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ASSESSMENT OF ANTIDIABETIC ACTIVITY OF Artemisia amygdalina Decne IN STREPTOZOTOCIN INDUCED DIABETIC RATS

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Abstract:
This study aims to assess the antidiabetic effects of the hydroethanolic extract of *Artemisia amygdalina* leaves in rats with streptozocin induced diabetes. Two dosages, 200 mg/kg and 400 mg/kg, of the hydroethanolic extract were administered orally to evaluate its antidiabetic activity. The results demonstrate a significant reduction in elevated blood glucose levels in both the extract-treated and standard groups. Additionally, a notable increase in animal body weight was observed. Consequently, it can be concluded that the hydroethanolic extract of *Artemisia amygdalina* exhibits significant antidiabetic properties in Wistar rats, potentially due to the presence of flavonoids. The extract also showed a significant protective effect against streptozocin induced diabetes in a dose-dependent manner.

KEYWORDS: Streptozotocin, antidiabetic, Diabetes rats.

Introduction

Diabetes mellitus, commonly referred to as diabetes, is a prevalent endocrine disorder characterized by persistently high blood sugar levels. This condition arises either from the pancreas' insufficient production of insulin or the body's cells becoming resistant to insulin's effects. Classic symptoms include increased thirst, frequent urination, weight loss, and blurred vision. Without proper treatment, diabetes can lead to various complications affecting the cardiovascular system, eyes, kidneys, and nerves. Approximately 1.5 million deaths annually are attributed to untreated or poorly managed diabetes[1].

The primary types of diabetes are type 1 and type 2, though other forms exist. Type 1 diabetes is typically treated with insulin replacement therapy, while type 2 diabetes can be managed with anti-diabetic medications, such as metformin and semaglutide, alongside lifestyle changes [2]. Gestational diabetes, which occurs during pregnancy, usually resolves after childbirth.

Diabetes significantly impacts both macrovascular and microvascular systems, doubling the risk of cardiovascular diseases. About 75% of diabetes-related deaths are due to coronary artery disease [3]. Additionally, diabetes increases the risk of stroke and peripheral artery disease. On a microvascular level, it can cause damage to the eyes, kidneys, and nerves.

Diabetic retinopathy, the leading cause of blindness in working-age adults, results from retinal damage, and other eye problems like cataracts and glaucoma may also occur. Regular eye examinations are essential for individuals with diabetes [4].

Diabetic nephropathy, a major contributor to chronic kidney disease and dialysis cases in the U.S., and diabetic neuropathy, which causes nerve damage, are other serious complications. Neuropathy can lead to sensory loss, neuropathic pain, and autonomic dysfunction, resulting in issues such as diabetic foot problems and non-traumatic lower-limb amputations [5].

Maturity onset diabetes of the young (MODY) is a rare form of diabetes inherited in an autosomal dominant manner, caused by single-gene mutations that impair insulin production. It is much less common than the main types of diabetes, accounting for only 1–2% of all cases. The name MODY stems from early theories about its nature. Due to the genetic defect, the age of onset and severity of the disease can vary, leading to at least 13 different subtypes. Individuals with MODY often manage the condition without insulin therapy [6].

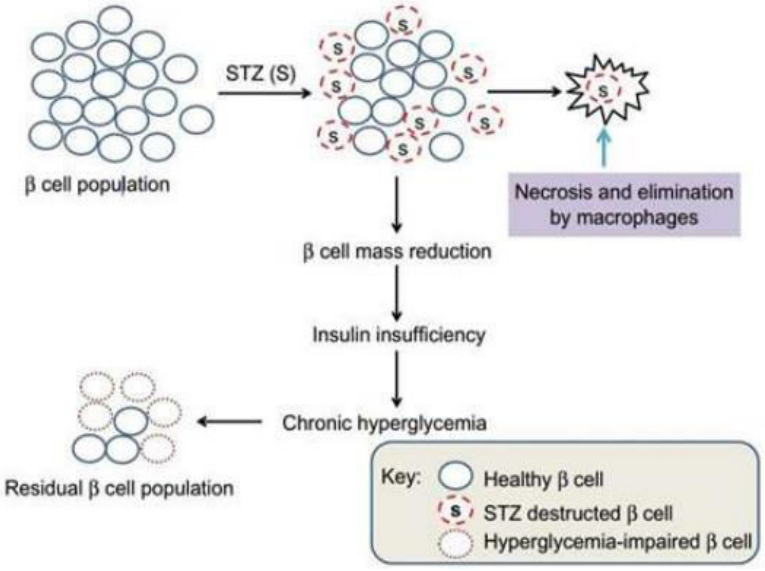
Some cases of diabetes result from tissue receptors not responding to insulin, even when insulin levels are normal, distinguishing it from type 2 diabetes. This form is very rare. Genetic mutations, whether autosomal or mitochondrial, can impair beta cell function, and abnormal insulin action may also have a genetic basis in some cases. Any condition that severely damages the pancreas, such as chronic pancreatitis or cystic fibrosis, can lead to diabetes. Additionally, diseases that cause excessive secretion of hormones that antagonize insulin can result in diabetes, which typically resolves once the hormone excess is addressed.

The ICD-10 diagnostic category malnutrition-related diabetes mellitus (code E12) was deprecated by the World Health Organization (WHO) in 1999 when the current classification system was introduced. Another form of diabetes, known as double diabetes, occurs when a person with type 1 diabetes develops insulin resistance, a characteristic of type 2 diabetes, or has a family history of type 2 diabetes [7]. This form was first identified in 1990 or 1991. Below is a list of disorders that may increase the risk of diabetes:

Streptozotocin (STZ) is an antidiabetic and anticancer agent widely used to induce both type-I and type-II diabetes in research settings. Initially isolated from *Streptomyces chromogenes* in the 1960s, its diabetogenic properties were first described in 1963. In studies evaluating hypoglycemic effects, animals are typically made diabetic by injecting alloxan or streptozotocin intraperitoneally (IP) or intravenously (IV). The diabetogenic effects result from the selective destruction of pancreatic beta cells, leading to insulin deficiency, hyperglycemia, polydipsia, and polyuria—symptoms characteristic of human type-I diabetes mellitus [8].

Various animal species, including mice, rats, and monkeys, are susceptible to the beta-cell cytotoxic effects of STZ. Free radicals play a significant role in STZ-induced diabetes by causing oxidative stress and depleting antioxidant systems in blood and tissues, especially the liver. The most common substances used to induce diabetes in rats are alloxan and

streptozotocin. STZ is taken up by pancreatic beta cells via the glucose transporter GLUT2. The primary cause of STZ-induced beta-cell death is the alkylation of DNA by the compound's nitrosourea moiety. Additionally, the production of nitric oxide (NO) and reactive oxygen species contributes to DNA fragmentation and other harmful effects of STZ. Mechanism of Streptozocin induced Diabetes model [9].



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

Diabetes Mellitus has become a global issue, driven by lifestyle changes such as reduced physical activity, increased consumption of fats, sugars, and calories, and higher stress levels, all of which impact insulin sensitivity and contribute to obesity. As a result, the prevalence of diabetes increased tenfold worldwide from 1.2% to 12.1% between 1971 and 2000. In India, it is estimated that 61.3 million people aged 20-79 were living with diabetes in 2011, with this number expected to rise to 101.2 million by 2030 [10].

Many synthetic drugs, like Glibenclamide-sulphonylureas, are used to treat diabetes in India, often as combination therapies. However, these drugs frequently have significant side effects. Literature suggests that herbal drugs tend to have fewer adverse effects compared to synthetic ones. The current study explores the antidiabetic potential of Artemisia amygdalina, which

has shown effectiveness in managing hyperglycemia and protecting against other metabolic abnormalities caused by diabetes in rats, supporting its traditional therapeutic use [11].

Herbal medicines are also much more cost-effective compared to allopathic medicines, making them an attractive alternative. This study aims to provide scientific validation for the use of *Artemisia amygdalina* leaves in treating diabetes by identifying the chemical compounds present in the plant and predicting their biological activities. Mild side effects have been reported for herbal drugs, according to existing literature. This study seeks to develop a novel plant-based antidiabetic drug, evaluated through both in vitro and in vivo methods.

MATERIAL AND METHODS

Materials:

Experimental Animals

- **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 per group
- **Acclimatization:** One week in the experimental room
- **Selection of animals:** After acclimatization, rats were subjected to gross observation to ensure good health and then randomly selected for the study
- **Environmental conditions:** Air-conditioned rooms with optimal air changes per hour, relative humidity, and temperature (20-25ºC), with a 12-hour light/dark cycle. Animals were maintained under standard conditions in an animal house approved by the Committee for 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), Seven Hills College of Pharmacy, tirupati.
- **Accommodation:** Animals were housed in polypropylene cages with stainless steel grill tops, provided with facilities for food and water, and bedding of clean paddy husk, which was renewed thrice a week to ensure hygiene and maximum comfort.
- **Diet:** "Amrut" brand pelleted feed provided ad libitum.
- **Water:** UV purified and filtered water provided ad libitum in polypropylene bottles with stainless steel sipper tubes.

Extraction:

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

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Determination of Acute Toxicity Studies:

Acute oral toxicity studies were conducted for the extracts of *Artemisia amygdalina*. Rats were fasted overnight with only water provided prior to oral dosing. The extract was then administered orally at different dose levels (100, 200, 500, 1000, and 2000 mg/kg body weight). Rats were observed continuously for 24 hours for any behavioral changes or adverse effects, and thereafter for any lethality. The extracts were found to be safe up to a dose level of 2000 mg/kg body weight, with no toxicological effects or lethality observed in any rat following oral administration of the *Artemisia amygdalina* extracts.

Results

Appearance and Percentage Yield of Hydroethanolic Leaves Extract of *Artemisia amygdalina* Decne

The extract appeared semisolid with a dark greenish color. The percentage yield was determined to be 10.15%.

Groups	0^{th} day	7^{th} day	14^{th} 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 presented as mean ± SEM; n = 6 per group. **P < 0.01 compared to the diabetic control at the same time point (one-way ANOVA followed by Dunnett's multiple comparison test).

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