plant species were identified and authenticated by the Botanical Survey of India, Howrah, India. Air-dried whole leafs were powdered in a mechanical grinder and the plant materials were extracted by methanol using

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the Soxhlet extraction apparatus. The solvent was completely removed under reduced pressure in a rotary evaporator. The concentrated extract was obtained by lyophilization and stored in vacuum desiccators (20 ℃) for further use. The yield of the methanol fraction was about 4.22%.

DRUGS AND CHEMICALS:

Trichloro acetic acid (TCA) from Merck Ltd., Mumbai, India; thiobarbituric acid (TBA), streptozotocin (STZ), 5,5′-dithiobis-2-nitro benzoic acid (DTNB), phenazoniummethosulfate(PMS), nicotinamide adenine dinucleotide (NADH), and reduced glutathione (GSH) from SISCOResearch Laboratory, Mumbai, India; potassium dichromate glacial acetic acid from Ranbaxy, Mumbai; and glibenclamide from Hoechst, India. All the other reagents used were of analytical reagent grade obtained commercially.

ACUTE TOXICITY STUDY:

As per the reported method (Organization for Economic Co-operation and Development 425) [11].

ANIMALS:

Adult male Wistar albino rats (170 - 200 g) were housed in a clean polypropylene cage with not more than four animals per cage and maintained under conditions of (25 ± 2) ˚C with 12 / 12 h dark/light cycle. They were fed a standard dry pellet diet (Hindustan Lever, Kolkata, India) and water ad libitum. The animals were acclimatized to laboratory conditions for one week prior to the experiment. All procedures described were reviewed and approved by the Institution of Animal Ethics Committee, NSHM College of Pharmaceutical Technology.

ORAL GLUCOSE TOLERANCE TEST:

The oral glucose tolerance test was performed in overnight fasted normal rats. Rats were divided into three groups (n= 6). Group, I served as normal control and received distilled water (5 mL /kg BW, p.o.) and groups II and III received methanol extract of *Aervasanguinolenta* (L.) at doses of 100 and 200 mg/kg BW, respectively. After these treatments, all groups received glucose (2 g/kg BW) orally. Blood was withdrawn from the tail vein just prior to and 30, 60, 120, and 240 min after oral glucose administration [12]. Blood glucose levels were measured using a single-touch glucometer.

INDUCTION OF DIABETES:

Diabetes mellitus was induced in overnight fasted rats weighing (170 - 200 g) by a single intraperitoneal injection of STZ 50 mg/kg BW (in citrate buffer 0. 01 M, pH 4.5). After 3 days, blood glucose levels were measured, and hyperglycemic (≥ 225 mg/d L blood glucose level) animals were taken for the investigation [13].

EXPERIMENTAL DESIGN AND TESTING OF FASTING BLOOD GLUCOSE LEVEL:

The rats were divided into five groups (n= 6). Except for group I, which served as normal non-diabetic control. Group II served as diabetic (STZ) control. Groups III and IV received methanol extract of *Aervasanguinolenta (L.)* or MEAS (100 and 200 mg/ kg BW, p.o., respectively), and group V received reference drug glibenclamide (0.5 mg/kg b.w., p.o.) daily for 15 days. Fasting blood glucose was measured on days 0, 7, 10, and 14 by using a one-touch glucometer. At 24 th hour of the last dose, blood was collected from overnight fasted rats from all animals in each group by cardiac puncture for estimation of serum biochemical

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parameters viz. Serum glutamate pyruvate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), serum alkaline phosphatase (SALP), total protein, and total cholesterol. Then the rats were sacrificed by cervical dislocation for the study of liver and kidney for antioxidant parameters like SOD, lipid peroxidation, reduced GSH, and CAT [12].

BODYWEIGHT:
The body weight of rats from each group was measured on days and 0, 5, 10, and 14. Weight was measured using standard digital weight balance to get accuracy [13].

ESTIMATION OF SERUM BIOCHEMICAL PARAMETERS:
Collected blood was used for the estimation of serum biochemical parameters viz., SGOT, SGPT, SALP, total cholesterol, serum triglycerides, and total protein using the standard kit method (Span Diagnostic Ltd. India) [14].

ESTIMATION OF LIVER AND KIDNEY ANTIOXIDANT PARAMETERS:
Lipid peroxidation, i.e., thiobarbituric acid reactive substances (TBARS) was estimated and expressed as mM / 100 g of tissue. Reduced GSH was determined and expressed as mg/ 100 g of tissue. CAT activity was assayed and expressed as u moles of H_2O_2 decomposed/min/mg of tissue. SOD was determined and expressed as U/min/mL.[15].

STATISTICAL ANALYSIS:
All results are expressed as the Mean ± SEM. The results were analyzed for statistical significance by one-way analysis of variance (ANOVA) followed by Dunnett's test using Graph Pad InStat version 5 (Graph Pad Software, USA).

RESULTS:
ORAL GLUCOSE TOLERANCE:
Glucose loading to normal rats increased serum glucose levels from 83±16 to 143±1.73 at 60 min and returned to normal at 240 min. MEAS administration improved glucose tolerance significantly ($P<0.05$) in a concentration-dependent manner at 60 min (Table 1). The effect of MEAS on glucose tolerance remained statistically significant ($P<0.05$) at 120 min with the higher dose (200 mg/kg)

Table-1:Effect of methanol extract of MEAS on oral glucose tolerance test in normal rats.

Groups	0 minutes	30 minutes	60 minutes	120 minutes	240 minutes
Normal	83.16±2.08	123±2.33	143±1.73	104.17±2.72	94.33±2.33
Low Dose	81.34±3.44	121.67±5.41	157.21±2.89	133±5.21	121.29±3.21
High Dose	79.87±3.41	123.56±2.31	137.89±4.5	105.45±3.67	91.73±2.34

Data are expressed as mean ± SEM (n=6).

EFFECT ON BODY WEIGHT:
Vehicle control animals were found to be stable in their body weight but diabetic rats showed a significant reduction in body weight during 15 days (Table 2). Streptozotocin caused bodyweight reduction, which was significantly reversed by MEAS after 7 days of treatment.

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Table-2:Effect of MEAS on body weight in STZ induced diabetic rats.

	Group	0 days	5 days	10 days	14 days
I	Normal saline (5 mL/kg)	178.85±0.05	179±4.20	179.54±0.28	180±1.40
II	STZ (50 mg/kg)	183.3±2.02	164.50±2.64	167.38±3.7	108.7+_4.66*
III	STZ + 100 mg/kg	159.3±2.33	142.3±1.85	139.30±2.02	132.46±3.05 *[a]
IV	STZ + 200 mg/kg	173.68±2.02	154.56±2.40	150.70±1.20	139.33±1.20*[a]
V	STZ + 0.5 mg/kg Glibenclamide	184.50±2.08	173.39±1.73	169±2.33	155.21±2.88*[a]

*P<0.05 compared with normal saline control on corresponding day; *[a]P<0.05 compared to STZ control group on corresponding day

FASTING BLOOD GLUCOSE (FBG) LEVELS:

The fasting blood glucose levels of normal, diabetic, and treated rats are summarized in (Table3). STZ at a dose of 55 mg/kg produced marked hyperglycemia as evident from significant (P<0.05) elevation in FBG level in the STZ control group as compared to the normal control group. The administration of MEAS in STZ- induced diabetic rats at doses of 100 and 200 mg/kg produced significant (P<0.05) and dose-dependent fall in blood glucose levels when compared with the STZ-control group. The FBG reducing the effect of MEAS at a dose of 200 mg/kg was found to be comparable to that of the reference drug glibenclamide (0.5 mg/kg).

Table-3:Effect of MEAS on fasting blood glucose (FBG) level in STZ induced diabetic rats.

Groups	**Day-0**	**Day-7**	**Day-10**	**Day-14**
Normal	76±3.21	76.67±3.75	81.67±2.72	80.3±4.33
STZ Control	376.3±14.21	397.3±12.35 a *	430±11.55 a *	422.7±6.74 a *
Low dose(100mg/kg)	378.7±12.44	365.3±13.21 b *	264.3±8.68 b *	205.7±12.33 b *
High Dose(200mg/kg).	387.3±11.68	337±8.05 c *	230±14.19 c *	192.7±3.84 c *
Standard drug	377.0±13	314.3±9.77 d *	214.7±8.98 d *	183.3±6.05 d *

Each volume expressed as MEAN±SEM, where n=6, a * normal control group vs. diabetic control group (b *, c *, d * all treated group vs. diabetic control group a *) on a corresponding day, p<0.05.

ESTIMATION OF GLYCOSYLATED HEMOGLOBIN (HbA1c):

Glycosylated hemoglobin was analyzed by using the commercially available kit (Beacon Diagnostic Pvt. Ltd. India) which is based on the principle of ion exchange resin method.

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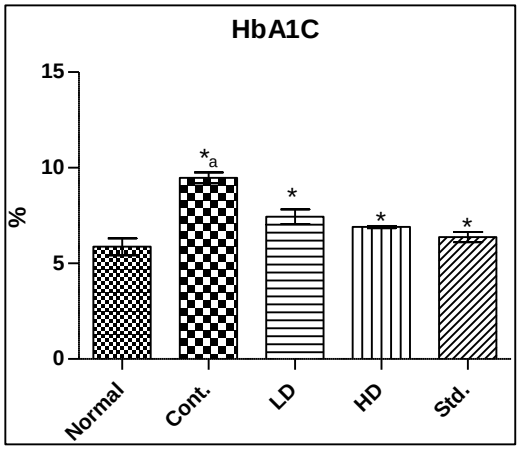
Figure-1: Effect of MEAS on glycosylated haemoglobin on STZ induced diabetic rats.

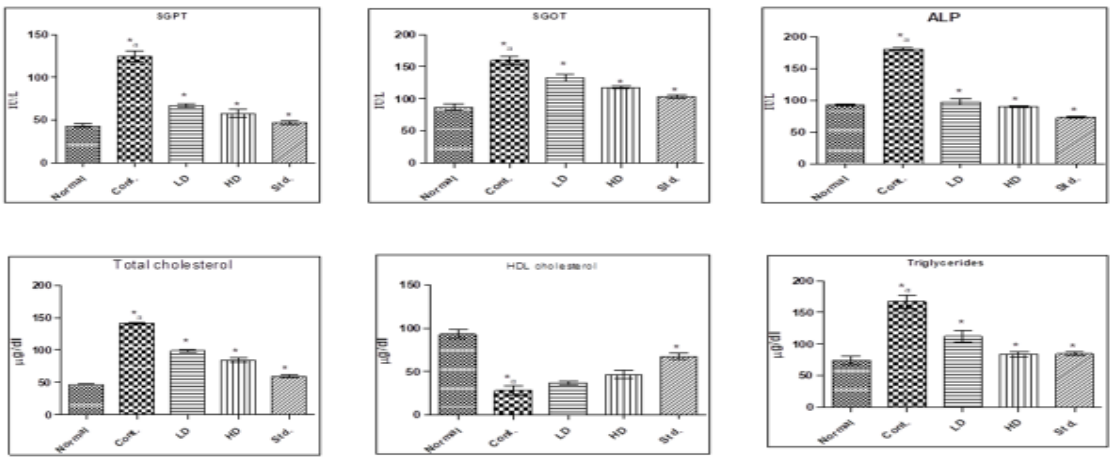


Values are represented as mean ± SEM, where n = 6. a* $p < 0.05$ when compared to normal control and * $p < 0.05$ when compare with diabetic control.

SERUM BIOCHEMICAL PARAMETERS:

Biochemical parameters like SGOT, SGPT, SALP, total cholesterol, and triglycerides in the STZ control group were significantly (P<0.05) elevated as compared to the normal control group (Figure No. 2). Treatment with MEAS at a dose of 200 and 100 mg/kg significantly (P<0.05) brought their levels towards normal values in a dose-dependent manner. Total protein was found to be significantly decreased in the STZ control group as compared with the normal control group (P<0.05). The administration of MEAS increased total protein content in diabetic animals significantly (P<0.05) as compared with the STZ control group (Figure No. 3).

Figure-2: Effect of MEAS on Serum biochemical parameter.



Values are represented as mean ± SEM, where n = 6. a* $p < 0.05$ when compared to normal control and * $p < 0.05$ when compare with diabetic control.

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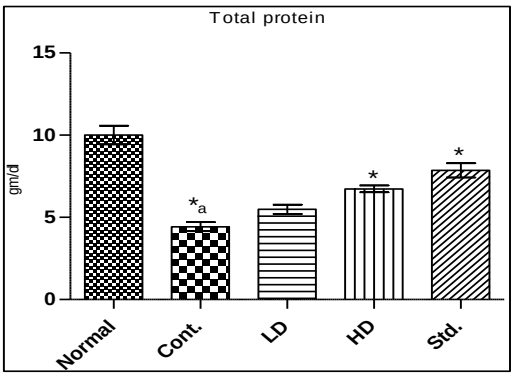
Figure-3: Effect of MEAS on Total protein level.

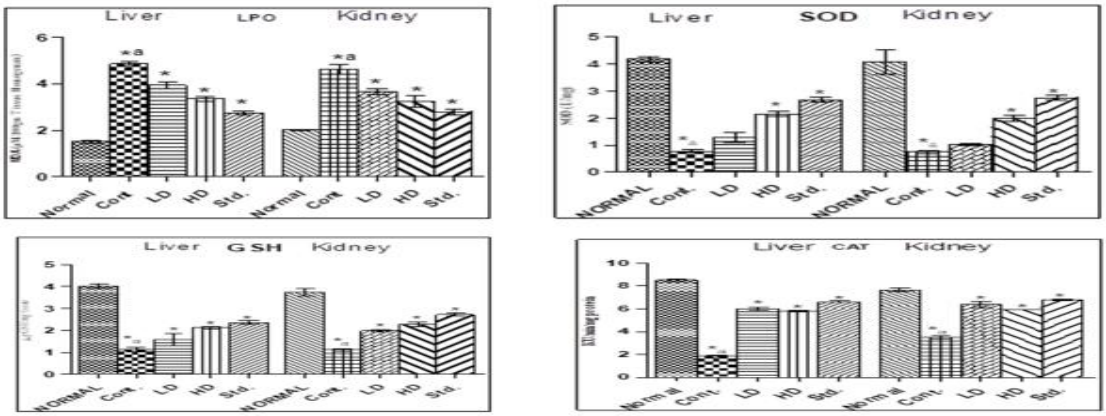


Values are represented as mean ± SEM, where n = 6. a* $p < 0.05$ when compared to normal control and * $p < 0.05$ when compare with diabetic control.

LIVER AND KIDNEY ANTIOXIDANT PARAMETERS:

The levels of TBARS were significantly (P<0.05) increased in STZ control animals as compared to the normal control group. Treatment with MEAS at 200 and 100 mg/kg significantly (P<0.05) reduced TBARS levels when compared with STZ control animals in a dose-related manner (Figure No. 4). The level of reduced glutathione (GSH) and SOD was significantly (P<0.05) depleted in the STZ control group as compared with the normal control group. Reduced GSH and SOD level was found to be significantly and dose dependently (P<0.05) elevated towards normal level upon administration of MEAS as compared with the STZ control group (Figure No. 4). There was a significant (P<0.05) reduction in catalase activity in the STZ control group compared with the normal group. The administration of MEAS recovered CAT activity significantly (P<0.05) towards normal when compared with STZ control animals (Figure No. 4).

Figure-4: Effect of MEAS on Liver and Kidney Antioxidant Profile.



Values are represented as mean ± SEM, where n = 6. a* $p < 0.05$ when compared to normal control and * $p < 0.05$ when compare with diabetic control

The present study was aimed to investigate the antihyperglycemic activity of methanolic extract of MEASleaf (MEAS) in STZ-induced diabetic rats. The results of the study revealed that MEAS at doses of 100 and 200 mg/kg significantly normalized elevated blood glucose level, body weight and restored serum and liver biochemical parameters towards normal values.

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Streptozotocin (STZ) is an antibiotic obtained from *Streptomyces achromogenes*. STZ enters pancreatic β-cells via the glucose transporter GLUT2 and causes alkylation of deoxyribonucleic acid (DNA). Its toxicity depends on the potent alkylating properties combined with the synergistic action of nitric oxide and reactive oxygen species that continue to DNA fragmentation. As the result of STZ action, pancreatic β cells are destroyed by necrosis [16]. STZ is not only damaging to the pancreatic β cells but also hepatocytes, nephrons, and cardiomyocytes.

Hyperglycemia was observed after 3 days of STZ induction. Treatment with MEAS in STZ-induced diabetic rats started reducing fasting blood glucose levels in a dose-dependent manner after 5 days and made them normoglycemic after 15 days. The antihyperglycemic effect of MEAS at a dose of 200 mg/kg was found to be comparable to the effect exerted by the reference drug glibenclamide at a dose of 0.5 mg/kg.

Induction of diabetes with STZ is associated with a characteristic loss of body weight, which is due to increased muscle wasting and loss of tissue proteins [17]. Diabetic rats treated with MEAS showed significant improvement in body weight as compared to STZ control animals; hence MEAS exhibited a marked effect in controlling the loss of body weight of diabetic rats.
Elevation of serum biomarker enzymes such as SGOT, SGPT and SALP was observed in diabetic rats indicating impaired liver function, which is obviously due to hepatocellular necrosis. The decreased total protein content in STZ-induced animals also substantiated the hepatic damage by STZ. Diabetic complications such as increased gluconeogenesis and ketogenesis may be due to elevated trans aminase activities [18]. The 14-day treatment with MEAS restored all the above-mentioned hepatic biochemical parameters towards the normal levels in a dose-dependent manner.

Hypercholesterolemia and hypertriglycemia have been induced in STZ-induced diabetic rats [19]. It is well known that in uncontrolled diabetes mellitus, there is an increase in total cholesterol in the blood, which may contribute to coronary artery diseases [20]. In the present study, the elevated serum total cholesterol and triglyceride levels in diabetic rats were brought down by MEAS treatment.

Oxidative stress in diabetes mellitus has been shown to coexist with impairment in the endogenous antioxidant status [21]. Our results indicated that MEAS strongly restored liver and kidney antioxidant parameters and decreased lipid peroxidation in diabetic animals. The reduction in liver antioxidant status during diabetes may be the result of counteraction against the increased formation of lipid peroxides [22]. A marked increase in the concentration of TBARS in STZ-induced diabetic rats indicated enhanced lipid peroxidation leading to tissue injury and failure of the endogenous antioxidant defence mechanisms to prevent overproduction of free radicals. Lipid peroxidation is usually measured in terms of TBARS as a biomarker of oxidative stress [23]. Treatment with MEAS inhibited hepatic and renal lipid peroxidation in diabetic rats as revealed by the reduction of TBARS levels towards normal levels, suggesting that MEAS could improve the pathologic condition of diabetes by inhibiting lipid peroxidation in diabetic rats.

Glutathione plays an important role in the endogenous non-enzymatic antioxidant system. It primarily acts as a reducing agent and detoxifies hydrogen peroxide in the presence of the enzyme glutathione peroxidase [24]. The depleted reduced glutathione (GSH) may be due to

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a reduction in GSH synthesis or degradation of GSH by oxidative stress in STZ-induced hyperglycemic animals [*25*].MEAS treatment significantly elevated the liver and kidney reduced glutathione levels towards normal in diabetic rats. The results showed that the antihyperglycemic activity of MEAS was accompanied by an enhancement in non-enzymatic antioxidant protection.

Enzymatic antioxidant mechanisms play an important role in the elimination of free radicals (ROS). Catalase (CAT) is haem containing enzyme catalyzing detoxification of H 2 O 2 to water and oxygen [26]. The inhibition of catalase activity as the result of STZ-induced hyperglycemia was reported earlier [27]. and similar findings were observed in our present study. MEAS treatment significantly recovered the hepatic and renal CAT activities towards normal in a dose-dependent manner.

Preliminary phytochemical studies showed the presence of alkaloids, triterpenes, steroids, flavonoids, and saponins in MEAS. Flavonoids are putative phenolic natural antioxidants, which would be responsible for the antioxidant property of MEAS. In the present study, the administration of MEAS to STZ-induced hyperglycemic rats demonstrated a prominent reduction in blood sugar level, normalization of serum biochemical profile including lipid contents, as compared to STZ control rats. Also, MEAS treatment resulted in significant modulation of lipid peroxidation, endogenous non-enzymatic (GSH), and enzymatic (CAT) antioxidant and detoxification status. Therefore, it can be concluded that the methanolic extract of *Aervasanguinolenta* leaves is remarkably effective against streptozotocin-induced diabetes in Wistar rats plausibly under its augmenting the endogenous antioxidant mechanisms.

CONCLUSION:

This is a significant study investigating the effects of *Aervasanguinolenta (L.)* in STZ induced diabetic Wistar rats exploring different mechanisms underlying their anti-diabetic potential exposed to 100–200 mg/kg MEAS showed a decrease in fasting blood glucose level.

From the above-conducted study, it may be concluded that the methanolic extract of *Aervasanguinolenta (L.)* leaves have been useful for restoring the enzyme parameters of the test subject as compared to the control. It has also been helpful in the restoration of the serum biochemical parameters of the test subject. Hence the plant extract shows considerable potential as an anti-diabetic drug.

Taken together, our results showed that MEAS triggered the normalization of biological parameters. Based on our data we can assume that MEAS has potent anti-diabetic activity. These results corroborate the ethnopharmacological use of MEAS as an anti-diabetic agent and open new perspectives to use it as a potential herbal adjuvant treatment during diabetic treatment.

CONFLICT OF INTEREST STATEMENT:

We declare that we have no conflict of interest.

ACKNOWLEDGMENTS:

The authors acknowledge the Department of Pharmaceutical Technology, NSHM Knowledge Campus, Kolkata - Group of Institution and are also thankful to the Department of

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 01, 2021

Pharmaceutical Technology Faculty of Engineering and Technology, Jadavpur University, Kolkata, India for providing necessary infrastructure and help.

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