International Scholars Journals

International Journal of Medical Sociology and Anthropology Vol. 2 (4), pp. 001-005, April, 2012. Available online at www.internationalscholarsjournals.org © International Scholars Journals



*Full Length Research Paper*

# Effect of *Berberis aristata* on lipid profile and coagulation parameters

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Accepted 08 January, 2012

**Herbs have been a great source of natural substances used to treat and prevent several cardiovascular diseases such as hypertension, atherosclerosis, angina pectoris, arrhythmia etc. Blood lipid levels and coagulation parameters are probably the major determinant of the development of cardiovascular diseases, hence the present study has been specifically designed to investigate the effect of *Berberis aristata* on lipid profile and coagulation parameters after high cholesterol diet for 45 days. The study was conducted on healthy rabbits of either sex. Biochemical tests were performed at the completion of dosing, that is, on 30th day and again after 45 days. *Berberis Aristata* (25 mg/kg) revealed a significant reduction in serum cholesterol, triglycerides and low density lipoprotein levels; more over, there was an increase in thrombin and fibrinogen time; however studies on large number of animals and humans are required before reaching any conclusion.**

**Key words:** *Berberis aristata,* lipid profile, coagulation parameters.

## INTRODUCTION

The popularity of herbal drugs is increasing all over the world because of lesser side effects as compared to synthetic drugs (Srivastava et al., 2006). Historically, all medicinal preparations were derived from plants, whether in the form of plant parts, crude extracts and mixtures. Today, a substantial number of drugs developed from plants are active against a number of diseases.

*B. aristata* (Berberidaceae) is an important medicinal plant, also known as 'daruharidra', widely distributed between altitudinal ranges of 1,850 to 3,300 m over the Himalaya. It is a large deciduous shrub, about 1.8 to 3.6 m high with 10 to 20 cm stem diameter. Twigs are whitish or pale yellowish brown erect cylindrical, smooth and strongly striate. Leaves 3.8 to 10 × 1.5 to 3.3 cm, obovate or elliptic, entire or spinous-toothed, flowers are numerous and stalked while fruit is a small berry about 7 to 10 mm. The roots are thick, woody, yellowish brown, cylindrical, knotty and covered with a thin brittle bark (Ali et al., 2008).

Rasaut, which is a very valuable preparation, is obtained from this plant and are used for the treatment of diseases such as ophthalmic, jaundice and skin diseases. The bark of its root is a valuable medicine in intermittent and remittent fevers (Parmar and Kaushal, 1982). The extract of *B. aristata* (root) has strong potential to regulate glucose homeostasis through decreased gluconeo-genesis and oxidative stress (Singh and Kakkar, 2009). The fruits are also given as a cooling laxative to children (Parmar and Kaushal, 1982) and as a tonic remedy for liver and heart (Janbaz and Gilani, 2000). The principal activity of this plant is due to the presence of berberine, oxyacanthine, berbamine, and palmatine (Musumeci et al., 2003) among which berberine exhibits multiple pharmacological activities (Fang et al., 2004). It has febrifugal, hypotensive, immuno-stimulating, anti-inflammatory, antimicrobial (Musumeci et al., 2003), anti-protozoal, anticholinergic and antiarrhythmic activities. It also has antibacterial, antiamoebic, antifungal, anti-helminthic, leishmanicidal, tuberculostatic properties (Soffar et al., 2001) and some central nervous system activity as well (Kulkarni and Dhir, 2007). Bacteria related diarrhea, parasitic intestinal infections and ocular infections (conjunctivitis, trachoma) are the most prominent clinical uses of berberine (Musumeci et al., 2003). It has been reported that berberine exhibits local

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anesthetic, enzyme inhibitory, antipyretic and anti-amnesic activities (Vaidya, 2006).

Lipoprotein abnormalities are considered as a highly modifiable risk factor for cardiovascular disease (CVD) (Allen et al., 1996). Cholesterol and triglycerides are the most important plasma lipids, crucial for formation of cell membrane, synthesis of hormones and offer a source of free fatty acids (Feroz et al., 2011). Increase level of cholesterol and low density lipoprotein cholesterol (LDL-C) are usually promoted arteriosclerosis while HDL-C retard or prevent the development of arteriosclerosis (Odetola et al., 2004).

The coagulation system has been intended as a possible mechanism of thrombogenesis and atherosclerosis in patients with hyperlipidemia. While hyperlipidemia is a risk factor for ischemic heart disease, suggesting that hypercoagulability may perform a role in patients with hyperlipidemia (Aoki et al., 1997); therefore, the present study has been specifically designed to evaluate the effects of *B. aristata* on lipid profile and blood coagulation in hyperlipidemia induced rabbits.

## MATERIALS AND METHODS

### Animal selection

The present study was carried out on 14 healthy white rabbits of either sex weighing from 1100 to 1600 g. Animals were housed individually in cages, under controlled condition of temperature 23 ± 2°C and humidity, 50 to 60%. All animals were given green leafy diet and water regularly.

In the present study, rabbits were selected as experimental animals because of several reasons, that is, biochemical changes produced in rabbits are comparatively similar as observed in humans. Sufficient amount of blood samples can easily be obtained. Generally physiology of rabbits is similar to humans; rabbits are easily available, easy to handle and economical (Feroz et al., 2009, 2010, 2011; Qamar et al., 2011).

### *B. aristata* extract

Extract of *Berberis aristata* was obtained from Herbion Pakistan Private limited. The main constituent of *B. aristata* including berberine, oxyacanthine, berbamine and palmatine, among which berberine is the main constituent having important medicinal properties.

### Experimental design

All animals were equally divided into 2 groups, that is, control and treated. Apparent health of these animals was monitored during the conditioning period under the laboratory environment for a week before administration of drug particularly noticing loss of hair, color of hair, diarrhea, aggressive behavior, loss of activity and hematuria. Animals of both group received high cholesterol diet (HCD) on daily basis for a period of 45 days, that is, 0.125 g/kg cholesterol supplied by Merck in 0.5% corn oil. After 45 days, animals of treated group were administered *B. aristata* orally for period of 30 days in the dose of 25 mg/kg during the first phase of study, while animals of control group were administered normal saline through same route equivalent to the volume of respective doses according to their body weight. Body weights of the animals were measured weekly. During the second phase of study, animals of treated group were further administered *B. aristata* for 15 more days making a total period of 45 days and compared with control for the same period. Blood samples were collected thrice from the ear vein of animals, first after 45 days of HCD then again after 30 and 45 days dosing of *B. aristata*.

### Estimation of lipid profile

Blood sample of about 5 ml were collected in gel tube. Serum was immediately separated out by centrifugation at 3000 rpm for 15 min in 14K Humax centrifuge. Lipid profile were analyzed on Humalyzer 3000 (semi-automatic chemistry analyzer, Model # 16700) (Human Germany) using standard kits supplied by Human. Cholesterol and low density lipoprotein cholesterol (LDL-C) was estimated by CHOD-PAP method; triglyceride by GPO-PAP methods (Trinder, 1969), and high density lipoprotein cholesterol (HDL-C) by the method of Friedewald et al. (1972).

### Estimation of coagulation parameters

Blood sample of about 3 ml were collected in coagulation tubes containing 3.2% sodium citrate. Plasma was separated by centrifugation at 3000 rpm for 15 min in 14 K Humax centrifuge. Thrombin time (TT), prothrombin time (PT), activated partial thromboplastin time (aPTT) and fibrinogen were measured by Humaclot duo, using standard reagent kits supplied by Human (Chan et al., 2007).

### Gross toxicities

The gross toxicities were observed on weekly basis during administration of *B. aristata* for a period of 45 days.

### Mortality rate

Mortality rates were observed in animals receiving HCD and *B. aristata* during the total period of experiment. The number of animals died during these intervals was also noted.

### Statistical analysis

All values were compared with the control by taking mean and standard error to the mean by using student t-test. Values of $P<0.05$ were considered as significant and $P<0.01$ as highly significant. All statistical procedures were performed according to the method of Alcaraz and Jimenez (1989).

## RESULTS

### Gross toxicities

No gross toxicities were observed in any group of animals during the total period of experiment.

### Mortality rate

Table 1 reveals the comparison of mortality rate in animals

**Table 1.** Overall percentage mortality rate comparison table.

| Animal group | Mortality rate (%) |
|---|---|
| Control | 0/7 (00.00) |
| High cholesterol diet | 0/7 (00.00) |
| *B. aristata* | 0/7 (00.00) |

Mortality rate = No. of animals expired / Total animals (percentage).

**Table 2.** Effects of *B. aristata* on lipid profile after 30 days.

| Animal group | Parameter (mg/dl) | | | |
|---|---|---|---|---|
| | Cholesterol | Triglyceride | HDL-C | LDL-C |
| Control | 132.4 ± 22 | 234.0 ± 17 | 4.49 ± 0.75 | 176.7 ± 7.4 |
| *B. aristata* | *64.4 ± 7.6 | *164.7 ± 18 | *2.14 ± 0.26 | **88.1± 7.9 |

n = 7; Average value ± S.E.M; *P < 0.05 significant as compared to control; **P <0.01 highly significant as compared to control.

**Table 3.** Effects of *B. aristata* on lipid profile after 45 days.

| Animal group | Parameters (mg/dl) | | | |
|---|---|---|---|---|
| | Cholesterol | Triglyceride | HDL-C | LDL-C |
| Control | 85.2 ± 18 | 115.4 ± 17 | 1.743 ± 0.16 | 141.4 ± 12 |
| *B. aristata* | 36.14 ± 3.2* | 47.4 ± 7.6** | 1.814 ± 0.12 | 55.66 ± 1.5** |

n = 7; Average value ± S.E.M; *P < 0.05 significant as compared to control; **P <0.01 highly significant as compared to control.

animals of control group; animals received HCD and *B. aristata* for a period of 45 days. No death was observed in the animals of control group and other groups.

## Lipid profile

Table 2 reveals the comparison of cholesterol, triglyceride, HDL-C and LDL-C in animals of control group and animals given *B. aristata* in the dose of 25 mg/kg after 30 days while a similar comparison between the same groups of animals after 45 days is presented in Table 3.

Animals given *B. aristata* in a dose of 25 mg/kg for a period of 30 days showed highly significant decrease in LDL-C level, that is, 88.1 ± 7.9 mg/dl as compared to control, that is, 176.7 ± 7.4 mg/dl, while cholesterol, triglycerides, and HDL-C were significantly decrease to 64.4 ± 7.6, 164.7 ± 18 and 2.14 ± 0.26 mg/dl in comparison to control values, that is, 132.4 ± 22, 234.0 ± 17 and 4.49 ± 0.75 mg/dl, respectively.

Animals received *B. aristata* in a dose of 25 mg/kg for a period of 45 days showed highly significant decrease in the levels of triglycerides and LDL-C, that is, 47.4 ± 7.6 and 55.66 ± 1.5 mg/dl in comparison to control values, that is, 115.4 ± 17 and 141.4 ± 12 mg/dl, while cholesterol was significantly decreased to 36.14 ± 3.2 mg/dl as compared to control, 85.2 ± 18 mg/dl. However, there was insignificant increase in the level of HDL-C, 1.814 ± 0.12 mg/dl as compared to control values, 1.743 ± 0.16 mg/dl.

## Coagulation parameters

Table 4 reveals the comparison of TT, PT, aPTT and fibrinogen time in animals of control group and animals given *B. aristata* in the dose of 25 mg/kg after 30 days while a similar comparison between the same groups of animals after 45 days is presented in Table 5.

Animals given *B. aristata* in the dose of 25mg/kg for a period of 30 days showed highly significant increase in TT and fibrinogen time, that is, 35.70 ± 2.1 and 57.6 ± 7.4 s in comparison to control animals, that is, 17.84 ± 1.7 and 26.01 ± 2.9 s. However, there was no significant change in PT and aPTT as compared to control.

Animals administered *B. aristata* in the dose of 25 mg/kg for a period of 45 days showed highly significant and significant increase in TT and fibrinogen time, that is, 35.59 ± 1.8 and 52.2 ± 8.4 s as compared to control, that

**Table 4.** Effects of *B. aristata* on blood coagulation after 30 days.

| Animal group | Parameter (s) | | | |
|---|---|---|---|---|
| | TT | PT | aPTT | Fibrinogen |
| Control | 17.84 ± 1.7 | 7.11 ± 0.60 | 30.5 ± 6.2 | 26.01 ± 2.9 |
| *B.aristata* | **35.70 ± 2.1 | 7.64 ± 0.80 | 31.26 ± 3.6 | **57.6 ± 7.4 |

n = 7; Average value ± S.E.M; *P < 0.05 significant as compared to control; **P <0.01 highly significant as compared to control.

**Table 5.** Effects of *B. aristata* on blood coagulation after 45 days.

| Animal group | Parameter (s) | | | |
|---|---|---|---|---|
| | TT | PT | aPTT | Fibrinogen |
| Control | 16.56 ± 1.4 | 5.871 ± 0.22 | 33.04 ± 3.5 | 26.41 ± 2.3 |
| *B.aristata* | 35.59 ± 1.8** | 5.300 ± 0.12* | 29.3 ± 4.1 | 52.2 ± 8.4* |

n = 7; Average value±S.E.M; *P < 0.05 significant as compared to control; **P <0.01 highly significant as compared to control.

is, 16.56 ± 1.4 and 26.41 ± 2.3 s, while PT was significantly decreased to 5.300 ± 0.12 s as compared to control 5.871 ± 0.22 s. However there was no significant change in aPTT as compared to control.

## DISCUSSION

Herbal medicines have been known to self- prescribed by the patients for health maintenance and treatment of minor ailment and chronic illnesses (Aziz and Tey, 2009). A large and increasing number of patients use medicinal herbs; therefore, physicians should be aware of the benefits, risks and uncertainties of popular medicinal herbs (O'Hara et al., 1998).

There is a strong correlation between blood lipids and coagulation parameters. Hence alterations in lipid levels influence thrombosis by modifying the activity of coagulation proteins, platelets, and fibrinolytic factors (Eitzman et al., 2000).

Tables 2 and 3 reveal the effect of *B. aristata* on lipid profile after HCD. *B. aristata* at the dose of 25 mg/kg revealed a significant reduction in serum cholesterol, triglycerides and LDL-C. High plasma concentrations of cholesterol, particularly LDL-C, are one of the principal risk factors for atherosclerosis (Ross, 1999). There has been a correlation among increased LDL-C and atherosclerosis; since LDL- C gets deposited in the walls of the blood vessel forming atherosclerotic plaque. There are studies which recommend that lowering LDL-C reduces the risk of coronary heart disease (Aghasadeghi et al., 2008). The hypolipidemic effects of *B. aristata* may be due to the presence of berberine alkaloid, since berberine act at both endothelium and the underlying vascular smooth muscle to induce relaxation. Its vasorelaxant and antiproliferative effects may contribute to a long-term benefit of berberine in the vascular system (Ko et al., 2000) and could play a major role in the management of metabolic diseases associated with high CVD risk (Cicero and Ertek, 2009). There was also a significant decrease in the level of HDL- C level after 30 days, which may be due to infection and inflammation in general, while due to any disease state in particular (Deniz et al., 2006).

The process of blood coagulation is a very complex cascade of chemical reaction and plays an important role in an organism's response to vascular injury on one hand, while thrombosis or CVD on the other hand (Orfao et al., 2008).

Tables 4 and 5 reveal the effect of *B. aristata* on coagulation parameters such as TT, PT, aPTT and fibrinogen after HCD. Present study revealed highly significant increase in TT after 30 and 45 days at 25 mg/kg dose of *B. aristata* that indicates deficiency of fibrinogen or inhibition of thrombin (Lane et al., 2005). Hence prolonged TT may be the results of reduced activity of coagulation factors because some factors such as IX and X (Di Cera, 2008) XI and XII are essentially required for thrombin generation (Gailani and Renne, 2007).

The present study also reveals significant increase in fibrinogen time, that is, decreased fibrinogen level. There is evidence that increased plasma fibrinogen level has been recognized as an independent risk factor for vascular diseases (Chan et al., 2007); hence *B. aristata* reduces the risk of vascular diseases by decreasing the fibrinogen level. On the other hand there was significant decrease in prothrombin time which may be due to the increase production in coagulation factors such as V, VII and X, since prolonged PT indicates deficiency in these

coagulation factors (Chan et al., 2007).

In the present study, there is significant decrease in cholesterol, triglyceride and LDL-C at the same time there is increase in TT and fibrinogen time indicating the probable decrease in the risk of atherosclerosis. Hence there are links between lipids and the haemostatic mechanisms which affect atherosclerotic, vasomotor and thrombotic components of ischemic heart disease. Lipid lowering treatment with statins stabilizes atheromatous plaque and has antithrombotic effects (Tousoulis et al., 2002) which might be *B. aristata* producing its effects in similar manner.

## Conclusion

The present study was conducted to evaluate the effects of *B. aristata* on lipid profile and coagulation parameters. The overall results of the study reveal *B. aristata* in the dose of 25 mg/kg has hypolipidemic effects and has some influence on blood coagulation which may be of value in cardiovascular diseases.

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