Pakistan Veterinary Journal

ISSN: 0253-8318 (PRINT), 2074-7764 (ONLINE)
Accessible at: www.pvj.com.pk

RESEARCH ARTICLE

Antihyperlipidemic and Hepatoprotective Activity of *Dodonaea viscosa* Leaves Extracts in Alloxan-Induced Diabetic Rabbits (*Oryctolagus cuniculus*)

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ARTICLE HISTORY

Received: May 06, 2011
Revised: June 28, 2011
Accepted: June 29, 2011

Key words:
ALT
Antihyperlipidaemic
AST
Dodonaea viscose
HDL-cholesterol
Hepatoprotective
LDL-cholesterol
Rabbits
Total cholesterol
Triglyceride

ABSTRACT

Hyperlipidemia is associated with diabetes and hepatotoxicity has emerged as a common clinical complication by antidiabetics. The present study was conducted to determine the antihyperlipidemic and hepatoprotective activity of *Dodonaea viscosa* leaves extracts in the alloxan-induced diabetic rabbits. The rabbits (n = 70) were divided into seven groups including normal and diabetic control, the remaining were aqueous, aqueous:methanol (70:30), aqueous:methanol (50:50), aqueous: methanol (30:70), and methanol extracts given for 30 days. Serum levels of triglycerides, total cholesterol, LDL-cholesterol, HDL-cholesterol, ALT and AST were estimated by using commercially available kits. The oral administration of aqueous:methanol (70:30) extract of the *Dodonaea viscosa* leaves significantly ($P<0.01$) decreased the raised parameters (triglyceride, total cholesterol and LDL-cholesterol) to normal values. But the extract has significantly increased HDL-cholesterol, ALT and AST levels. For the aqueous:methanol (70:30) extract given animals**,** the average serum level of total cholesterol was 60.00±1.30 mg/dL, LDL-cholesterol was 92.80±2.29 mg/dL, HDL-cholesterol was 31.80±1.0 mg/dL and triglyceride was 15.40±0.75 mg/dL while the average serum levels of ALT and AST were 45.60±3.08 and 27.20±1.36 IU/dL, respectively. It is concluded from the study that aqueous:methanolic (70:30) extract of *Dodonaea viscosa* leaves exerts antihyperlipidemic and hepatoprotective effects in the alloxan-induced diabetic rabbits.

To Cite This Article: Ahmad M, Q Mahmood, K Gulzar, MS Akhtar, M Saleem and MI Qadir, 2012. Antihyperlipidemic and hepatoprotective activity of *Dodonaea viscosa* leaves extracts in alloxan-induced diabetic rabbits (*Oryctolagus cuniculus*). Pak Vet J, 32(1): 50-54.

INTRODUCTION

Drugs of natural origin are considered to be less toxic and free from adverse effects than synthetic ones. Even though active compounds of many herbal drugs were unknown, they have been widely prescribed by the practitioners of the traditional medicines due to their minimal adverse effects and low cost (Valiathan, 1998). The traditional system of medicines, Ayuardia, Siddha and Unani are based on the experience in the use of plant products in treatment of many diseases (Asolkar *el al.,* 1992). WHO has estimated that 4 billion people (80% of the world population) use herbal medicines for some aspect of primary healthcare. Alternative treatment for diabetes has become increasingly popular during the last several years including medicinal herbs and nutritional supplementation (Sinha *et al.,* 1996).

Dodonaea viscose (L.) locally known as *Sanatha* is an indigenous medicinal plant that has been used empirically since centuries as a hypoglycaemic agent in the ethnomedicinal practices (Ahmad *et al.,* 2006). The antidiabetic activity of *Dodonaea viscosa* leaves extracts has been recently confirmed (Muthukumran *et al.,* 2011). Hyperlipidemia is associated with diabetes (Wojtowicz *et al.,* 2004) and hepatotoxicity has emerged as a common clinical complication by antidiabetics (Chatila and West, 1996). However, as far as ascertained, no detailed scientific study seemed to have been carried out to assess the antihyperlipidemic and hepatoprotective activity of *Dodonaea viscose* in diabetic subjects. Therefore, the present study was conducted to determine the antihyperlipidemic and hepatoprotective activity of *Dodonaea viscosa* leaves extracts in the alloxan-diabetic rabbits.

MATERIALS AND METHODS

Plant material: Leaves of *Dodonaea viscosa* were collected from hilly areas of District Khoshab, Pakistan. *Dodonaea viscosa* leaves were identified in the Department of Biological Sciences, University of Sargodha, Sargodha, Pakistan. A voucher specimen has been kept for future reference. The leaves were completely dried under the shade and powdered finely with an herbal grinder. The powdered material was stored in well closed cellophane bags at 4ºC in the refrigerator before use.

Experimental animals: Healthy adult rabbits (*Oryctolagus cuniculus*) weighing 1-1.5 kg were kept at animal house of the Department of Pharmacy, University of Sargodha, Sargodha. The animal were housed in stainless cages under standard laboratory condition (light period: 8:00 am to 8:00 pm, 21±2°C, relative humidity 55%, green fodder and water were available ad libitum).

Chemicals: The chemicals used in the study include ALT and AST Kits (Fluitest, Biotechnologies AG, Germany; Triglyceride, Total cholesterol, LDL-cholesterol and HDL-cholesterol kits by Fluitest, Biotechnologies AG, Germany; Alloxan monohydrate by Research Organics, USA; Methanol by Merck Chemical Co., Germany; and Gum tragacanth by Hi-Media Lab, USA.

Preparation of *Dodonaea viscosa* leaves extracts: Aqueous, aqueous:methanol (70:30, 50:50, 30:70) and methanol extracts of *Dodonaea viscosa* leaves were prepared by cold maceration. All the extracts accept aqueous were dried with help of rotary evaporator. The water extract was dried by using lyophilizer.

Induction of experimental diabetes: Diabetes was induced in the subjects according to the methods used by Moorthy *et al.* (2010). Rabbits weighing 1-1.5 kg were made diabetic by injecting intravenous injection of 80 mg/kg of 10% alloxan monohydrate dissolved in isotonic saline (Takahashi, 1995). The control group only receives same volume of saline solution. Eight days after injecting the alloxan-monohydrate blood glucose level of surviving rabbits was determined by glucose-oxidase method. Rabbits with blood glucose level greater than 250 mg/dL were considered diabetic and were employed for further study.

Preparation and administration of drug suspensions: The amount of leaves extracts for each animals was calculated on body weight basis and triturated with about 10 ml of 2% aqueous gum tragacanth solution and the final volume was always made upto 20 ml. Then the suspension was administered orally to each animal by using a stomach tube and disposable syringe (Akhtar and Iqbal, 1991). Each rabbit was given 500 mg/kg of leaves extracts.

Study design: The rabbits were divided into seven groups of ten animals each. Group 1 and 2 served as untreated normal and diabetic control; and were administered orally 20 ml of 2% aqueous gum tragacanth solution continuously for 30 days. The remaining groups were administered aqueous, aqueous:methanol (70:30), aqueous: methanol (50:50), aqueous:methanol (30:70), and methanol *Dodonaea viscosa* leaves extracts (500 mg/kg OD) continuously for 30 days. After 30 days blood samples were collected for the study.

Estimation of antihyperlipidaemic effects: Serum levels of triglycerides, total cholesterol, LDL-cholesterol and HDL-cholesterol were estimated by using spectro-photometer. Estimation of serum lipids was done by the methods used by Qadir *et al*. (2008).

Triglycerides: Three Cuvettes were washed with distilled water and labeled as Blank, standard and sample. 20 µl distilled water, 20 µl standard and 20 µl sample, was pipetted in each cuvette respectively. Chromogen reagent, 2 ml was added to each cuvette. Contents of all the cuvettes were mixed thoroughly and incubated for 5 minutes at room temperature. The wavelength of spectrophotometer was set at 500 nm. Result command was given to spectrophotometer and after some time results were displayed. The blood triglycerides levels were calculated by applying the following formula.

$$\text{Triglycerides mg/dl} = \frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \times 200$$

Total Cholesterol: Three Cuvettes were washed with distilled water and labeled as blank, standard and sample. 20 µl distilled water, 20 µl standard and 20 µl sample was pipetted in each cuvette respectively. Chromogen reagent, 2 ml was added to each cuvette. Contents of all the cuvettes were mixed thoroughly and incubated for 5 minutes at 37°C. The wavelength of spectrophotometer was set at 500 nm. Result command was given to spectrophotometer and after some time results were displayed. The blood cholesterol levels were calculated by applying the following formula.

$$\text{Cholesterol mg/dl} = \frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \times 200$$

LDL-Cholesterol: For sample preparation; 100 µl samples and 1000 µl precipitant were placed in a tube. After through mixing the tube was allowed to stand for 15 minutes at room temperature and then was centrifuged at 1500 rpm for 15 minute. Supernatant was separated from the sediment and cholesterol was measured by the CHOD-PAP method. The LDL-cholesterol levels were calculated by applying the following formula.

LDL-cholesterol mg/dl = Total cholesterol – Cholesterol in supernatant.

HDL-Cholesterol: For sample preparation; 200 µl samples and 500 µl precipitant were placed in a tube. After through mixing the tube was allowed to stand for 10 minutes at room temperature and then was centrifuged at 4000 rpm for 10 minute. Supernatant was separated from the sediment and cholesterol was measured by the CHOD-PAP method.

Estimation of hepatoprotective effects: The most efficient screening tests for liver damage are serum alanine transaminase and aspartate transaminase (Theal and Scott, 1996).

Alanine transaminase (ALT): To 800µl of working reagent 50µl serum was added, mixed well and optical density (OD) was recorded.
Activity (U/L) = ΔOD/min. x 1746

Aspartate transaminase (AST): To 800µl of working reagent 50µl serum was added, mixed well and the change in optical density (ΔOD) per minute was recorded.
Activity (U/L) = ΔOD/min. x 1746

Statistical Analysis: Analysis of variance technique (completely randomized design) was applied to test the significance difference at 5% and 1% significance level. Duncan's multiple Range (DMR) test was applied to check the difference among means using Minitab (15) and Microsoft Excel (2003).

RESULTS

Antihyperlipidemic effects: Effects of *Dodonaea viscosa* leaves extracts on serum triglyceride, cholesterol, LDL-cholesterol and HDL-cholesterol (mg/dL±SEM) levels in alloxan-induced diabetic rabbits after 30 days of extract administration are given in Table 1. The serum levels of triglyceride (22.20 ± 1.53 mg/dL) and total cholesterol (71.60±1.97 mg/dL) of group 3 treated with aqueous extract were found to be significantly (P<0.05) lowered as compared to untreated alloxan-induced diabetic (group 2). Whereas, the serum level of HDL-cholesterol (29.00±1.30 mg/dL) of group 3 treated with aqueous extract were found to be significantly (P<0.05) increased as compared to untreated alloxan-induced diabetic. The serum levels of triglyceride (15.40±0.75 mg/dL), total cholesterol (60.00±1.30 mg/dL), and LDL-cholesterol (92.80±2.29 mg/dL) of group 4 treated with aqueous:methanol (70:30) extract were found to be significantly (P<0.01) lowered as compared to untreated alloxan-induced diabetic group 2. Whereas, the serum level of HDL-cholesterol (31.80±1.0 mg/dL) of group 4 treated with Aqueous:methanol (70:30) extract were found to be significantly (P<0.05) increased as compared to untreated alloxan-induced diabetic group 2. The serum level of HDL-cholesterol (34.40±3.89 mg/dL) of group 5 treated with Aqueous:methanol (50:50) extract were found to be significantly (P<0.005) increased as compared to untreated alloxan-induced diabetic group 2 (Table 1).

Hepatoprotective effects: Effects of *Dodonaea viscosa* leaves extract on serum ALT and AST levels in alloxan-induced diabetic rabbits after 30 days of extract administration are given in table 2. The serum levels of ALT (31.20±2.82 IU/dL) and AST (24.80±1.24 IU/dL) of group 3 treated with aqueous extract were found to be significantly (P<0.05) lowered as compared to untreated alloxan-induced diabetic group 2. The serum levels of ALT (45.60±3.08 IU/dL) and AST (27.20±1.36 IU/dL) of group 4 treated with aqueous:methanol (70:30) extract were found to be significantly (P<0.01) lowered as compared to untreated alloxan-induced diabetic group 2. The serum level of AST (32.17±4.31 IU/dL) of group 5 treated with Aqueous: methanol (50:50) extract were found to be significantly (P<0.005) decreased as compared to untreated alloxan-induced diabetic group 2.

DISCUSSION

Diabetes mellitus is one of the most common chronic disease and is associated with hyperlipidemia and co-morbidities such as obesity, hypertension. Hyperlipidemia is a metabolic complication of both clinical and experimental diabetes (Saravanan and Pari, 2005). Alloxan, a beta cytotoxin, induces "chemical diabetes" (alloxan diabetes) in a wide variety of animal species by damaging the insulin secreting pancreatic cell, resulting in a decrease in endogenous insulin release, which paves the ways for the decreased utilization of glucose by the tissues (Omamoto *et al.,* 1981).

Apart from the regulation of carbohydrate metabolism, insulin also plays an important role in the metabolism of lipids. Insulin is potent inhibitor of lipolysis. Since it inhibits the activity of the hormone sensitive lipases in adipose tissue and suppresses the release of free fatty acids (Loci *et al*., 1994). During diabetes, enhanced activity of this enzyme increases lipolysis and releases more free fatty acids in to the circulation (Agardh *et al*., 1999). Increased fatty acids concentration also increases the β-oxidation of fatty acids, producing more acetyl CoA and cholesterol during diabetes. In normal condition, insulin increases the receptor-mediated removal of LDL-cholesterol and decreased activity of insulin during diabetes causes hypercholestrolemia. Hypercholestrolemia and hypertri-glycridemia have been reported to occur in diabetic rats

Table 1: Effects of *Dodonaea viscosa* leaves extracts on serum triglyceride, cholesterol, LDL-cholesterol and HDL-cholesterol (mg/dL±SEM) levels in alloxan-induced diabetic rabbits after 30 days of extract administration.

Groups	Total cholesterol	LDL-Cholesterol	HDL-Cholesterol	Triglyceride
Normal control	67.40±1.29^{b}	79.40±2.58^{b}	33.80±1.53^{b}	19.80±0.86^{b}
Diabetic control	88.80±3.38^{a}	129.60±2.34^{a}	19.40±0.93^{a}	33.40±1.97^{a}
Aqueous extract	71.60±1.97^{b}	107.00±3.30^{ab}	29.00±1.30^{b}	22.20±1.53^{b}
Aqueous:methanol (70:30) extract	60.00±1.30^{c}	92.80±2.29^{c}	31.80±1.0^{b}	15.40±0.75^{c}
Aqueous:methanol (50:50) extract	80.18±2.13^{a}	120.15±1.14^{a}	34.40±3.89^{d}	28.40±2.98^{a}
Aqueous:methanol (30:70) extract	82.12±1.32^{a}	122.13±3.45^{a}	22.31±1.32^{a}	33.45±3.12^{a}
Methanol extract	90.22±2.22^{a}	119.23±4.64^{a}	18.22±4.22^{a}	35.90±1.12^{a}

Values bearing superscripts in the same column differ significant among the groups: (^{b}) = P<0.05, (^{c}) = P<0.0, (^{d}) = P<0.005 as compared to (^{a}).

Table 2: Effects of *Dodonaea viscosa* leaves extract on serum ALT and AST levels (IU/dL) in alloxan-induced diabetic rabbits after 30 days of extract administration.

Groups	ALT	AST
Normal control	31.20±2.82^{d}	24.80±1.24^{c}
Diabetic control	91.60±3.19^{a}	92.60±3.93^{a}
Aqueous extract	64.00±2.78^{b}	37.40±3.75^{b}
Aqueous:methanol (70:30) extract	45.60±3.08^{c}	27.20±1.36^{c}
Aqueous:methanol (50:50) extract	84.13±4.09^{a}	32.17±4.31^{c}
Aqueous:methanol (30:70) extract	87.43±1.34^{a}	72.60±2.13^{a}
Methanol extract	96.21±2.91^{a}	89.12±2.73^{a}

Values bearing superscripts in the same column differ significant among the groups: (^{b}) = P<0.05, (^{c}) = P<0.0, (^{d}) = P<0.005 as compared to (^{a}).

(Bopanna *et al.,* 1997). The increased concentration of cholesterol could result in a relative molecular ordering of the residual phospholipids resulting in a decrease in membrane fluidity (Dario *et al*., 1996). The increased concentration of free fatty acids in liver and kidney may be due to lipid breakdown and this may cause increased generation of NADPH, which results in the activation of NADPH dependent microsomal lipid peroxidation. Liver and kidney phospholipids were increased in diabetic control rats. Phospholipids is present in cell membrane and make up vast majority of the surface lipoprotein forming a lipid bilayer that acts as an interface with both polar plasma environment and non-polar lipoprotein of lipoprotein core (Cohn and Roth, 1996).

In alloxan-induced diabetic rabbits, hypercholesterol-emia and hypertriglyceridemia also occurs (Wojtowicz *et al.,* 2004). In our study a marked increase in cholesterol and triglyceride levels was observed in diabetic rabbits, which is in agreement with the above findings.

A significant hypolipidemic effect of the effective drug is desirable in the management of diabetes and its complications (Luc and Fruchart, 1991). In present study administration of aqueous extract of the *Dodonaea viscosa* leaves significantly ($P<0.05$) decreased the raised parameters (triglyceride, total cholesterol and LDL-cholesterol) to normal values. The aqueous extract of *Dodonaea viscosa* leaves, however, has significantly ($P<0.05$) increased HDL-cholesterol levels. This increase in HDL-cholesterol level is a positive sign as HDL-cholesterol is known as good cholesterol which has relation to diminish the cardiac problems. The administration of aqueous:methanol (70:30) extract of the *Dodonaea viscosa* leaves significantly ($P<0.01$) decreased the raised parameters (triglyceride, total cholesterol and LDL-cholesterol) to normal values. The aqueous: methanol (70:30) extract of *Dodonaea viscosa* leaves, however, has significantly ($P<0.05$) increased HDL-cholesterol levels. The other (aqueous:methanol 50:50, aqueous:methanol 30:70, methanol) extracts have no effect on serum levels of triglyceride, total cholesterol and LDL-cholesterol and HDL-cholesterol in diabetic rabbits except aqueous:methanol (50:50) extract which raise the HDL-cholesterol significantly ($P<0.005$). The observed antihyperlipidemic effect may be due to decreased cholesterogenesis and fatty acid synthesis exerted by the extract supplementation to alloxan-diabetic rabbits (Bopanna *et al.,* 1997).

Confirming the findings of Akhtar *et al*. (2009) and Ahmad *et al.* (2008), it has been observed that levels of ALT and AST were elevated in alloxan-induced diabetic rabbits. This effect may be due to cytotoxic effect of alloxan that results in leakage of enzymes from hepatic tissues which migrate to blood circulation (Stanely *et al.,* 1999). The administration of toxins, cirrhosis of liver, hepatitis, liver cancer and diabetes cause metabolic changes in the liver and result in increased serum AST and ALT levels (Chalsani *et al.,* 2004).

The administration of the aqueous and aqueous:methanolic (70:30) extract of *Dodonaea viscosa* leaves continuously to the animals for 30 days has significantly ($P<0.05$ and $P<0.01$ respectively) reduced the levels of these enzymes in treated rabbits. From these present findings, it is evident that aqueous:methanolic (70:30) extract of *Dodonaea viscosa* leaves have protected the adverse effects of lipid peroxide-mediated tissue damage in alloxan-induced diabetic rabbits. Thus the treatment with aqueous:methanolic (70:30) extract would be expected to also decrease the risk of hepatic failure, associated with the type-2 diabetic subjects.

The present study has thus duly supported the alleged medicinal use of the plant drug in the Eastern Traditional medicine and have scientifically described the antihyperlipidemic, hepatoprotective efficacy and safety of the aqueous: methanolic extract of *Dodonaea viscosa* leaves. It seems sufficient to proceed and to conduct further activity-oriented fractionation and isolation of active principle(s) studies on this abundantly available indigenous medicinal plant.

Conclusions

In view of the above discussion, it has become evident that aqueous:methanolic (70:30) extract of *Dodonaea viscosa* leaves has been observed to exert significant and consistent antihyperlipidemic and hepatoprotective effects in the alloxan-induced diabetic rabbits which also point out the presence of such active principle(s) which have the maximum solubility in aqueous:methanolic (70:30) solution. However, further studies would be essentially required to elucidate the exact mechanism(s) of antihyperlipidemic, and hepatoprotective activities of the aqueous: methanolic (70:30) extract of *Dodonaea viscosa* leaves and to establish its efficacy and safety for further clinical use.

Acknowledgment

Authors are thankful to Mr. Naeem Qaisar, Mr. Manzoor Qadir, Mr. Shafeeq-ur-Rehman and Mr. Zeeshan Haidar Kazmi from Department of Pharmacy, University of Sargodha, Sargodha, Pakistan, for their contribution to this work.

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