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Evaluation of Antidiabetic activity of Artemisia amygdalina decne in Streptozotocin induced Diabetic rats.

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ABSTRACT: The aim of the present study is to evaluate the antidiabetic effect of Hydroethanolic extract of Artemisia amygdalina leaves in Streptozocin induced diabetic rats. Two different dose levels of 200 and 400 mg/kg/p.o. Hydroethanolic extract were used for antidiabetic activity. The present study reveals that elevated levels of blood glucose levels significantly decrease estimated parameters in extract treated and standard groups. Animal body weight was significantly increased. Hence from the above results it can be concluded that the Hydroethanolic extract of Artemisia amygdalina was shown significant antidiabetic agent in Wistar rats might be due to presence of flavonoids. The Hydroethanolic extract of Artemisia amygdalina was shown significant protective effect against the Streptozocin induced diabetes and the effect was found to be in a dose dependent manner.

KEYWORDS: Streptozotocin,antidiabetic, Diabetes rats.

I. INTRODUCTION

Diabetes mellitus, often known simply as diabetes, is a group of common endocrine diseases characterized by sustained high blood sugar levels.1,2 Diabetes is due to either the pancreas not producing enough insulin, or the cells of the body becoming unresponsive to the hormone's effects.3 Classic symptoms include thirst, polyuria, weight loss, and blurred vision. If left untreated, the disease can lead to various health complications, including disorders of the cardiovascular system, eye, kidney, and nerves.4 Untreated or poorly treated diabetes accounts for approximately 1.5 million deaths every year.1 The major types of diabetes are type 1 and type 2, though other forms also exist. The most common treatment for type 1 is insulin replacement therapy (insulin injections), while anti-diabetic medications (such as metformin and semaglutide) and lifestyle modifications can be used to manage type 2. Gestational diabetes, a form that arises during pregnancy in some women, normally resolves shortly after delivery.

Diabetes poses significant risks to both macrovascular and microvascular systems.[10,11] It doubles the likelihood of cardiovascular issues, with around 75% of diabetes-related deaths attributed to coronary artery disease. Alongside cardiovascular complications, diabetes increases the risk of stroke and peripheral artery disease. On the microvascular level, damage can affect the eyes, kidneys, and nerves. Diabetic retinopathy, the leading cause of blindness among working-age individuals, stems from retinal damage. Other eye issues like cataracts and glaucoma can also arise. Regular visits to optometrists or ophthalmologists are advised. Diabetic nephropathy, contributing to more than half of dialysis cases in the U.S., is a significant cause of chronic kidney disease. Diabetic neuropathy, which involves nerve damage, manifests through sensory loss, neuropathic pain, and autonomic dysfunction, leading to complications like diabetic foot problems and non-traumatic lower-limb amputations.

Maturity onset diabetes of the young (MODY) is a rare autosomal dominant inherited form of diabetes, due to one of several single-gene mutations causing defects in insulin production.38 It is significantly less common than the three main types, constituting 1–2% of all cases. The name of this disease refers to early hypotheses as to its nature. Being due to a defective gene, this disease varies in age at presentation and in severity according to the specific gene defect; thus, there are at least 13 subtypes of MODY. People with MODY often can control it without using insulin.39 Some cases of diabetes are caused by the body's tissue receptors not responding to insulin (even when insulin levels are normal, which is what separates it from type 2 diabetes); this form is very uncommon. Genetic mutations (autosomal or mitochondrial) can lead to defects in beta cell function. Abnormal

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insulin action may also have been genetically determined in some cases. Any disease that causes extensive damage to the pancreas may lead to diabetes (for example, chronic pancreatitis and cystic fibrosis). Diseases associated with excessive secretion of insulin-antagonistic hormones can cause diabetes (which is typically resolved once the hormone excess is removed). The ICD-10 (1992) diagnostic entity, malnutrition-related diabetes mellitus (ICD-10 code E12), was deprecated by the World Health Organization (WHO) when the current taxonomy was introduced in 1999.40 Yet another form of diabetes that people may develop is double diabetes. This is when a type 1 diabetic becomes insulin resistant, the hallmark for type 2 diabetes or has a family history for type 2 diabetes.41 It was first discovered in 1990 or 1991. The following is a list of disorders that may increase the risk of diabetes:42

• Genetic defects of β-cell function
o Maturity onset diabetes of the young
o Mitochondrial DNA mutations
• Genetic defects in insulin processing or insulin action
o Defects in proinsulin conversion
o Insulin gene mutations
o Insulin receptor mutations
• Exocrine pancreatic defects (Type 3c diabetes, i.e. pancreatogenic diabetes)
o Chronic pancreatitis
o Pancreatectomy
o Pancreatic neoplasia
o Cystic fibrosis
o Hemochromatosis
o Fibro calculous pancreatopathy
• Endocrinopathies
o Growth hormone excess (acromegaly)
o Cushing syndrome
o Hyperthyroidism
o Hypothyroidism
o Pheochromocytoma
o Glucagonoma
• Infections
o Cytomegalovirus infection
o Coxsackievirus B
• Drugs
o Glucocorticoids
o Thyroid hormone
o β-adrenergic agonists
o Statins

Streptozotocin (STZ) is an antidiabetic and anticancer agent that has been widely used for inducing type-I as well as type-II diabetes. Streptozotocin was initially isolated from streptomyces chromogenes in the 1960s, with its diabetogenic properties not described until 1963.71 In the experiments of hypoglycemic effects evaluation animals are made diabetic usually by injecting alloxan or streptozotocin intraperitoneally (IP) or intravenously (IV). The diabetogenic effects are due to the selective destruction of pancreatic beta-cells. As a result of this action, the animal experiences insulin deficiency, hyperglycemia, polydipsia and polyuria all of which are characteristic of human type-I diabetes mellitus.72 Several animal species, including the mouse, rat and monkey are sensitive to the pancreatic beta-cell cytotoxic effect of STZ. Free radicals play a crucial role in the streptozotocin-induced diabetes that produced oxidative stress and depletion of antioxidant systems in both blood and tissues, particularly the liver.73 The most common substances inducing diabetes in rat are alloxan and streptozotocin. STZ is taken up by pancreatic beta-cells via glucose transporter GLUT2. The main cause of STZ-induced beta-cell death is the alkylation of DNA by the nitrosourea moiety of this compound. However, the production of NO. and reactive oxygen species may also be involved in DNA fragmentation and other deleterious effects of STZ.

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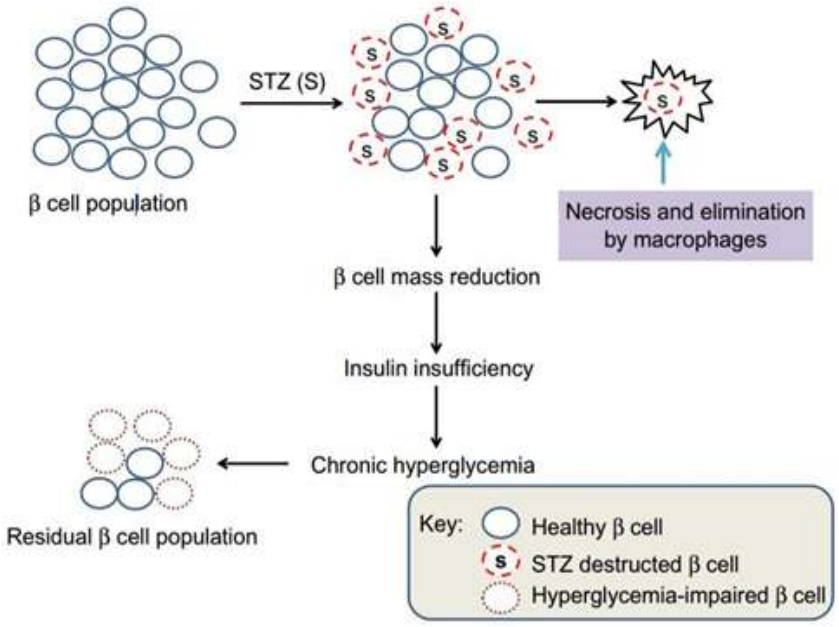
Mechanism of Streptozocin induced Diabetes model.



List of Plant and their parts reported as antidiabetic

S. No	Name of Plant	Parts	Family
1.	Cinnamomum zeylanicum	Bark	Lauraceae[74]
2.	Allium cepa	Bulb	Amaryllidaceae[74]
3.	Cassia auriculata	Flower	Leguminosae[74]
4.	Carum carvi	Fruits	Apiaceae[74]
5.	Aloe barbadensis	Leaves	Liliaceae[74]
6.	Nelumbo nucifera	Rhizome	Nelumbonaceae[74]
7.	Clausena anisata	Roots	Rutaceae[74]
8.	Acacia arabica	Seeds	Leguminosae[74]
9.	Ipomoea batata	Tubers	Convolvulaceae[74]
10.	Amaranthus spinosus	Stem	Amaranthaceae[74]

NEED FOR STUDY

The Diabetes Mellitus is worldwide problem due to the lifestyle changes lead to decreased physical activity, increased consumption of fat, sugar and calories, and higher stress levels, affecting insulin sensitivity and obesity. Based on the above causative factor to increased tenfold, from 1.2% to 12.1%, between 1971 and 2000 entire world. It estimates is estimated that 61.3 million people aged 20-79 years live with diabetes in India (2011). This number is expected to increase to 101.2 million by 2030. There are many synthetic drugs used for the treatment of diabetes such as Glibenclamide-sulphonylureas were used in India as combination therapy because of its more side effects were reported. Several literatures indicated that the herbal drugs are less adverse effect when compared with synthetic drugs. The current study revealed the antidiabetic potential of Artemisia amygdalina effective in hyperglycemia and that it can effectively protect against other metabolic aberrations caused by diabetes in rats, which seems to validate its therapeutic traditional use.

Allopathic medicines are very costly in contrast, herbal medicines are very cheap. This cost effectiveness makes them all the more alluring. The work provides scientific validation for the use of leaf against diabetes by revealing the chemical compounds may be present in the plant. The prediction of biological activity of the chemical

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compounds present in the extract wills also supports the invitro results after its phytochemical analysis. Herbal drugs were expelled mild side effects reported in literature. The present study is attempted to develop a novel plant- based antidiabetic drug, which will be evaluated by using Invitro and Invivo methods.

II. MATERIAL AND METHODS

Materials:

Experimental animal

Species: Wistar rats. Strain: Wistar Sex: Male or female

Source: Vaarunya Biolabs private limited, Bangalore-560074, Karnataka.

Body weight: 180-220 g.

Identification: By cage card and body markings. Number of animals: 6 in each group.

Acclimatization: One week in experimental room.

Selection of animals: After acclimatization the animals were subjected to a gross observation to ensure that the selected rats were in good state of health. Rats were randomly selected for final allotment of the study.

Environmental condition: Air-conditioned rooms with optimal air changes per hour, relative humidity, temperature (20-25ºC) and elimination cycle set to 12hour light and 12hour in dark. The animals were maintained under standard condition in an animal house approved by the Purpose of Control and Supervision of Experiments on Animals (CCSEA). The study protocol was approved by the Institutional Animal Ethics Committee (IAEC), Office of institutional animal ethical committee (IAEC) Hillside college of Pharmacy and research centre, Bangalore.

Accommodation: Animals were housed in polypropylene cages with stainless steel grill top. Facilities for food and water bottle and bedding of clean paddy husk. The husks in the cages were renewed thrice a week to ensure hygiene and maximum comfort for animals.

Diet: "Amrut" brand pelleted feed was provided ad libitum.

Water: UV purified, and filtered water was provided ad libitum in polypropylene bottles with stainless steel sipper tubes.

Extraction:

The whole plant was used for the extraction. The plant leaves were completely shade-dried and coarsely ground. The extracts were prepared by continuous hot extraction using hydro ethanol (1: 1) as solvent. Extracts obtained were concentrated, dried, and kept in desiccators for further use. [110.111]

Determination of Acute toxicity studies:

Acute oral toxicity study was performed for the extracts of Artemisia amygdalina. The rats were kept on fasting overnight, being provided only water prior to oral dosing. Then the extract was administered orally at different dose levels, that is 100, 200,500,1000 and 2000mg/kg of body weight. The rats were observed continuously for 24 h for behavioural and any adverse change and thereafter for any lethality.112,113 The extracts were found to be safe up to the dose level of 2000 mg/kg of body weight in rats. The extracts did not induce any toxicological effect in any rat. There was no lethality found by oral administration of any extract of Artemisia amygdalina.

Preliminary phytochemical screening of hydroethanolic leaves extract of Artemisia amygdalina.

The hydroethanolic extract of Artemisia amygdalina was subjected to the following chemical tests todetermine the presence of different phytochemicals as per the experimental procedure from standard book.

- Tests for carbohydrates:

A small quantity of the extract was dissolved in 4 ml of distilled water and filtered. The filtrate was subjected to different tests to detect the presence of carbohydrates.

- Molisch' test: Filtrate was treated with 2-3 drops of 1% alcoholic α – naphthol solution and 2 ml of conc. sulfuric acid was added along the sides of the test tube. The appearance of brown ring at the junction of two liquids shows the presence of carbohydrates.
- Fehling's test: A small portion of the extract was treated with Fehling's solution 1&2 and then heated on a water bath. A brick red colored precipitate was formed, which indicatesthe presence of carbohydrates.

- Test for glycosides:

- Liebermann's Test: A portion of the extract was hydrolyzed with hydrochloric acid for few hours on a water bath and the hydrolysate was subjected to following tests to detect thepresence of different glycosides.
- Legal's test: To the hydrolyze 1ml of pyridine and few drops of sodium nitroprusside solutions were added and then it was made alkaline with sodium hydroxide solution. The

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appearance of pink to red color shows the presence of glycosides.

- Keller-killiani test: To 2ml of extract, add 1 ml of GAA and 1drop of 5% Fecl3 shake well and add few drops of conc.H2SO4 through the sides of the test tube. A reddish- brown color appears at the junction of the two liquid layers; the upper layer appears as bluish green.It indicates the presence of glycosides.

 Test for alkaloids:

- Hager's: Test Few drops of Hager's reagent was added to 2 ml of the extract and shaken gently. Yellow precipitate was obtained, indicating the presence of alkaloids.

 Test for proteins:

Small quantities of the extracts were dissolved in a few ml of water and treated with followingreagents.

- Million's reagent: Appearance of red colour shows the presence of protein and free aminoacid.
- Ninhydrin reagent: Appearance of purple color shows the presence of proteins and free amino acids.
- Biuret's test: Equal volume of 5%sodium hydroxide solution and 1 % copper sulphate solution was added. appearance of pink or purple color shows the presence of proteins and amino acids.

 Test for phenolic compound and Tannins:

2 ml of the extract was added to 2ml of distilled water in a test tube and then filtered. A fewdrops of 0.1% ferric chloride were added to the filtrate. A green precipitate was obtained, indicating the presence of tannins.

- Ferric chloride test: The filtrate was treated with 5% FeCl3 solution. A violet precipitatewas formed which indicates the presence of phenolic compounds and tannins.
- Lead acetate test: Few ml of filtrate was treated with lead acetate solution; a whiteprecipitate was formed which indicates the presence of phenolic compounds and tannins.
- Ellagic acid test: To 2 ml of filtrate, added 5% GAA and 5%NaNO2 solution. A brown precipitate was formed, which indicated the presence of tannins/phenoliccompounds.

 Test for flavonoids:

A few drops of 10% lead acetate solution were added to 1ml of the extract. The presence offlavonoids was confirmed by the formation of yellow color.

- Alkaline reagent test: The extract was treated with aqueous sodium hydroxide solution.
- Blue to violet color (anthocyanins) yellow color (flavones), yellow to orange (flavanones)
- Shinoda's test: Small quantities of the extract were dissolved in alcohol, to them piece of magnesium followed by Co. Hydrochloric acid was added drop wise and heated. The appearance of magenta color indicated the presence of flavonoids.

 Tests for fixed oils and fats:

- Spot test: Small quantities of various extract were separately pressed between two filter papers. The appearance of oil stain on the paper indicated the presence of fixed oil.
- Saponification test: Few drops of 0.5N alcoholic potassium hydroxide were added to smallquantity of various extracts along with a drop of phenolphthalein, the mixture was heated ona water bath for 1-2 hours, formation of soap or partial neutralization of alkali indicated thepresence of fixed oils and fats.

 Tests for steroids and triterpenoids: A small quantity of extracts was dissolved in 5ml ofCHCl3 separately and the solution was subjected to the following tests:

- Liberman – Burchard test: Treat the extract with few drops of acetic anhydride, boil and cool. Then add con. Sulphuric acid from the side of test tube, brown ring is formed at thejunction two layer and upper layer turns green which shows presence of steroids and formation of deep red indicates presence of triterpenoids.
- Salkowski test: Treat the extract with few drops of conc. Sulphuric acid, red color at lower layer indicates presence of steroids and formation of yellow colored lower layer indicates presence of triterpenoids.

 Test for mucilage's and gums: Small quantities of extract were added separately to 25 ml of absolute alcohol with constant stirring and filtered. The precipitates were dried in oil andexamined for its swelling property for the presence of gum and mucilage.

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

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- If the response to the test is high, it can be noted as +++ which indicates that the 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.

Table 3: Hypoglycemic Test design

S. No	Groups	Treatment	Route
1.	Normal control	Carboxymethylcellulose (0.5% ,0.3ml/100g)	P.O.
2.	Positive control	Glibenclamide (2ml/kg)	P.O.
3.	Hydroethanolic leaves extract of artemisia amygdalina	200mg/kg	P.O.
4.	Hydroethanolic leaves extract of artemisia amygdalina	400mg/kg	P.O.

Table 4: Oral Glucose Tolerance Test design

S. No	Groups	Treatment	Route
1.	Normal control	Carboxymethylcellulose (0.5% ,0.3ml/100g)	P.O.
2.	Positive control	Glibenclamide (2ml/kg)	P.O.
3.	Hydroethanolic leaves extract of artemisia amygdalina	200mg/kg	P.O.
4.	Hydroethanolic leaves extract of artemisia amygdalina	400mg/kg	P.O.

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Table 5: Experimental design

Five groups of rats six in each groups received the following treatment schedule for 14 days.

Groups	Treatment	Dose and Route
I	Normal control (Normal saline)	10ml/kg. P.O.
II	Streptozocin treated control	50mg/kg, I.P.
III	Streptozocin+ Glibenclamide	2ml/kg, P.O.
IV	Streptozocin+Hydroethanolic leaves extract of artemisia amygdalina	200mg/kg, P.O.
V	Streptozocin+ Hydroethanolic leaves extract of artemisia amygdalina	400mg/kg. P.O.

III. RESULTS

- Appearance and percentage yield of Hydroethanolic leaves extract of Artemisia amygdalina decne.

Extract was semisolid and dark greenish colour, and the percentage yield was found to be 10.15%.

Table 6: Results of the Phytochemical screening of artemisia amygdalina decne.

S. No	Chemical constituents	Results
1.	Alkaloids	Present
2.	Flavonoids	Present
3.	Saponins	Present
4.	Amino acids	Absent
5.	Triterpenoids	Present
6.	Tannins	Absent
7	Anthraquinones	Present
8.	Cardiac glycosides	Present
9.	Steroids	Absent
10.	Proteins	Absent

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Table 7: Results of effect of extracts of Artemisia amygdalina in Hypoglycemic Test:

Treatment	Dose (mg/kg)	Blood glucose level (mg/dl)		
		0 min	0.5 hrs	1 hrs
CMC	0.5%	67.00±2.43	67.15±2.56	71.85±2.37
Positive Control (Glibenclamide)	2	68.00±0.63	51.83±4.03***	30.82±1.52***
Hydroethanolic leaves extract of Artemisia amygdalina	200	67.80±2.24	59.17±3.48*	58.33±3.58*
Hydroethanolic leaves extract of Artemisia amygdalina	400	67.00±2.43	52.00±2.31*	33.17±1.14*

The glucose levels were analyzed by using glucometer and each value is the mean ± standard error (n= each group consist of 6 animals) ($p<0.001$) **& ($p<0.0001$) *** as compared to normal control & positive control group evaluated by one way, ANOVA followed by Dunnet 't' test.

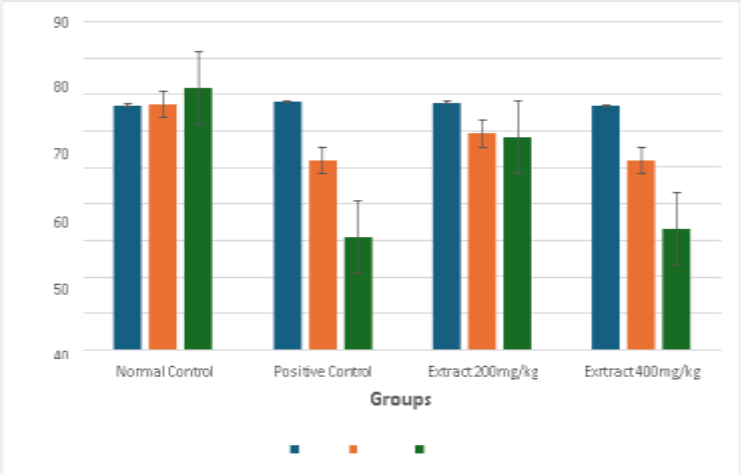

Fig 5: Diagrammatic representation of Hypoglycemic test

The hypoglycemic test results have shown Table No:7 which indicated Hydroethanolic extract of Artemisia amygdalina treated animals 200 & 400, significantly decreased in blood glucose level.

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Table No: 8, Results of the effects of Hydroethanolic extract on blood Glucose levels.

S. No	Treatment	Blood glucose level (mg/dl) day		
		Day1	Day7	Day14
1.	Normal control (10 ml/kg P. O)	78.83±2.83	74.7±4.014	75.7± 4.94
2.	Negative control	264.2±3.86	269.1±2.9	275.2±2.5
3.	Positive control (Glibenclamide 2mg/kg P. O)	254.83±2.48	135.63±3.8***	112±2.8***
4.	Hydroethanolic leaves extract of Artemisia amygdalina (200mg/kg)	259±3.5	250.3±3.13**	244.2±3.25**
5.	Hydroethanolic leaves extract of Artemisia amygdalina (400mg/kg)	263±4.55	173.1±2.88***	161.1±1.8***

The values were expressed as Mean ± S.E.M. (n=6 animals in each group).

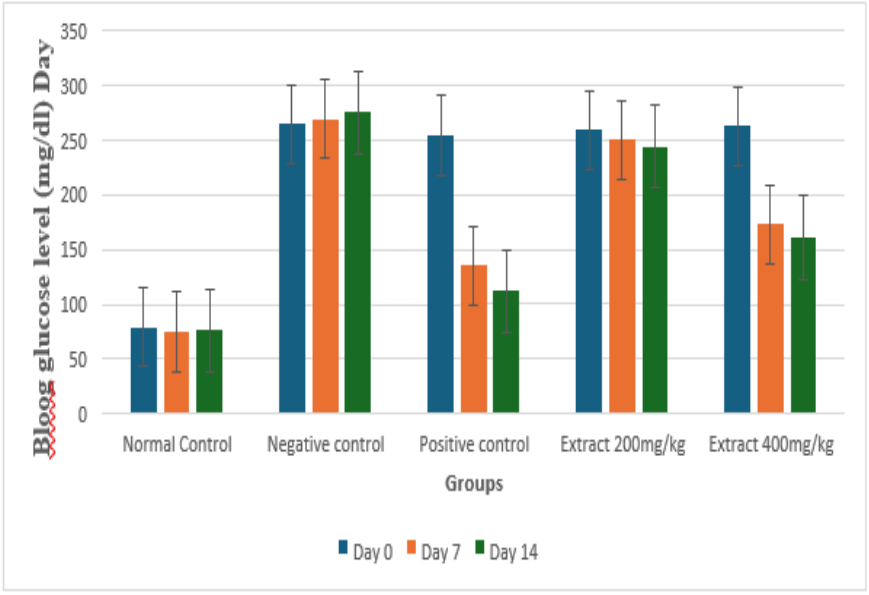

Fig 6: Diagrammatic representation of Hydroethanolic extract of Artemisia amygdalina on blood Glucose levels.

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Table 9: Results of the effect of extracts of Artemisia amygdalina Oral Glucose Tolerance Test

Treatment	Dose(mg/kg)	Blood Glucose Level (mg/dl)				
		0 hrs	0.5 hrs	1 hrs	1.5 hrs	2 hrs
CMC	0.5%	67.00±2.43	142.5±6.29	187.5±9.46	172.5±12.25	157.5±12.38
Positive Control (Glibenclamide)	2	68.00±0.63	104.2±7.32***	110.5±6.98***	93.67±1.30***	83.67±1.30***
Hydroethanolic leaves extract of Artemisia amygdalina	200	67.80±2.24	128.3±6.00	147.3±2.404*	138.5±5.66*	128.5±5.66*
Hydroethanolic leaves extract of Artemisia amygdalina	400	67.00±2.43	115.0±6.191**	121.2±6.18**	103.3±4.76***a	93.33±4.76*** a

The glucose levels were analyzed by using glucometer and all values are expressed as Mean±SEM (n=6), Group 2 was compared with group 1, Groups — 3,4 were compared with group 2; *p<0.05, **p<0.01, p<0.001evaluated by one way, ANOVA followed by Dunnet 't' test

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Table 10: Effect of extracts of Artemisia amygdalina on body weight in streptozotocin induced diabetic rats

Groups	0th day	7th day	14th day
Normal Control	120 ± 1.79	135 ± 3.13	155 ± 2.68
Negative control	125 ± 1.34	118 ± 1.79	107 ± 3.13
Positive control (Glibenclamide 2mg/kg P. O)	125 ± 1.79	133 ± 2.68	142 ± 3.13**
Hydroethanolic leaves extract of Artemisia amygdalina (200mg/kg	127 ± 2.24	132 ± 2.24	139 ± 3.5 8**
Hydroethanolic leaves extract of Artemisia amygdalina (400mg/kg	122 ± 2.68	128 ± 3.13	140 ± 2.24**

The values are expressed as mean ± SEM; n=6 in each group. $**P<0.01$ as compared with diabetic control at the same time (one-way ANOVA followed by Dunnett's multiple comparison test).

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