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CLINICAL RESEARCH

Evaluate the Influence of *Xanthium strumarium L.* Extract on Blood Sugar Levels in Healthy and Diabetic Mice

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ABSTRACT

The use of medicinal plants for diabetes mellitus treatment is an old tradition that has grown even more significant in the current day. The goal of this study was to see how *Xanthium strumarium L*, an Iraqi traditional medication, affected blood glucose levels in normal and alloxan-induced diabetic mice. Chemical identification of phenols, flavonoids, tannins, terpenes, steroids, glycosides, and saponins was carried out on an aqueous extract of *Xanthium strumarium*. The aqueous extract comprises phenols, flavonoids, tannins, terpenes, and glycosides chemicals, according to the observations. Both normal and alloxan-induced diabetic mice were used to assess the parameters of our investigation. Thirty male mice were placed into six equal groups at random: Group I (control): Negative mice were kept, and only distilled water was given to them. Normal mice were given aqueous extract of *X. strumarium* at a dosage of 500 mg/kg/day in Group II. Normal mice were given with an aqueous extract of X in Group III. *Strumarium* at a daily dosage of 250 mg/kg to develop experimental diabetes, the other three groups were given a single dose of alloxan (100 mg/kg) subcutaneously. Control positive, alloxan-induced diabetic mice were treated with only distilled water in Group IV (Diabetic). Alloxan-induced diabetic mice were treated with an aqueous extract of X in Group V. strumarium at a daily dosage of 500 mg/kg alloxan-induced diabetic mice were treated with aqueous extract of X in Group VI. For 10 days, strumarium was given at a dosage of 250 mg/kg/day. Normal mice treated with aqueous extract showed no significant changes in body weights or blood glucose levels, with the exception of those treated with a high dosage of aqueous extract, who showed a significant drop (P 0.05) in blood glucose levels. After treatment with a high dosage of aqueous extract of *X. strumarium*, diabetic mice showed a substantial reduction in glucose levels. Finally, continued

administration with *X. strumarium* extracts for a period of 10 days or longer resulted in a substantial drop in blood glucose levels in mice.

KEYWORDS

Xanthium strumarium L; Chemical composition; Hypoglycemic activity; Alloxan induced diabetic mice

INTRODUCTION

Diabetes mellitus, meaning simply diabetes, is a set of illnesses marked by high blood glucose levels caused by problems with the body's capacity to make and/or use insulin. It is a disease characterised largely by hyperglycemia, which increases the risk of microvascular injury (retinopathy and neuropathy [1,2]. It's linked to a shorter lifespan, greater morbidity from diabetes-related microvascular problems, a higher risk of macrovascular consequences (ischemic heart disease, stroke, and peripheral vascular disease), and a worse quality of life [3]. In the development of diabetes, several pathogenetic mechanisms are involved. These include activities that cause the pancreas' beta cells to die, resulting in insulin deficiency, as well as others that cause insulin resistance. The inability of insulin to act on target tissues as a result of insensitivity or absence of insulin causes aberrant glucose, lipid, and protein metabolism [4].

Herbal medicine is a rapidly expanding field of medicine that requires attention. For thousands of years, plants have played an important role in human health and increasing the quality of life, and they have served as valuable components of medicines [5]. Medical practises and herbal medications for their primary health care requirements [6-8].

This is due to the fact that medicinal plants offer benefits (cheap cost and minimal side effects) over commonly used pharmaceuticals, which are costly and have been linked to hazardous side effects [9]. *Diabetes mellitus* is a metabolic disease characterised by hyperglycemia and changes in carbohydrate, lipid, and protein metabolism, as well as a partial or absolute lack of insulin production and/or activity. Despite the availability of a variety of oral hypoglycemic medications in addition to insulin, there is no viable treatment for diabetes [10].

Diabetes mellitus has emerged as a significant health-care issue in the twenty-first century. According to estimates, 424.9 million adults in the United States have diabetes, and 592 million people globally will have diabetes by 2035 [11,12]. Diabetes treatment costs are projected to be as high as $825 billion each year [12]. Several traditional medicinal herbs have recently been studied in experimental animals for their anti-diabetic properties. More than 1200 species of plants are utilised in the treatment of *diabetes mellitus* across the world, and a significant number of them have demonstrated efficient hypoglycemic action in laboratory tests. The pharmaceuticals can be used to create novel pharmacological leads and as a dietary supplement to existing medicines [13]. *Xanthium strumarium* is a traditional hypoglycemic herb. In rats, the herb has strong hypoglycaemic action [14,15]. *Xanthium strumarium*, often known as Cocklebur, is a widespread medicinal plant found in North America, Brazil, China, Malaysia, and the hotter areas of India [16]. Xanthium is a member of the Asteraceae family, which has more than 20 species worldwide and three species in China with one variety.

X. strumarium is an annual herbaceous plant that grows to a height of 20 cm - 90 cm. Its stems are upright, branching, and speckled, with small white hairs dispersed throughout the surface. Cauline leaves generally

alternate with petiole, and the edges are toothed [17]. Cooling, laxative, fattening, anthelmintic, tonic, digestive, antipyretic, increases appetite, voice, complexion, anodyne, antirheumatic, appetiser, diaphoretic, diuretic, emollient, and sedative are some of the therapeutic characteristics of *Xanthium strumarium*. The herb can be used to treat long-term instances of malaria, rheumatism, renal illness, and TB [18]. Anodyne, antibacterial, antifungal, antimalarial, antirheumatic, antispasmodic, antitussive, cytotoxic, hypoglycaemia, and stomachic activities are all found in the fruits of *Xanthium strumarium*. They're used to treat allergic rhinitis, sinusitis, catarrh, rheumatism, rheumatoid arthritis, constipation, diarrhoea, lumbago, leprosy, and pruritus when taken internally [17]. The purpose of this study was to assess the effects of aqueous extracts of *Xanthium strumarium* on alloxan-induced diabetic mice as a hypoglycemic medication for the treatment of *diabetes mellitus*, utilising normal and experimental alloxan-induced diabetic mice as the study animals

MATERIAL AND METHODS

Plant Material

From January 2020 to April 2020, this study was carried out. The plant *Xanthium strumarium* utilised in this study was acquired from Sulaimany University and identified in January 2020 at Baghdad University's College of Agriculture. Until used, the plants were kept at room temperature (20°C - 25°C).

Figure 1: *Xanthium strumarium L.*

Preparation of Extract

Sterilization particles and other adherent material, such as tiny sand particles, were found in the raw *X. strumarium* leaves. The material was cleaned to remove as many contaminants as feasible, then grinds were used to decrease the particle size of the sample [19].

The dried aerial portions of *X. strumarium* (leaves) were pulverised and extracted using distilled water as the solvent. In the aqueous extraction, 25 grammes of the processed plant were macerated for 24 hours in a shaking incubator at 40°C in 250 ml of boiling distilled water. The generated extract was then evaporated in an incubator at 37°C, and the resulting crude extract was stored at -20°C until it was used to make the needed dosages [20]. Every two days, a new extract was produced and stored in a glass jar in the refrigerator.

Laboratory Animals

The study's animals were cared for at Al-Nahrin University's Animal Hospital of the Biotechnology Research Center. A sample of 30 white male mice (Mus musculus) were used in the investigation. They were obtained from (biotechnology research centre/Al-Nahrin University) and were between the ages of 2 months - 4 months and 25

grammes - 35 grammes when the tests began. Mice were acclimatised for one week before being utilised in the studies.

Chemical Detection of Plant Extracts

- Phenols: An equal amount of aqueous ferric chloride (1%) was combined with potassium iron cyanide to make phenols (1 percent). The reagent was combined with equal parts water or alcoholic plant extract. A good outcome is indicated by the appearance of blue-green colour [21].
- Flavonoids: The detecting solution was made by combining 10 mL ethanol (50%) with 10 mL potassium hydroxide (50%) and then adding 5 mL of this solution to 5 mL of the plant extract. The presence of flavonoids was shown by the development of yellow colour [22].
- Tannins: Tannins were detected using the technique described in [22]. 50 mL of each extract was split evenly between two conical flasks in this method. In the first flask, lead acetate solution (CH3COOPb) (1 percent w/v) was added, and the appearance of jelly pellets was considered a positive reaction; in the second flask, ferric chloride solution (FeCl2) (1 percent w/v) was added, and the appearance of blue colour was an indicator for the presence of tannins.
- Glycosides: This technique was carried out according to the instructions in [22].

Non-Hydrolysed Extract

In the test tube, an equal amount of plant extract was combined with Fehling reagent and then heated for around 10 minutes in the water bath. The appearance of red precipitate suggests a successful outcome.

Hydrolysed Extract

A few droplets of dilute HCl were added to 5 ml of the plant's aqueous extract, which was then cooked for 20 minutes in a boiling water bath. The acidity was neutralised with NaOH solution, and an equivalent volume of Fehling reagent was added. The appearance of red precipitate suggests a successful outcome.

- Saponins: This technique was carried out according to the instructions in [22]. Saponins were identified using two methods: - In a test tube, a solution of plant powder was violently agitated. The development of foams that remain standing for an extended period of time suggests a favourable outcome.
- A five-millilitre solution of plant powder was mixed with 1 millilitre - 3 millilitres of a ferric chloride solution containing three percent ferric chloride. The appearance of white precipitate suggests a successful outcome.
- Terpenes and steroids: after mixing one ml of a plant powder solution with a few drops of chloroform, a drop of acetic anhydride, and a drop of strong sulphuric acid, a brown precipitate indicating the presence of terpenes emerged. The presence of steroids is indicated by the development of a dark blue tint after a few minutes [23].

Designing Experiments

The goal of the study was to see how two dosages of aqueous extract of a herbal combination (250 mg/kg and 500 mg/kg) affected the studied parameters in normal and alloxan mice.

The plant extracts were administered orally as a single dosage (0.2 ml) each day for 10 days using a gavage needle, and the mice were killed on day 8 for laboratory testing. In this study, thirty male mice were split into five sex groups (five mice each group):

- Group I (control) were only given distilled water.
- Group II: normal mice were given a dosage of 500 mg/kg/day of aqueous extract of *X. strumarium*.
- Group III: normal mice were given a 250 mg/kg/day dosage of *X. strumarium* aqueous extract.
- Group IV: Alloxan-induced diabetic mice were administered with just distilled water in Diabetic.
- Groups V: alloxan-induced diabetic mice were given a dosage of 500 mg/kg/day of aqueous extract of *X. strumarium*.
- Group VI: alloxan-induced diabetic mice were given a 250 mg/kg/day dosage of *X. strumarium* aqueous extract.

Blood Glucose Level

The blood glucose level was determined using commercially available dextrose measuring strips, which were read using the Accu-Chek active system.

Sample required and testing time

The Accu-Chek active metre requires 1 litre - 2 litres of blood each test and takes around 5 seconds to complete.

Test principle

A test region containing sensitive substances can be found on each test strip. A chemical reaction (glucose dye oxidoreductase mediator reaction) occurs when blood is administered to this region, causing the colour of the test area to change. The metre detects the change in colour and transforms the signal into a blood glucose reading.

Acute Toxicity Studies

Female and male Swiss albino mice were used in an acute toxicity investigation on plant aqueous extract. The mice were starved overnight, and their weights were recorded immediately before they were used. A control group and three treatment groups were randomly assigned to the mice, with each group consisting of four mice (3 male and 3 female). The vehicle was given to the control group, while the aqueous extract of the investigated plant was given orally in doses of 1000, 2000, and 5000 mg/kg to the treatment groups. [24] Then they were watched for three days to see whether there was any change in their overall demeanour or physical activity.

RESULTS AND DISCUSSION

Diabetes mellitus (DM) is a set of metabolic diseases characterised by hyperglycemia caused by a partial or absolute absence of insulin, insulin's effects on target tissues, or both [25-31]. It is the most prevalent endocrine illness, and by 2010, it is expected that more than 200 million people worldwide would have diabetes, with another 300 million developing the disease by 2025. In diabetes patients, blood glucose concentration regulation is essential. Medicinal herbs have been a natural source of powerful anti-diabetic medicines for ages. Many different types of plants and herbs are used in this context in Iraqi areas. Our objective is to see if the antidiabetic activity of *X. strumarium*, which is utilised in Iraqi folk medicine, may alleviate the metabolic abnormalities associated with alloxan-induced diabetic albino mice.

Percentage of Extracts

Aqueous extraction yielded 2.55 g, or 8.38 percent, of the basic plant material per 25 g.

Characterization of Chemical Composition

Flavonoids, phenols, tannins, glycosides, and terpenes were found in the active components of an X. strumarium, but saponins and steroids were not found in the aqueous extracts (Table 1). These findings were in agreement with Ahmad, Sheeraz, and colleagues (2016) [26] who established that, the phytochemical analysis of the ethanolic extracts of *X. strumarium* used in this study revealed the presence of sesquiterpene lactones (perhaps xanthanolide type), alkaloids, amino acids, carbohydrates, gums, glycosides, flavonoids, and tannins. One or more chemical components may be present in plants with hypoglycemic and antihyperglycemic properties. In *X. strumarium*, chemicals and compounds extracted from the plant, including as caffeic acid, carboxyatractyloside, and phenolic compounds, have been shown to lower blood glucose levels (Kamboj and Saluja 2010) [16,30]. These findings backed up the usage of *X. strumarium* in India's traditional medical system to treat diabetes. To explain the specific mechanism of the anti-hyperglycemic action of the *X. strumarium* plant, further extensive chemical and pharmacological research is required [26].

Table 1: Organic composition of the aqueous extract of *X. strumarium*.

Extraction Test	Aqueous Extract
Phenols	+
Flavonoids	+
Terpenes	+
Saponins	-
Glycosides	+
Steroids	-
Alkaloids	+

Key: (+): Positive, (-) : Negative

Acute Toxicity Studies

Acute toxicity studies revealed that giving animals graded doses of crude petroleum or aqueous extract (up to a dose of 5000 mg/kg body weight) of X. strumarium leaves extracts up to 2000 mg/kg did not cause significant changes in behaviours like alertness, motor activity, breathing, restlessness, diarrhoea, convulsions, coma, or appearance. The crude extracts of the plant did not cause any mortality up to 2 g/kg body weight. During the experiment, these impacts were observed (72 hours). The plant extracts had no adverse effects in a single dosage, indicating that the medium lethal dose (LD50) in mice might be larger than 2 g/kg body weight.

General Parameters and Body Weight of Experimental Mice

The focus of this research was to see if extract from the *X. strumarium* plant has any anti-diabetic properties. Normal mice given distilled water (control) showed no changes in physiological activity or body weight during the course of the treatment, suggesting that the experimental variables (nutrition, humidity, and light) had no influence on body weight. When compared to non-treated diabetic mice, mixture-treated diabetic mice exhibited evidence of recovery in body weight gains at the end of the trial. During the trial, *X. strumarium* extract had no influence on body weight in normal groups (Table 2).

Alloxan causes the production of superoxide radicals, which dismutase to hydrogen peroxide, resulting in a huge rise in cytosolic calcium concentration and the fast death of pancreatic cells. This causes a significant number of cells to die, resulting in a decrease in endogenous insulin release, which allows tissues to utilise less glucose [27], as well as an increase in the breakdown of stored carbs, lipids, and proteins to compensate for the glucose deficit. Carbohydrates, fats, and proteins are used as energy sources, resulting in weight loss. Diabetes effectively regulates with *X. strumarium* extract do not experience the dramatic weight loss seen in the non-treated diabetic group. This might be due to the extract's flavonoid and/or terpenoid content, which could be responsible for potentiating insulin action, boosting glucose intake by tissues, and ultimately reducing the breakdown of stored carbs, lipids, and proteins [28].

Table 2: Body weight of normal and alloxan-induced diabetic mice before and after treatment with dose of aqueous extract of *X. strumarium*.

Treatment Groups		Dose (mg/kg)	Weight (g) ± SE	Weight (g) ± SE
			Before treatment	After treatment
Normal + (distilled water)		0.0	27.5 ± 0.6	27.8 ± 0.8
Normal Mice	Aqueous (*X. strumarium*)	250	30.7 ± 0.6	30.9 ± 1.7
	Aqueous (*X. strumarium*)	500	30.1 ± 0.4	30.7 ± 0.6
Diabetic + (distilled water)		0.0	31.2 ± 0.5	29.8 ± 1.2
Diabetic Mice	Aqueous (*X. strumarium*)	250	30.7 ± 0.8	28.9 ± 3.3
	Aqueous (*X. strumarium*)	500	30.5 ± 1.5	26.0 ± 0.9*

*Significant difference ($P \leq 0.05$) between means before and after treatment for each group

Blood Glucose Level

In diabetes patients, blood glucose concentration regulation is essential. When diabetic mice were given an aqueous extract of *X. strumarium*, their blood glucose levels (BGLs) were lower than in the control diabetic group.

During the treatment period, the blood glucose level in normal mice administered with distilled water (control) was monitored, revealing that the experimental circumstances (nutrition, humidity, and light) had no influence on the blood glucose level. The non-treated diabetic group saw a significant increase in blood glucose levels. When diabetic mice were given extracts, their blood glucose levels dropped significantly compared to diabetic mice who were not given extracts. During the trial, only the high dosages of aqueous extract caused a substantial reduction in blood glucose levels in normal mice. The glucose levels in the blood are recorded in (Table 3). According to our findings, oral administration of *X. strumarium* extracts had a hypoglycemic impact in both normal and diabetic mice. This finding was supported by (Kamboj and Saluja 2010), who reported blood sugar levels in normal and experimental rats at the beginning of therapy, as well as during the first, seventh, and fourteenth days. When compared to normal rates, alloxan-induced diabetes rates indicate a substantial rise in blood glucose levels. Blood glucose levels were significantly reduced ($p = 0.05$) after oral administration of compound-II and crude ethanol extract (300 mg/kg and 500 mg/kg). It's possible that the identified compound-II, Sesquiterpene lactone, is a xanthanolide [16]. When compared to a same dose of crude ethanol extract, a dose of 500 mg/kg resulted in a greater reduction ($p = 0.05$) in blood glucose levels. In 14 days of therapy, the conventional medication Glibenclamide reduced blood glucose levels. The fasting mean blood glucose levels on day 1 (after being diabetic), i.e. 276.8022.62 mg/dl, were decreased to 174.6012.66 mg/dl and 335.6031.89 mg/dl were lowered to 198.8023.89 mg/dl, respectively, following treatment with compound II (300 mg/kg and 500 mg/kg). Treatment

with ethanolic extract (300 mg/kg and 500 mg/kg) decreased the fasting mean blood glucose levels on day 1 (after becoming diabetic), i.e. 349.80 29.32 mg/dl to 259.0017.28 mg/dl and 343.80 20.22 mg/dl to 248.3012.85 mg/dl, respectively. On day 14, diabetic mice treated with Glibenclamide exhibited a reduction of 51.05 percent when compared to diabetic control (Positive control) animals, corresponding to a reduction of 25.95 percent and 27.77 percent, respectively. After 14 days of therapy, blood glucose balance improved in a dose-dependent way. When compared to the corresponding compound I at a dose of 300 mg/kg and ethanol extract, the impact of compound II at a dose of 500 mg/kg body weight demonstrated considerably greater reduction. Compound II and crude ethanol extract of V. cinerea reduced blood glucose levels in alloxan-induced mice in a dose-dependent manner, according to this study [16]. The continuous treatment of mice with *X. strumarium* extracts for ten days resulted in a substantial decrease in blood glucose levels. These findings supported the traditional usage of the *X. strumarium* plant as an anti-diabetic drug and for the treatment of a variety of illnesses. Glibenclamide, a common medication for treating diabetes, has been used for many years to increase insulin production from pancreatic cells [26]. It's possible that Sesquiterpene lactone (Compound II) has a mode of action similar to glibenclamide.

Table 3: Blood glucose levels in normal and alloxan-induced diabetic mice were affected by an aqueous extract of *X. strumarium*.

Treatment Groups		**Dose (mg/kg)**	**Glucose (mg/dl) Before treatment**	**Glucose (mg/dl) After treatment**
Normal + (distilled water)		0.0	156.2 ± 6.0	159.2 ± 10.2
Normal Mice	Aqueous (*X. strumarium*)	250	191.0 ± 6.0	186.0 ± 10.8
	Aqueous (*X. strumarium*)	500	185.5 ± 10.4	165.1 ± 10.5*
Diabetic + (distilled water)		0.0	502.0 ± 12.2	530.2 ± 14.8
Diabetic Mice	Aqueous (*X. strumarium*)	250	512.5 ± 15.4	390 ± 13.1*
	Aqueous (*X. strumarium*)	500	425.2 ± 14.2	260 ± 10.8*

*Significant difference (P ≤0.05) between means before and after treatment for each group

Statistical Analysis

All findings were first written down in a notebook, then typed into a PC computer and double-checked by another individual for correctness. The data was presented as a mean standard deviation (SD) (of 30 animals). According to [29], the statistical analysis was carried out utilising a student's two-tailed-test software application. P Statistical significance was defined as a value less than 0.05.

CONCLUSION

Phenols, flavonoids, tannins, saponins, glycosides, and terpenes were among the active components found in the aqueous extract of *X. strumarium*. In both normal and alloxan-induced diabetic mice, aqueous extract of *X. strumarium* shows hypoglycemic action in a dose-dependent manner. Our findings show that the aqueous extract of these plants has anti-diabetic properties when compared to each plant individually, which we evaluated in a prior study.

CONFLICTS OF INTEREST

None.

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