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PHARMACOLOGICAL EVALUATION OF ANTIDIABETIC ACTIVITY OF *ALOE VERA* IN LABORATORY ANIMALS

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Abstract:

In India, the number of people suffering from diabetes is believed to be rising steadily and the current antidiabetic therapies are frequently reported to have adverse side effects. Ethno medicinal plant use has shown promise for the development of cheaper, cost-effective antidiabetic agents with fewer side effects. The aim of this study was to investigate the antidiabetic activity and mechanism of action of Methanolic extract prepared from Aloe vera. Since this claim has not been investigated scientifically, the aim of this study was to evaluate the antidiabetic effect and phytochemical screening of streptozotocin-induced diabetic Mice.

Aloe vera widely used in traditional system of medicine for the treatment of diabetes mellitus in the present study, Methanol extract of Aloe vera (MEAV) were subjected to phytochemical investigation and evaluated for antidiabetic activity in STZ induced diabetic rats. MEAV (100, 200 mg/kg) and Glibenclamide (5mg/kg) were administered orally in STZ (60mg/kg, i.p.) induced diabetic rats. In acute oral toxicity (OECD Guide line 423) study, administration of MEAV no mortality up to 1000 mg/kg was observed. OGTT, fasting blood glucose level, body weight, plasma insulin, were evaluated in normal and diabetic rats. preliminary phytochemical investigation revealed the presence of alkaloids, flavonoids, glycosides, tannins as the major constituents in the methanol extract of Aloe vera. These results suggest that MEAV (200mg/kg) showed antihyperglycemic activity in STZ induced diabetic rats.

Keywords: *Diabetes mellitus, Herbal medicine, Aloe vera, streptozotocin and Anti diabetic activity.*

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INTRODUCTION:

Diabetes Mellitus (DM):

Diabetes is one of the most common non-communicable diseases and a serious life-long condition appearing worldwide. The etiology of diabetes is a complex interaction of genetic and environmental factors. It is a heterogeneous group of metabolic disorders characterized physiologically by dysfunction of pancreatic beta cells and deficiency in insulin secretion or insulin activity and clinically by hyperglycemia or impaired glucose tolerance and other manifestable disorders. It is an endocrinological syndrome abnormally having high levels of sugar in the blood. This may be either due to insulin not being produced at all, is not made at sufficient levels, or is not as effective as it should be.

Diabetes is still a serious health problem all over the world since it is associated with increased morbidity and mortality rate. When compared with the general population, mortality and morbidity increase in diabetes is mainly due to the associated chronic complications both specific (microvascular) and nonspecific (macrovascular). Since the disease prevails in both genders and in all age groups, the general public has a concern about its control and treatment[1].

1.2-Classification of DM

Diabetes is classified by underlying cause. The most common forms of diabetes are categorized as

Type 1, or insulin-dependent diabetes mellitus (IDDM) - an autoimmune disease in which the body's own immune system attacks the pancreatic beta cells, rendering it unable to produce insulin and

Type 2 or non - insulin - dependent diabetes mellitus (NIDDM) - in which there is resistance to the effects of insulin or a defect in insulin secretion.

Type 2 diabetes commonly occurs in adults associated with obesity. There are many underlying factors that contribute to the high blood glucose levels in these individuals. An important factor is the resistance to insulin in the body essentially ignoring its insulin secretions. A second factor is the decreased production of insulin by the cells of the pancreas. Therefore, an individual with Type 2 diabetes may have a combination of deficient secretion and deficient action of insulin. In contrast to Type 2 diabetes, Type 1 diabetes most commonly occurs in children and is a result of the body's immune system attacking and destroying the beta cells. The trigger for this autoimmune attack is not clear, but the result is the end of insulin production[2].

Multiple risk factors for the development of Type 2 diabetes mellitus[3]:

- Family history (parents with diabetes).
- Obesity (i.e., ≥20% over ideal body weight or body mass index ≥25kg/m$^{2)}$.
- Habitual physical inactivity.
- Impaired glucose tolerance.
- Hypertension (≥140/90mm Hg in adults).
- High density lipoprotein (HDL) cholesterol ≤ 35mg/dl and/or triglyceride level ≥ 250mg/dl.

1.3-History

The term “Diabetes” was first used around 250 B.C. It is a Greek word meaning “to syphon”, reflecting how diabetes seemed to rapidly drain fluid from the affected individual. The Greek physician Aretaeus noted that affected individuals passed increasing amounts of urine as if there was “liquefaction of flesh and bones into urine”. The complete term “diabetes mellitus” was coined in 1674 by Thomas Willis. Mellitus is Latin for honey, which is how Willis described the urine of diabetics[5].

Historical accounts reveal that as early as 700-200 BC, diabetes mellitus was a well recognized disease in India and was even distinguished as two types, a genetically based disorder and other one resulting from dietary indiscretion. Ancient Hindu writings document how black ants and flies were attracted to the urine of diabetics. The Indian physician Sushruta in 400 B.C. described the sweet taste of urine from affected individuals, and for many centuries to come, the sweet taste of urine was a key to the diagnosis.

Physicians have observed the effects of diabetes for thousands of years. One of the effects of diabetes is the presence of glucose in the urine (glucosuria). For much of the time, little was known about this fatal disease that caused weight loss of body, extreme thirst, and frequent urination. It was in 1922 that the first patient was successfully treated with insulin. Till the mid-1800s, the treatments offered for diabetes varied tremendously. A breakthrough in the puzzle of diabetes came in 1889. German physicians Joseph von Mering and Oskar Minkowski surgically removed the pancreas from dogs. The dogs immediately developed diabetes. Now that a link was established between the pancreas and diabetes, research focused on isolating the pancreatic extract that could treat diabetes. Dr. Frederick Banting succeeded in his experiments of isolating a pancreatic extract. The diabetic dog was kept alive for eight days by regular injections until supplies of the extract, at that time called "isletin", was exhausted. Experiments on dogs showed that extracts from the pancreas caused a drop in blood sugar, caused

glucose in the urine to disappear, and produced a marked improvement in clinical condition.

A young boy, Leonard Thompson, was the first patient to receive insulin treatment in the year 1922 and lived for thirteen years. Over the next 70 years, insulin was further refined and purified. A revolution came with the production of recombinant human DNA insulin in 1978. Instead of collecting insulin from animals, new human insulin could be synthesized. In 1923, Banting and Macloed were awarded the Nobel Prize for the discovery of insulin. In his Nobel Lecture, Banting concluded the following about their discovery: "Insulin is not a cure for diabetes; it is a treatment."

6. MATERIALS AND METHODS:

Instruments

Following instruments were required for the study:

Table No: 6.1- List of Instruments used for study

Name of the instrument	***Source***
Centrifuge	Dolphin
Digital weighing balance	Horizon
Glucometer	Horizon
Heating mantle	ASGI®
Refrigerator	Videocon
Soxhlet extractor	ASGI®
Condenser	ASGI®
Burette stand	Dolphin
Round bottom flask	ASGI®, Amar
Mixer	Videocon
Oven	ASGI®
Water bath	ASGI®
Stirrer/glass rod	ASGI®
Watch glass	ASGI®
Whatmann filter paper	Manipore microproducts, Ghaizabad.
Butter paper	ASGI®
Spatula	ASGI®
Rubber pipes	ASGI®

Collection of plant material:

Aloe vera plant material was collected from local areas of Hyderabad, Telangana, India. *Aloe vera* was washed under tap water and were efficiently dried under shade for about one week and protected from deterioration.

Preparation of extract:

Leaves of Galinsoga parviflora plant were, dried in shade and coarsely powdered and, then process of removal of fat conducted in the glass jar with petroleum ether then, the defatted powder was extracted in methanol by soxhlation. Then it was dried by evaporation in water bath.

Preliminary phytochemical screening of Methanolic extract of *Aloe vera*

The Methanolic extract of *Aloe vera* was used for testing preliminary phytochemical screening in order to detect major chemical groups.

Test for carbohydrates

Molisch's test: Dissolved small quantity of 300mg alcoholic and dried leaves extract powder of Pimenta dioica separately in 4ml distilled water and filtered. The filtrate was subjected to Molisch's test.

Fehling's test: Dissolve a small portion of extract in water and treat with Fehling's solution.

Phenols test: The extract was spotted on a filter paper. A drop of phosphomolybdic acid reagent was added to the spot and was exposed to ammonia vapours.

Test for flavanoids

Shinoda test: To 2 to 3ml of extract, a piece of magnesium ribbon and 1ml of concentrated HCl was added.

Lead acetate test: To 5ml of extract 1ml of lead acetate solution was added.

Test for tannins

Braemer's test: To a 2 to 3ml of extract, 10% alcoholic ferric chloride solution was added.

Test for steroid/terpenoid

Liebermann-Burchardt test: To 1ml of extract, 1ml of chloroform, 2 to3ml of acetic anhydride and 1 to 2 drops of concentrated Sulphuric acid are added.

Test for alkaloids

Draggendorf's test: A drop of extract was spotted on a small piece of precoated TLC plate and the plate was sprayed with modified Draggendorf's reagent.

Hager's test: The extract was treated with few ml of Hager's reagen.

Wagner's test: The extract was treated with few ml of Wagner's reagent.

Tests for Glycosides

Legal's test: Dissolved the extract [0.1g] in pyridine [2ml], added sodium nitroprusside solution [2ml] and made alkaline with Sodium hydroxide solution.

Test for Saponins

Foam test: 1ml of extract was dilute with 20ml of distilled water and shaken with a graduated cylinder for 15 minutes.

Test for Anthraquinones

Borntrager's test: About 50 mg of powdered extract was heated with 10% ferric chloride solution and 1ml of concentrated HCl. The extract was cooled, filtered and the filtrate was shaken with diethyl ether. The ether extract was further extracted with strong ammonia.

Test for Amino acids

Ninhydrin test: Dissolved a small quantity of the extract in few ml of water and added 1ml of ninhydrin reagent.

Test for fixed oils and fats

Press small quantity of the petroleum ether extract between two filter paper.

Note: the results for the above experiments can be noted as follows.

- If the response to the test is high it can be noted as +++ which indicates that the particular group is present as the major class.
- If the response is average then note it as ++ indicates the presence in moderate quantity.
- If the response is very small then note it as + indicating the presence of only in traces.
- If no response is then negative.

Experimental Animals:

Healthy Sprague Dawley Rats (8 week of age) of weighing 150-250 gm were selected for the study. The animals were housed in polypropylene cages with wire mesh and husk bedding and maintained under standard environmental conditions (temperature 22+ 2°C), relative humidity 55-60%, light dark cycle of 12 hours each and rats were fed with standard pellets diet (Amrut Feeds, Sangli) and water was given ad libitum during course of study. The animals were housed and treated according to the rules and regulation of CPCSEA and IAEC. The protocol for the study was approved by the Institutional Animal Ethical Committee (IAEC) with reference no. 650/PO/Re/S-2002/2024/CPCSEA/05.

Apparatus and Instruments:

Cooling centrifuge, Semiautomatic Biochemistry auto-analyzer, Desiccators, Micropipette, Digital weighing balance and Glass wares, *Glucometer*.

Acute toxicity studies:

Acute oral toxicity study was performed as per OECD-423 guidelines (acute toxic class method). Wistar rats (n=6) of either sex selected by random sampling techniques were employed in this study. The animal was kept fasting for overnight providing only water. Then the extracts (ACAE) were administered orally at the dose of 2000 mg/kg. The animals were observed for toxic symptoms and behavioral changes continuously for the first 4 hrs after dosing. Finally, the number of survivors was noted after 24 hrs. From the next day onwards, each day 1 hour the behavioral change, clinical symptoms or mortality was observed in the same animals for the next 14 days.

Experimental Design:

For this study rats were divided into following groups (n=6)

Group 1 (Vehicle Control): Rats received only normal saline solution.

Group 2 (Negative Control): Diabetes in rats was induced by using streptozotocin.

Group 3 (Low Dose of methanolic extract of *Aloe vera* 100mg/kg): Diabetic rats were treated with low dose of methanolic extract of *Aloe vera* orally for 21 days.

Group 4 (High Dose of methanolic extract of *Aloe vera* 200 mg/kg): Diabetic rats were treated with high dose of methanolic extract of *Aloe vera* orally for 21 days.

Group 5 (Standard): Diabetic rats were treated with Glibenclamide (5 mg/kg) orally for 21 days.

Estimation of blood glucose level in different groups as mentioned above.

7. RESULTS:

Phytochemical studies

Table No 7.1: Results of Methanolic extract of *Aloe vera*

Class of compounds	Tests performed	Results
Carbohydrates	Molisch's test Fehling's test	-
Phenols	Phosphomolybdic acid test	+
Flavonoids	Shinoda test Lead acetate test	+ +
Tannins	Braemer's test	-
Alkaloids	Wagner's Mayer's Draggendrof's test	+ + +
Glycosides	Legal's test Brontranger's test	+ +
Saponins	Foam test	+
Sterols	Salkowski's test	-
Amino acids	Ninhydrin test	-
Terpenoids	Lieberman Burchardt test	+

+Present in moderate amount
-Absence

The phytochemical studies results revealed that the Molisch's test no characteristic observation indicated the absence of carbohydrates, by phosphomolybdic acid test blue coloration of the spot indicated the presence of phenols. Shinoda test and Lead acetate test gave pink or red coloration of the solution indicated the presence of flavonoids Flocculent white precipitate also indicated the same. There is no dark blue or greenish grey coloration of the solution indicated the absence of tannins in the drug. No characteristic observation for steroids and dark pink or red coloration of the solution indicated the presence of Terpenoids. Orange coloration of the spot indicated the presence of alkaloids. Yellow or reddish-brown precipitation indicated the presence of alkaloids. Pink to red Colour solution indicates the presence of glycosides. No layer of foam formation indicates the absence of Saponins. If the response to the test is indicated table-1high it can be noted or which indicates that the particular group is present as the major class. If the response is average then note it as indicates the presence in moderate quantity and note it as indicating the presence of only in traces. If no response is then negative.

Table no. 7.2: Effect of *Aloe vera* on blood glucose level of STZ induced diabetic rats

Groups	Blood glucose level (mg/dl) Days				
	0 Day	5 Days	10 Days	15 Days	20 Days
Normal control	102.83±4.13	101.83 ±4.579	101.83 ±4.579	101.83 ±4.579	101.83 ±4.579
Negative control	104.3±4.65$^{@}$	226.93±4.131$^{@}$	233±4.817$^{@}$	243.5±4.370$^{@}$	249.16±4.215$^{@}$
Low dose (100mg/kg)	103.22±3.66*	210.16±4.070*	196.5±2.429**	186.83±2.137**	177.33±2.658**
High dose (200mg/kg)	102.8±3.10*	212±2.898*	183±3.749**	184.83±3.710**	172±2.098**
Standard Drug	100.92±3.05*	206.83±3.710*	193±4.243**	178.5±3.082**	166.83±2.229**

Results are expressed as Mean ± SD (n=6)
$^{@}$p<0.01 Compared with corresponding normal control group
**p < 0.01 compared with diabetic control group
*p < 0.05 Compared with diabetic control group

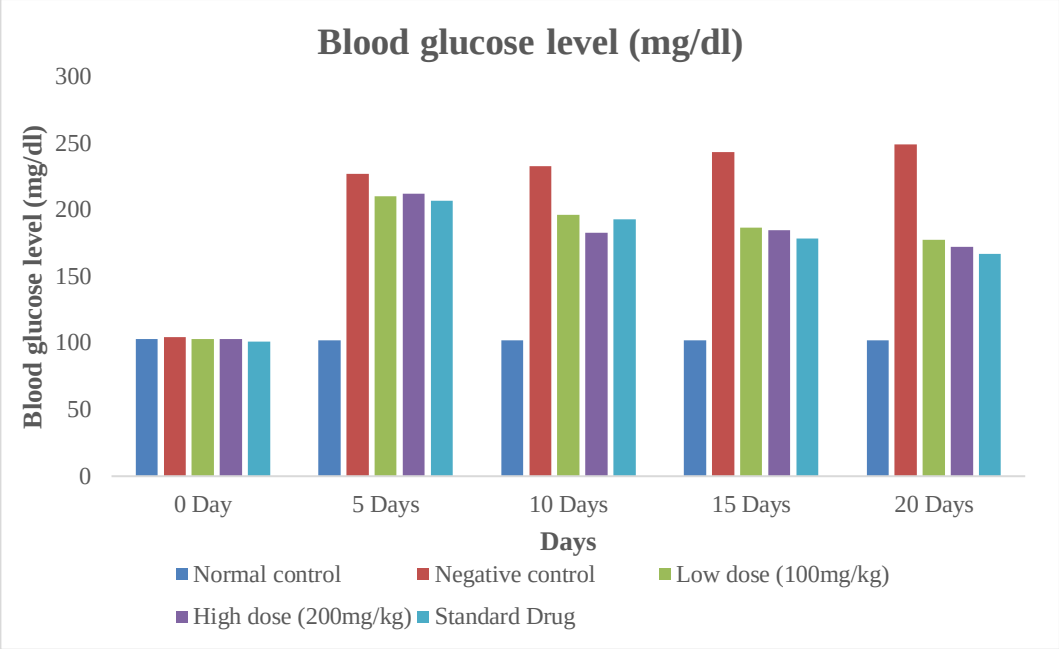

Fig no. 7.1: Effect of *Aloe vera* on blood glucose level of Streptozotocin induced diabetic rats

Table no. 7.2 and figure no 7.1 shows the Effect of *Aloe vera* on blood glucose level of Streptozotocin induced diabetic rats. There was significant ($p<0.01$) increase in the blood glucose level in all the groups compared to Normal control group of rats on day 5 to day 20. After the confirmation of diabetes, rats were treated methanolic extract of *Aloe vera* for 20 days. After treatment, there was a significant ($p<0.05$) reduction in the blood glucose level in Streptozotocin extract (100mg/kg) and a significant ($p<0.01$) reduction in blood glucose level in Streptozotocin extract (200mg/kg) compared to diabetic control group on day 15 and day 20 day.

DISCUSSION:

Diabetes mellitus is group of metabolic disorders characterized by hyperglycemia, glycosuria and hyperlipaemia. Diabetes was affected approximately 177 million people worldwide in year 2000 and it is expected to increase up to 300 million till year 2025. Diabetes is not a single disease it's group of heterogeneous syndromes such as heart attack, stroke and peripheral vascular disease. Diabetes mellitus is divided into four categories.

Diabetes mellitus (DM) is a prevailing global health metabolic disorder, with an alarming incidence rate and a huge burden on health care providers. DM is characterized by the elevation of blood glucose due either to a defect in insulin synthesis, secretion, binding to receptor, or an increase of insulin resistance. The internal and external factors such as obesity, urbanizations, and genetic mutations could increase the risk of developing DM.

For more study about diabetes, rodents such as rat, mouse, hamster, guinea pigs and the rabbits are suitable models. They are used for natural development of study. At present time best and quickest way to induce diabetes is with use of chemicals (alloxan, streptozotocin, dithizone, monosodium glutamates etc.), viruses and genetically diabetic rats. In recent years, scientists and technologists have worked toward refining techniques that have led to the discovery of chemical agents that physiologically alter the function of the pancreas. The main advantage of using such chemicals is that body changes during and after the induction of diabetes can be observed. The five major diabetogenic agents are chemicals, biological agents, peptides, potentiators, and steroids but most commonly used chemicals agents are alloxan and streptozotocin.

Different Agents are used for induction of diabetes mellitus. Alloxan is most prominent chemical compound used in diabetogenic research. In research it is used for induction of Type 1 diabetes. Alloxan is a urea derivative which causes selective necrosis of the β- cells of pancreatic islets. It has been widely used to induce experimental diabetes in animals such as rabbits, rats, mice and dogs with different grades of disease severity by varying the dose of alloxan used. But the mortality rate is too high with alloxan. Streptozotocin (STZ) Streptozotocin is naturally occurring chemical; used to produce Type- 1 diabetes in animal model and Type- 2 diabetes with multiple low doses. It is also used in medicine for treating metastatic cancer of islets of Langerhans. Streptozotocin have less mortality rate than other agent which are used for inducing diabetes mellitus. Dithizone induced the symptoms of diabetes in cats, rabbits, golden

hamsters and in mice. In dithizonised diabetic animals, the levels of serum zinc, iron, and potassium were found to be higher than normal but copper and magnesium levels were unchanged. Gold thioglucose Gold thioglucose is diabetogenic compound, which is induced hyperphagia and severe obesity induced Type -2 diabetes. Gold thioglucose developed obesity induces diabetes in genetically normal mouse strains. Gold thioglucose treated DBA/2 (Dilute Brown Non- Agouti), C57BLKs, and BDF1 mice gained weight rapidly and significantly increase non fasting plasma glucose level within 8- 12 weeks.

Induction of diabetes with Streptozotocin decreases Nicotinamide-adenine dinucleotide (NAD) in pancreas islet beta cells and causes histopathological effects in beta cells which probably intermediates induction of diabetes. In this study, we used Streptozotocin for our experiments in induction of experimental diabetes mellitus. In the study, the Streptozotocin makes pancreas swell and at last causes degeneration in Langerhans islet beta cells and induces experimental diabetes. It also changes normal metabolism in diabetic rats in comparison with normal rats.

Intra-peritoneal injection of 60mg/kg dose of Streptozotocin in adult Wistar rats, makes pancreas swell and at last causes degeneration in Langerhans islet beta cells and induces experimental diabetes mellitus in the 2–4 days. Induction of experimental diabetes mellitus is indeed the first step in the plan of purification of pancreatic Langerhans islet cells of normal rats. Streptozotocin induces one type of diabetes which is similar to diabetes mellitus with non-ketosis hyperglycemia in some animal species.in this study for induction of experimental diabetes in male adult rats weighted 150–250 grams, 60mg/kg of Streptozotocin was injected intravenously. Three days after degeneration of beta cells, diabetes was induced in all animals. Then check blood sugar level with the help of glucometer. We found that STZ at 60mg/kg IP significant increase (P< 0.0001,) blood glucose level.

Herbal medicine, also called botanical medicine or phytomedicine, refers to using a plant's seeds, berries, roots, leaves, bark, or flowers for medicinal purposes. Herbalism has a long tradition of use outside conventional medicine. It is becoming more mainstream as improvements in analysis and quality control, along with advances in clinical research, show the value of herbal medicine in treating and preventing disease. Herbal medicine is the use of plants to treat disease and enhance general health and wellbeing. Herbs can interact with other pharmaceutical medications and should be taken with care.

Aloe vera (Cav.) is a member of the Asteraceae family traditionally used for treatment of various ailments such as malaria, flu, cold, colorectal cancer, liver problems and inflammation. The medicinal properties of *Aloe vera* are due to the presence of various secondary metabolites including flavonoids, saponins, terpenoids and tannins. The literature survey revealed that *Aloe vera* possesses several pharmacological properties such as antibacterial, antifungal, antioxidant. This plant contains flavonoids according to the literature study.

Pharmacological properties of *Aloe vera* Antibacterial activity, Antioxidant activity, Anti-arthritic and antiplatelet activities, Anti-inflammatory activity, Antifungal activity.

Flavonoids are furtherly classified into 6 subclasses: flavanols, flavones, flavanones, isoflavones, flavanols, and anthocyanidins. Naturally occurring flavonoids possess anti-diabetic effects. As in vitro and animal model's studies demonstrate, they have the ability to prevent diabetes and its complications. Addressing the antidiabetic effects of dietary flavonoids and their underlying molecular mechanisms. Flavonoids improve the pathogenesis of diabetes and its complications through the regulation of glucose metabolism, hepatic enzymes activities, and a lipid profile. Most studies illustrate a positive role of specific dietary flavonoids on diabetes, but the mechanisms of action and the side effects need more clarification. Overall, more research is needed to provide a better understanding of the mechanisms of diabetes treatment using flavonoids.

We had five group, group 1 which was normal control, group 2 which was negative control group, group 3 low dose of *Aloe vera* (100mg/kg), group 4 high dose of *Aloe vera* (200mg/kg), group 5 standard drug Glibenclamide (5 mg/kg).

Animal treated with methanolic extract of *Aloe vera* shown significant (P<0.01) decrease in blood sugar at low dose 100mg/kg (P<0.01) and high dose 200mg/kg (P<0.01) at different interval of 5 days, 10 days, 15 days, and 20 days. As compare to negative control, this anti-diabetic effect of *Aloe vera* may due to presence of flavonoids.

8. CONCLUSION:

Methanolic extract *of Aloe vera* is found to be more effective in the treatment of diabetes mellitus as determined by its statistically significant p value < 0.001 in streptozotocin induced diabetic rats. The mechanism of anti-diabetic activity of *Aloe vera* may be due to enhancing the effect of insulin and by stimulating the insulin secretion from beta cells of pancreas. Hence this study suggests that *Aloe vera* Methanolic extract has a potent anti diabetic effect which could be used for the management of diabetes effectively. Further studies to find out the mechanism of this plant for its antidiabetogenic effect and there is a need for bioactivity guided investigation to isolate the lead compound

responsible for the antidiabetic activity. The present study suggested that the isolation of active constituents from Methanolic extract of *Aloe vera* and characterize the compounds by using preliminary phytochemical studies.

From this study, it can be concluded that methanolic extract of *Aloe vera* has hypoglycemic potential against the STZ- Induced diabetic experimental Wistar rats. And this activity may be because of presence of flavonoids in this plant.

FUTURE SCOPE:

To Determination the leaves constitute responsible for producing anti-diabetic activity.

To find out the underline mechanism for anti-diabetic potential

To carry out the clinical study by formulating and developing herbal based treatment regimen that is useful in treatment and management diabetes mellitus.

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