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# Hypoglycemic, Hypolipidimic and Protective Effects of *Arbutus andrachne* Extract in Streptozotocin Induced Diabetic Rats

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**Abstract:** The aim of this study is to investigate the anti-hyperglycemic effect, lipid profile and the activity of certain hepatic enzymes of the ethanolic extract of the plant *Arbutus andrachne* on streptozotocin-induced diabetic rats. About 30 Wistar albino rats weighing between 180-200 g were randomly classified into four categories of six albino rats. The normal control group (group A) was treated orally with distilled water. The diabetic control group (group B) was induced by streptozotocin. So, this group is considered as a negative control. The non diabetic rats (group C) which was treated with the ethanolic extract of the plant *A. andrachne* that collected from Jerash/Jordan of a dose 200 mg $kg^{-1}$. The last group (Group D) which included the diabetic rats that treated with 200 mg $kg^{-1}$ of the ethanoilc extract of the plant *A. andrachne*. The treatment was carried out daily for 14 days. The glucose, triglycerides, cholesterol and hepatic enzymes levels were quantified in serum of experimental rats. Study was carried out in Faculty of Pharmacy/Applied Science University (December, 2018) and Botany Lab, Department of Biological sciences/University of Jordan. The results unambiguously showed that there was significant declines ($p<0.05$) in triglycerides and glucose levels in albino rats that treated with *A. andrachne* ethanolic extract compared with group B, the control group of diabetic rats. Significant reduction ($p<0.05$) in hepatic enzymes -AST and ALT-levels were also observed in rats treated with the plant ethanoilc extract compared with group B experimental rats. However, no significant changes in the cholesterol level were observed in the treated rats compared with the control group. Data in this piece of research revealed that the plant *A. andrachne* ethanolic extract has both hypoglycemic and hypolipidimic effect. This extract is suggested to reduce the liver damage induced by streptozotocin through maintaining the activity of hepatic enzymes.

**Key words:** Anti-diabetic, *A. andrachne*, liver enzymes, streptozotocin, hypoglycemic agent, medicinal plants

## INTRODUCTION

Diabetes mellitus is a chronic disease occurs due to either an autoimmune disorder or insulin resistance. Autoimmune disorder (type I diabetes) appears as a result of β-cells failure to secrete insulin (Aja *et al*., 2015). Interrupted signal transduction pathway occurs as a result of defects of insulin receptors which is routinely called type II diabetes leading to elevated blood glucose level (hyperglycemia) (Bamidele *et al*., 2014). One possible line of hyperglycemic treatment can be performed by intensive use of insulin. However, in certain cases this strategy may be ineffective to reduce glucose level and as a result hypoglycemic intervention should be implemented. In this research, *A. andrachne* ethanolic extract is investigated to detect whether it has hypoglycemic effects on rats or not. Diabetes is associated with a wide group of abnormalities including dyslipidemia, increased transcript of inflammatory biomarkers, changes in normal levels of hepatic enzymes and hemodynamic changes (WHO., 1985).

The dyslipidemia that linked to type II diabetes and insulin resistance can be recognized by increased triglycerides as well as decreased cholesterol level. Discrepancy in levels of triglycerides and cholesterol is highly risky for cardiovascular system (Baumgartner *et al*., 2011). Several plant species were reported to reduce levels of lipids in diabetes as a way to reduce severe symptoms of this disease. In this research, the probability of hypolipidimic effect of *A. andrachne* extract is investigated.

Different techniques were implemented to induce diabetes experimentally one of the most efficiently technique is to use the chemical Streptozotocin

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(STZ). Streptozotocin enters pancreatic β-cells by GLUT2 receptors which then modify DNA through, alkylation which therefore, causes activation of poly ADP-ribosylation. Furthermore, streptozotocin produces harmful quantities of Nitric Oxides which down regulates aconitase activity. Streptozotocin participates in pancreatic β-cells destructions through necrosis (Szkudelski, 2001).

Treatment with medicinal plants comparing to synthetic drugs is characterized by low cost, less toxicity and undesirable side effects or contraindications (Dieye *et al*., 2008). Management of diabetes through using a wide variety of plant extracts has been highly recommended in the recent few years. One of these suggested plants is *A. andrachne* L. which has edible fruits and belongs to the family Ericaceae that includes about 50 genera and more than 1350 species. South Asia and Mediterranean are their native (Bacic *et al*., 1992). *A. andrachne* is distributed in different parts of Jordan, mainly in the north areas. It is found as a shrub or tree growing up to 5 m. The leaves of *A. andrachne* are elliptic and glabrous. March to April is the time for flowering while the fruits time is from October to November. The different parts of *A. andrachne* have used for treatment of disorders of urinary tract (Bamidele *et al*., 2014). The fruits and roots of *A. andrachne* have been used for allaying joints pain and wound healing (Serce *et al*., 2010). Glycosides, terpenoids and phenolic compounds are active ingredients that isolated from the ethanolic extract of *A. andrachne* stem (Bacic *et al*., 1992). *Arbutus* fruit extract may prevent chronic SD-induced impairment of hippocampal memory by its antioxidative potential (Alzoubi *et al*., 2018). Even though *A. andrachne* has been widely accepted as an important medicinal plant for treating a wide range of diseases, its effects on diabetes have not been reported. Therefore, this research is investigated the effects of this popular plant in Jordan-on various aspects of diabetes for the first time.

In this study, however was attempting to explore the biochemical effect of *A. andrachne* extract on blood glucose, lipid profile and liver enzymes levels. So, the present study is performed to study the proposed mechanism beyond anti hyperglycemic and hypolipidimic influences of *A. andrachne* on streptozotocin induced diabetic rats.

## MATERIALS AND METHODS

**Plant materials:** The leaves of the plant *A. andrachne* were collected by Sawsan Oran from Jeresh/Jordan during Summer 2018 and completely dried. The plant has been taxonomically identified by Professor Sawsan Oran, plant taxonomy (Department of Biological Sciences, The University of Jordan). Voucher specimens of collected plants were deposited at Jordan University herbarium.

**Preparation of plant extract:** Collected leaves of *A. andrachne* were air dried for approximately 4 weeks at room temperature (23-27°C). Dried plant materials were powdered using an electrical blender. About 60 g of each dried powdered plant material was dissolved separately in 600 mL of absolute ethanol (solvent to sample ratio of (10:1 v/w) solvent to dry weight ratio) by using a reflux for 72 h with 60°C. The extraction was then filtered through Whitman No. 1 filter papers. The filtrates were concentrated (evaporated of solvents) by using rotary evaporator with 40°C and subsequently left to completely dry (Serce *et al*., 2010).

**Experimental design:** Thirty Wistar albino rats weighing between 180-200 g were obtained from the animal house of the Faculty of Pharmacy, Applied Science University. The rats were divided into four groups of six rats. Each group was kept on different cages. The grouping was done as follows:

- Group A, control (non-diabetic rats)
- Group B, diabetic rats were induced with streptozotocin (negative control)
- Group C, non diabetic rats treated with *A. andrachne* extract at a dose of 200 mg $kg^{-1}$
- Group D, diabetic rat's intubation with *A. andrachne* extract. The administration was done twice daily for 14 days

**Induction of diabetes mellitus:** Streptozotocin was dissolved in citrate buffer (pH 4.5) to induce diabetes in rats of groups C and D by intra-peritoneal injection at dose 60 mg $kg^{-1}$ of body weight using insulin syringes. Diabetes induction was occurred after 3 days confirmed by testing the fasting blood glucose level using glucometer (Rees and Alcolado, 2005) also the symptoms of polyuria, polydipsia and glycosuria in diabetic rats was observed. Animals with blood sugar level more than 200 mg $dL^{-1}$ were considered to be diabetic (Cerieello and Motz, 2004).

**Blood collection and preparation:** At the end of experiment, blood samples were collected by cervical dislocation of rats under chloroform anesthesia and drain into heparinized tubes and transferred into plain centrifuge tubes. They were then centrifuged within 1 h of collection at 4000× g for 10 min on a centrifuge to separate the sera from the clot (Ochei and Kolhatkar, 2007).

**Determination of blood glucose level:** Blood glucose level was determined by the Glucose Oxidase Method (GOM) using reactive strips and a single touch glucometer.

**Serum lipids profile estimation:** Enzymatic colorimetric method was used to measure the serum total cholesterol and triglycerides levels using Mannheim diagnostic kits.

**Determination of liver enzymes:** Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) were measured using commercial kits (Ochei and Kolhatkar, 2007).

**Data analysis:** All the values were shown as mean standard deviation. One-way Analysis of Variance (ANOVA) was used to studying and analyzing the data followed by post-hoc tests. The results are considered significant at $p<0.05$.

## RESULTS AND DISCUSSION

Table 1 shows body weight of control and diabetic rats with and without treatment with *A. andrachne* extract. After 14 days of experiment, there was a significant decrease ($p<0.05$) in the diabetic rats group (II) body weight compared with the control (group I). Administration of *A. andrachne* extract with diabetic experimental animals (group IV) has increased body weight significantly, comparing with the normal rats body weight.

Treating experimental rats with streptozotocin increased blood glucose level by more than four folds (Fig. 1). When diabetic albino rats were treated with *A.andrachne* extract, glucose level decreased significantly ($p<0.05$). After this treatment, glucose level returned to almost the normal level before streptozotocin treatment. *A. andrachne* extract cured diabetic rats completely.

Comparing to the control rats group, triglycerides level increased significantly ($p<0.05$) in the STZ-treated diabetic rats group. However, no significant change was observed for cholesterol (Fig. 2). When STZ-diabetic rats were treated with the *A. andrachne* extract, a significant reduction was observed ($p<0.05$) in the serum level of triglycerides whereas no significant changes in the level of cholesterol was observed.

Changes in the level of hepatic enzymes including Aspartate aminotransferase and Alanine aminotransferase were also investigated in this study. Figure 3 clearly shows a significant reduction ($p<0.05$) in the level of AST and ALT enzymes after treating albino rats with *A. andrachne* ethanolic extract comparing to the experimental animals in the control group.

Nowadays, using synthetic drugs to decrease serum glucose and lipid level in diabetic patients with hyperlipidemia and hyperglycemia is relatively reduced because of their side effects and using medicinal plant extracts has been increased (Baumgartner *et al*., 2011).

The current research was initially designed to explore the effect of *A. andrachne* ethanoilc extract on body weight of streptozotocin-induced diabetic albino rats. Additionally, levels of glucose, triglycerides and cholesterol as well as aspartate amino transferase and alanine amino transferase liver enzymes were also investigated in the diabetic animals.

Table 1: Effect of *Arbutus rachne* extract on the body weight of control and experimental animals

| | | Body weight | |
|---|---|---|---|
| Groups | Variables | Initial | Final |
| I | Control | 190.2±16.6 | 210.5±15.2 |
| II | Diabetic | 195.5±12.7 | 165.3±16.3[a] |
| III | *Arbutus andrachne* | 191.3±17.5 | 194.1±13.4[b] |
| IV | Diabetic+*A. andrachne* | 194.2±16.7 | 196.8±4.40 |

All data are presented as Mean±SD

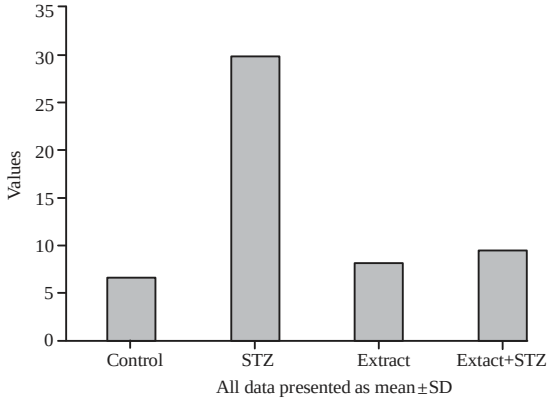


Fig. 1: Effect of *Arbutus andrachne* extract on glucose level in normal and diabetic rats

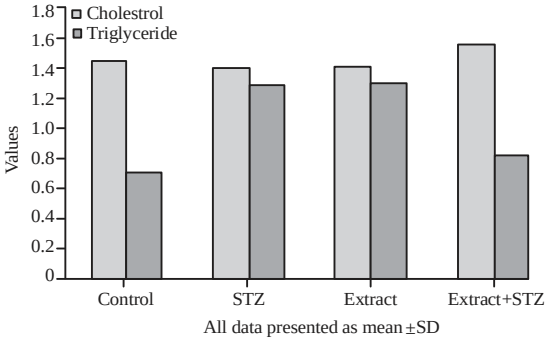


Fig. 2: Effect of *Arbutus andrachne* extract on cholesterol and triglycerides in normal and diabetic rats

Firstly, body weight of streptozotocin-induced albino rats has been found to be significantly decreased at the end of the experimental work. In contrast, *A. andrachne* ethanoilc extract helps rat bodies to completely avoid weight reduction.

The decreasing in the body weight of diabetic rats is in agreement with the results by Oyedemi *et al*. (2011) who found the same effect of streptozotocin on diabetic animals by destruction of muscle protein which leading to

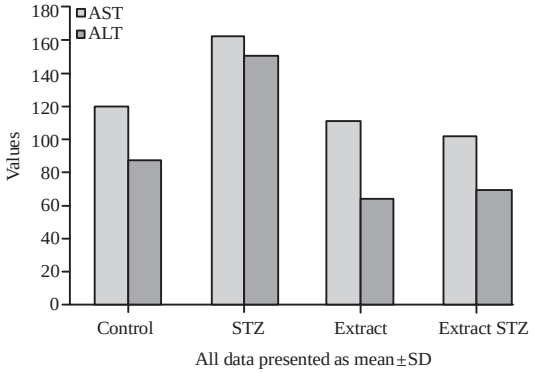


Fig. 3: Levels of liver enzymes in streptozotocin-induced diabetic albino rats after treatment with *Arbutus andrachne* extract.

lose weight but the oral administration of *A. andrachne* ethanoilc extract was normalizing body weight of the animals which may be due to the ability of the treatment to elevate blood glucose level as well as maintain muscle wasting.

On the other hand, this study is also investigated the antihyperlipidemic effect of *A. andrachne* ethanoilc extract in streptozotocin induced diabetic rats. The elevation of the triglycerides in streptozotocin-induced diabetic rats is due to the activity of mobilization of free fatty acids from the adipose tissues and the decrease of the insulin uptake and metabolism (Abu-Zaiton, 2019). According to the data that obtained from this study, *A. andrachne* ethanoilc extract has been found to have both hypoglycemic and hypolipidimic effects on streptozotocin-induced diabetic Wistar albino rats. In addition, according to the different phytochemicals that found in *A. andrachne*, *A. andrachne* has reduced the liver damage and normalizing the hepatic enzymes AST and ALT that happened because of streptozotocin induction (Issa *et al*., 2008). *A. andrachne* could improve glucose utilization in animal tissues, leading to prevent lipid peroxidation and regulate of lipolytic hormones. There are different plants that have reported to have anti-hyperlipidemic efficiency in such a manner. Many researchers have reported that active ingredients which isolated from plants extracts have induce a significant anti-hyperlipidemic effects due to their abilities to prevent of the cholesterol absorption and activate excretion by bile (Akpan *et al*., 2012).

On the other side, the significant decrease in the level of glucose of streptozotocin-induced diabetic animals may be arise as a result of inhibiting glucose absorption by one or more of the effective compounds of *A. andrachne* ethanoilc extract and the regenerating of pancreatic cells could be a possible for the antihyperglycemic potential activity of the *A. andrachne* ethanoilc extract. The possibility of regulating activity or expression of enzymes involved in the metabolic pathways of the examined compounds is not excluded (Kyung *et al*., 2006). It will be interesting to analyze the components of the ethanoilc extract and identifying the active compounds. However, more investigations are needed for evaluation the potential activity of *A. andrachne* and its extact traditional usage in diabetes treatment. Further studies for phytochemicals and toxicological information of *A. andrachne* should be study before administration and treatment with its extracts which will increase the efficiency of coming research.

## CONCLUSION

The results of the present study demonstrate that the ethanolic extract of *A. andrachne* has hypoglycemic and hypolipidimic effects. In addition, *A. andrachne* has a protective effect on the hepatic enzymes and this will decrease the probability of liver damaged by streptozotocin.

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