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Antidiabetic Potential of *Carthamus oxycantha* M.Bieb. Seeds in Alloxan Induced Diabetic Rats

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Abstract

Ethnopharmacological Relevance: Diabetes Mellitus is one of the most common disorders of metabolic abnormalities. It is characterized by hyperglycemia followed by abnormalities in insulin release, insulin work, or both. This persistent hyperglycemia is concerned with long-term complications, dysfunction and collapse of various organs, notoriously the kidneys, heart, nerves, blood vessels and eyes. The seeds of the *Carthamus oxycantha* have been used by the practitioners as a traditional remedy for diabetes mellitus in the rural areas of district Jhang as well as other areas of Pakistan. ***Aim of the Study***: The purpose of the present study was to reveal the antidiabetic capability of seeds of *Carthamus oxycantha* in short-term and long-term studies. ***Materials and Methods***: Aqueous ethanolic extract of seeds was prepared by a rotary evaporator. The antidiabetic activity of the seeds was assessed by using normoglycemic and glucose loaded rats. However, two kinds of studies *i.e.* short-term as well as long-term treatment were carried out in alloxan induced diabetic rats for the finalized both doses *i.e.* 50 mg/kg and 100 mg/kg. Blood samples were tested by an electrochemical technique using a glucometer. ***Results***: The promising results were achieved for the antidiabetic potential of the ethanolic extract of seeds of *Carthamus oxycantha* at both of the doses *i.e.* 50 mg/kg and 100 mg/kg. The antihyperglycemic potential was also evaluated in normoglycemic and glucose loaded animals. Treatment with 100 mg/kg AEECO presented significant reduction ($p < 0.05$) as well as highly significant reduction ($p < 0.01$) in short term and long term study. Statistical data showed that AEECO presented comparable effects to that of the standard drug Glibenclamide at 0.5 mg/kg. Phytochemical studies of AEECO also disclosed the presence of flavonoids, resins, glycosides, steroids and alkaloids.

In conclusion, the antidiabetic properties of AEECO may be attributed either due to the release of insulin or possibly due to the peripheral uptake of glucose. It may also be due to protection of beta cells from toxic effects of alloxan or the presence of flavonoids may exhibit various biological activities as they have been stated for their antidiabetic potential. However, further studies are required to explore the active moieties responsible for antidiabetic potential.

Keywords

Diabetes Mellitus, *Carthamus oxycantha*, Alloxan, Glibenclamide, AEECO

1. Introduction

Diabetes is characterized by a set of metabolic disorders marked by hyperglycemia followed by abnormalities in insulin release, insulin work, or both. Type 1 diabetes and type 2 diabetes are the two forms of diabetes. The beta cells of the pancreas are damaged in type 1 diabetes. As a result, the beta cells lose some or all of their ability to secrete insulin. It is further classified into two types: 1A type, in which the immune system attacks and destroys beta cells. This is a cell-mediated destruction. 1B is the second category, in which the cause is unknown. This variety is less common, but it is more common in Asian populations. Type 2 diabetes is characterized by defects in insulin action. Decreased glucose uptake by muscle cells is due to the defective insulin mechanism contributing to the elevated postprandial glucose. Type 2 diabetes is a complex condition marked by impaired fat and carbohydrate metabolism. Environmental factors and genetic determinants are among the many causes of diabetes 2. These factors have an impact on beta cell activity and insulin sensitivity. Both of these characteristics are significant in the development of type 2 diabetes. The persistent hyperglycemia in both types is concerned with long-term complications, dysfunction, and collapse of various organs, particularly the kidneys, heart, nerves, blood vessels and eyes [1].

There is 1 death in every 10 seconds because of diabetes [2]. As described by the WHO, 70% of the world's population uses medicinal plants to cure their diseases. *Carthamus oxycantha* M.Bieb. is locally recognized as kandyari and pholi. It is a member of the Asteraceae family. *Carthamus oxycantha* is a weed that has numerous well-known medical properties including anti-ulcerogenic [3]. Because of its spiky character, Cattle cannot eat it [4].

Azerbaijan, Afghanistan, India, Iraq, Iran, Pakistan, Kyrgyzstan, Turkmenistan, and Tajikistan are among the countries where *Carthamus oxycantha* can be found. Usually, this weed grows primarily near the boundaries of wheat fields [5] [6] [7]. The seeds of *Carthamus oxycantha* yield oils of two types; linoleic oil and oleic oil [8] [9]. The corollas and leaves of *Carthamus oxycantha* have been investigated for their antihyperglycemic activity [10]. Hence, the current study was undertaken to uncover the antidiabetic ability of seeds of *Carthamus oxycantha.*

2. Materials and Methods

2.1. Collection of Plant Material

In May and June *Carthamus oxycantha* was collected from the peripheral area of district Jhang Punjab, Pakistan. The voucher of the specimen (No. DBS01/BSG/ID/2016/37) of the plant was deposited in the herbarium division of the institution. The seeds of *Carthamus oxycantha* were separated and properly washed in tap water and additionally cleansed with distilled water. These were dried for 10 - 12 days in the shade. After the drying process, seeds were grinded in a china herbal grinder to obtain coarse powder for extraction purposes. The processed samples were protected from sunlight by storing them in an airtight container.

2.2. Preparation of Extract

The powdered seeds 2 kg of *Carthamus oxycantha* were soaked in an aqueous ethanolic mixture of 70% ethanol (Thermo Fisher Scientific, USA) and 30% distilled water for 72 hours and were stirred regularly. The extraction was performed three times, then filtration was carried out at room temperature through muslin cloth and afterward by whatmann filter paper (Merck). All the filtrate was collected to evaporate it in the rotary evaporator to get the extracts. The temperature of the rotary evaporator was maintained at 50˚C and pressure of −760 mmHg was generated. The extracts were dark green in colour. The aqueous extracts were dried at room temperature to get the solid mass. Then their percentage yield was calculated.

2.3. Preliminary Phytochemical Screening

Standard analytical methods were applied for preliminary screening of phytochemical Constituents found in the seeds (Table 1).

2.4. Experimental Animals Used

In the present study; Young, healthy male Sprague-Dawley rats (250 - 350 g) were used. All rats aged 4 - 5 months were acclimatized with free access to water and pellet diet under optimum temperature and humidity.

The research was conducted in accordance with internationally accepted principles for the use and care of laboratory animals. They were kept in a 12-hour light and dark cycle provided at an ambient temperature of 22˚C ± 02˚C and 55% humidity (National Institutes of Health, 1985). All animals were housed at the University of Lahore animal facility. The study protocol was accepted by the Ethics Committee of the Department of Pharmacology, the University of Lahore,

Table 1. Preliminary phytochemical screening.

Extract	Phytochemical constituents detected
Aqueous Ethanolic Extract of *Carthamus oxycantha* (AEECO)	Alkaloids, Flavonoids, Glycosides, Steroids, Resins, Organic acid, Phenolic compounds, Tannins.

Pakistan (Permit No. DOPUOL/69/08-15). All animals were treated according to standard guidelines provided by the National research council [11]. For both types of studies, blood samples were collected for blood glucose monitoring.

2.5. Experimental Groups

For both experiments, *i.e.* normoglycemic and loaded with glucose; Rats were divided into 3 groups of 5 rats each. Group 1 was regarded as normal control, and groups 2 and 3 were administered the extract. However, as far as short-term and long-term studies of alloxan (Sigma-Aldrich) induced diabetes are concerned, rats were randomly divided into 5 groups, each containing 5 animals. The non-diabetic group received 1.5 ml of normal saline as a physiological solution. Group 2 was considered as diabetic control, while Group 3 was treated with the standard drug glibenclamide (Sigma-Aldrich) (0.5 mg/kg orally). Group 4 and 5 were given the extract to be tested dissolved in NaCl vehicle in two doses *i.e.* 50 mg/kg and 100 mg/kg, respectively.

2.6. Statistical Analysis

A one-way analysis of variance (ANOVA) was applied and the results were expressed as the mean ± standard error of the mean (SEM). The data with p-values of 95% ($p < 0.05$) were considered statistically significant.

3. Results

3.1. Effect of Aqueous Ethanolic Extract of *Carthamus oxycantha* in Normoglycemic Rats

The two different doses were chosen to examine the hypoglycemic activity of AEECO on the blood glucose levels of the normoglycemic rats. Both doses, 50 mg/kg and 100 mg/kg *Carthamus oxycantha* showed a reduction in blood glucose levels in the normoglycemic rats. The 50 mg/kg did not bring any significant results in the 1st and the 3rd hour (**Figure 1**). However, it produced significant results after 5 hours ($p < 0.05$) and highly significant results after 7 hours ($p < 0.01$). The other dose of 100 mg/kg produced highly significant results at 5 and 7 hours ($p < 0.01$). The significant results were also observed after the 3rd hour (**Table 2**).

3.2. Evaluation of Antihyperglycemic Potential of Aqueous Ethanolic Extract of *Carthamus oxycantha* in Glucose Induced Hyperglycemia

This type of experiment was carried out to check whether the AEECO was able to reduce the blood glucose after loading the rats with 1 g/kg concentration of glucose orally. Extract of the plant was administered to the animals just after the administration of the glucose loading dose. After 1st hour of the glucose administration, there was a rise in blood glucose levels in all the groups (**Figure 2**).

After 3rd hour of the experiment, both the doses of AEECO (50 mg/kg and 100

Table 2. Effect of *Carthamus oxycantha* in normoglycemic rats.

BLOOD GLUCOSE LEVELS (mg/dl)					
Groups	**0 hr**	**1st hr**	**3rd hr**	**5th hr**	**7th hr**
Normal Control	75.67 ± 2.12	74.83 ± 2.37	76.00 ± 2.44	71.67 ± 1.99	71.83 ± 1.94
CO 50 mg/kg	91.67 ± 3.88	88.50 ± 4.28^{ns}	83.00 ± 4.62^{ns}	74.83 ± 4.54*	59.67 ± 2.91**
CO 100 mg/kg	90.17 ± 5.28	82.17 ± 5.53^{ns}	72.50 ± 4.33*	67.40 ± 3.59**	57.25 ± 4.03**

Results are expressed as, mean ± SEM (n = 5). *Significant ($p < 0.05$), **Highly Significant ($p < 0.01$) and ns = Non-Significant vs (0hour), CO = *Carthamus oxycantha*.

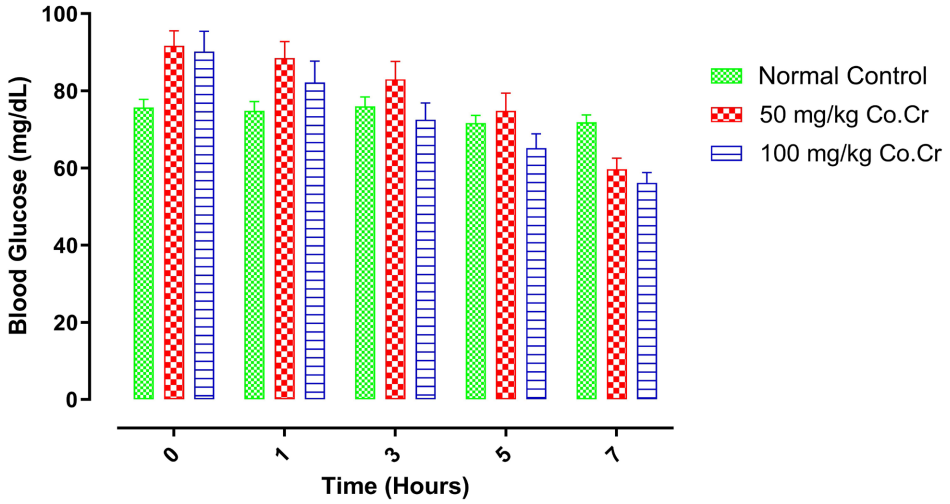

Figure 1. Effect of *Carthamus oxycantha* in normoglycemic rats.

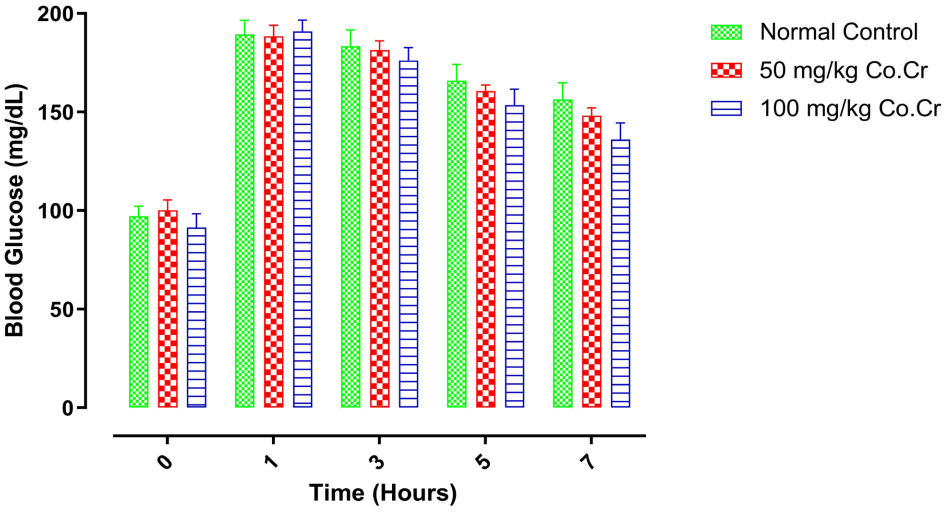

Figure 2. Effect of *Carthamus oxycantha* in glucose loaded rats.

mg/kg) were unable to produce a significant reduction in blood glucose concentrations. However, a highly significant reduction ($p < 0.01$) was noted after 5th and 7th hour for both concentrations of AEECO (50 mg/kg and 100 mg/kg) (Table 3 & Figure 2).

3.3. Determination of Antidiabetic Activities of Aqueous Ethanolic Extract of *Carthamus oxycantha* in Alloxan Induced Diabetic Models

Two types of studies were carried out in alloxan induced diabetic models. Short-term study and the long-term study. In the short-term study, the effects of AEECO were observed on diabetic rats up to the 7th hour. While in the long-term study, AEECO was administered orally up to seven days continuously on a daily basis. Total 5 groups (n = 5) were used for these experiments. One was normal control while the remaining 4 were diabetic. The 2nd group served as the diabetic control which showed elevated sugar levels up to the 7th day. The 3rd group received the glibenclamide 0.5 mg/kg daily. The highly significant ($p < 0.01$) results were obtained from this group from the 1st day up to the 7th day.

The 4th and 5th groups received 50 mg/kg and 100 mg/kg AEECO in both types of studies. The 50 mg/kg was able to reduce the blood sugar levels in short-term and long-term studies and produced significant results when compared to the zero hour. However, 100 mg/kg concentration produced highly significant results ($p < 0.01$) in 5th and 7th hour of the short-term study. In the long-term study, it also showed high reduction in blood glucose levels on 3rd, 5th and 7th days (Table 4 & Figure 3).

Table 3. Effect of *Carthamus oxycantha* in glucose loaded rats.

BLOOD GLUCOSE LEVELS (mg/dl)					
Groups	**0 hr**	**1st hr**	**3rd hr**	**5th hr**	**7th hr**
Normal Control	97.17 ± 5.04	189.33 ± 7.20	183.33 ± 8.32	165.83 ± 8.25	156.33 ± 8.50
CO 50 mg/kg	100.17 ± 5.22	188.33 ± 5.61	181.33 ± 4.8^{ns}	160.67 ± 3.14**	148.17 ± 3.87**
CO 100 mg/kg	91.50 ± 6.89	190.83 ± 5.76	176.17 ± 6.55^{ns}	153.50 ± 8.09**	136.00 ± 8.51**

Results are expressed as mean ± SEM (n = 5). *Significant ($p < 0.05$), **Highly Significant ($p < 0.01$) and ns = Non-Significant vs (1st hour), CO = *Carthamus oxycantha*.

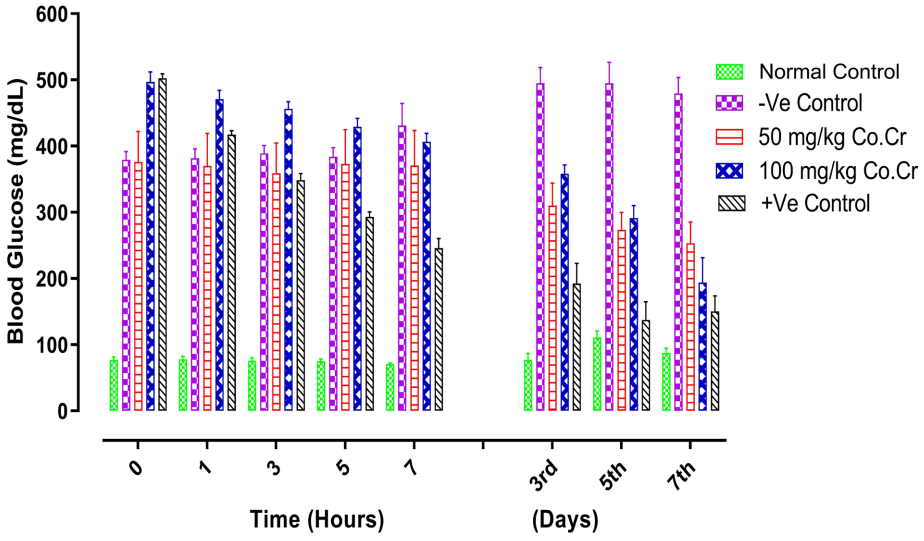

Figure 3. Effect of *Carthamus oxycantha* in alloxan induced diabetic rats.

Table 4. Effect of *Carthamus oxycantha* in alloxan induced diabetic rats.

BLOOD GLUCOSE LEVELS (mg/dl)								
Groups	**0 hr**	**1st hr**	**3rd hr**	**5th hr**	**7th hr**	**3rd day**	**5th day**	**7th day**
Normal Control	76.80 ± 4.74	77.80 ± 4.67	75.80 ± 4.22	75.00 ± 3.42	71.00 ± 1.30	76.60 ± 10.2	111.00 ± 9.47	87.40 ± 7.33
Diabetic Control	379.20 ± 12.5	381.60 ± 14.1	389.00 ± 12.0	384.00 ± 13.5	401.5 ± 19.9	480.8 ± 24.8	481.0 ± 36.5	479.8 ± 23.9
Glibenclamide 0.5 mg/kg	502.40 ± 6.71	417.20 ± 6.14**	348.6 ± 10.0**	293.20 ± 7.50**	246.0 ± 14.3**	192.4 ± 30.4**	158.0 ± 23.4**	150.4 ± 23.3**
CO 50 mg/kg	376.2 ± 46.0	370.2 ± 48.8ns	359.0 ± 45.5ns	328.8 ± 33.4ns	324.5 ± 34.2*	310.2 ± 33.8*	273.4 ± 26.3**	253.2 ± 32.1**
CO 100 mg/kg	483.00 ± 8.40	471.0 ± 13.1ns	456.2 ± 11.1ns	429.0 ± 12.9**	406.4 ± 12.6**	358.0 ± 13.7**	291.2 ± 18.9**	229.5 ± 15.2**

Results are expressed as, mean ± SEM (n = 5). *Significant ($p < 0.05$), **Highly Significant ($p < 0.01$) and ns = Non-Significant vs (0hour), CO = *Carthamus oxycantha*.

4. Discussion

For all age groups, the diabetes prevalence is estimated to be high. It has been known that there was 2.8% prevalence in 2000. It will continue to rise and will be 4.4% in the year 2030. Male are suffering more from diabetes as compared to females. People with age more than 65 years show more trends in developing diabetes which is a very important change demographically [12].

The diabetes is associated with significant complications and symptoms of depression. Basically depression has been associated with various diabetes complications like diabetic nephropathy, neuropathy and retinopathy. Sexual dysfunctioning is also the result of long-term complications of diabetes [13].

Cardiovascular complications are the main cause of morbidity and mortality in patients with diabetes. The pathological mechanism is not well understood but may include increased hypercoagulability, atherosclerosis and increased blood pressure. No doubt, diabetes is one of the risk factors for the heart failure development. The mechanism is not clarified but may involve resistance of insulin in the liver, adipose tissue and skeletal muscles. Insulin resistance if occurs in vasculature, may lead to atherosclerosis and endothelial dysfunction [14]. Diabetic acidosis is the major cause of the cardiovascular collapse. The diabetes duration is the important single factor responsible for arteriosclerosis of coronary vasculature [15].

Diabetes mellitus can be managed with oral hypoglycemic agents. In starting, monotherapy is applied but if required other agents can be added. However, in many patients insulin administration is necessary to meet the targeted sugar levels. In addition to the improved sugar control, the agents like metformin, sulfonylureas and insulin also decrease the occurrence of microvascular pathies like neuropathy, retinopathy and nephropathy [16].

The most widely used therapeutics are α-glucosidase inhibitors, biguanides, sulfonylureas and thiazolidinediones (TZDs) [17]. However, there are side effects associated with these agents like hypoglycaemia occurs due to sulphonylureas and gastrointestinal (GI) disturbances with biguanides [18].

In order to overcome these side effects, plants are also a big source of medicines to manage the diseases [19]. As described by the WHO, 70% of the world's population uses medicinal plants to cure their diseases. In this way, plants have a pivotal role in treating diseases.

In the recent study, aqueous ethanolic extract of *Carthamus oxycantha* (AEECO) was employed in two different doses of 50 mg/kg, 100 mg/kg. In normoglycemic, glucose-loaded, and alloxan-induced diabetic rats, both doses of the plant generated substantial outcomes. In normoglycemic and glucose-loaded animals, this drop in blood glucose might be attributed to insulin secretion or peripheral glucose uptake. In diabetic induced animals, the reduction in blood glucose levels could be owing to the beta cells' protection from the alloxan's toxic effects or their recovery after the initial harm. The phytochemical analysis of the AEECO was done in order to find some of the active chemical compounds. It was found that crude extract contains some biologically active compounds like terpenoids, flavonoids, tannins, alkaloids, steroids and glycosides.

The different types of active principles may be responsible for lowering blood glucose levels like steroids and flavonoids. Furthermore, the usefulness of the flavonoids has also been investigated in reducing diabetic complications like cardiac problems, retinopathy and neuropathy.

The response of diabetic rats was more pronounced to AEECO as compared to the normoglycemic models and glucose loaded animals. However, further investigations are required to elucidate and identify the actual moiety to determine the realistic mechanisms to develop the more potent active agent for antidiabetic activity.

5. Conclusion

The traditional usage of *Carthamus oxycantha* seeds as a hypoglycemic agent appears to be valid. This plant's seed extracts have a remarkable anti-diabetic effect that is comparable to the standard drug glibenclamide.

Conflicts of Interest

The authors declare no conflict of interest.

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Abbreviations

CO, *Carthamus oxycantha*; AEECO, Aqueous Ethanolic Extract of *Carthamus oxycantha*; WHO, World Health Organization; TZDs, Thiazolidinediones; GI, Gastrointestinal