Effect of *Peganum harmala* L. on Lipid parameters in hypercholesterolemia-induced male Wistar Rat.

*Accepted 3rd March, 2014*

**ABSTRACT**

Concentration of cholesterol and other lipids in human diet has been considered as an issue of public health. In the present study the effects of methanolic extract of *Peganum harmala* L. on serum lipid profile of rat were investigated in a 28-days feeding trial. Total of 48 rats (180±15) were divided into six groups: (control Hypercholesterolemia, control normal, controls normal with 8.11 mg/ml extract and controls hypercholesterolemia with 8.11 mg/ml extract) that were 4 weeks of feeding of high lipid and oil. Feeding, water and extract of *P. harmala* were provided *ad libitum*. At the end of 28 days, the blood samples for serum lipid profile were collected and determined. Serum samples were analyzed for total cholesterol, high density (HDL), low density lipoprotein (LDL) and triglycerides. Total cholesterol and LDL showed gradual significant decrease dose levels of *P. harmala* to 8 and 11 mg/ml which was significantly (P<0.05) reduced by methanolic extract of *P. harmala* and was the lowest in group ctrl+8 and 11 mg/ml. The same group had the highest (P<0.05) gross return compared to other treatments. It is concluded that methanolic extract of *P. harmala* (11 mg/ml) could be effectively used in rat to optimize serum lipid profile.

**Key words:** *Peganum harmala* L, lipid parameters, hypercholesterolemia, rat.

**INTRODUCTION**

Hypercholesterolemia is a problem faced by many societies and is a cause of concern for health professionals, since it constitutes one of the major risk factors for the development of cardiovascular diseases, such as atherosclerosis and its complications, acute infarction of the myocardium or hypertension (Gomes et al., 1998). In addition, there is a close correlation between these diseases and lipid abnormalities, especially high level of plasma cholesterol, and blood pressure (Mahan et al., 1998).

Medicinal plants have been used for centuries as remedies for human and animal ailments. They have many pharmacologically active chemical compounds (Chaturvedi et al., 2009), antibacterial (Shahi et al., 2012) and antifungal (Rosinai et al., 2009) agents. *Peganum harmala* belong is to the family of Zygophyllaceae and have been shown to possess a diverse range of medicinal properties. Numerous betacarboline alkaloids like harmaline, harmine, harmalol and harmol were present in *P. harmala* extract (Herraizi et al., 2010). *P. harmala* extract exhibited great variety of pharmacological and biological activities such as antibacterial and antifungal agents as well as monoamineoxidase (MAO) inhibition and hypothermia. Similarly analgesic, anti-inflammatory (Monsefi et al., 2004), disinfectant (Shahverdii et al., 2005), growth promoting (Qazan et al., 2005), cholesterol lowering and hepatoprotective effects (Hamdani et al., 2008) have also been reported. Present study was designed to examine the potential benefits of methanolic extract of *P. harmala* research article in terms of reducing serum cholesterol level Protective effects of *P. hamala* L. extract harmine and harmaline against human low density lipoprotein oxidation and also its analgesic effect were studied (Sharafet al., 1997). In modern medicine, plants play a significant role since they possess various therapeutically important
compounds having minimum side effects. Several researchers studied the anti oxidative actions of isolated molecules such as proteins from medicinal plants against hepato toxicity induced by toxins (such as thioacetamide and chloroform) (Gobel, 1841). This plant is used in traditional medicine as an imintic, lactagogue, antispasmodic, antipyretic, abortifacient, emetic (Kirtikar and Basu, 1935), anticancerous, antiviral (Al-Allaf, 1999) and anti-hypertensive agent. Hallucinogenesis (Verdian Rizi, 2007) and central monoamine oxidase inhibition effect (Fuller, 1986) such as binding to various receptors including 5-HT receptors and the benzodiazepine-binding site of GABAA receptors (Chuen-Chao, 2001) have been reported also. The principal compounds of this plant are carboline alkaloids such as harmine, harmaline, harmalol, harman, vasicine and vasicinon (Monsef, 2004). However, it has been reported that P. harmala contains some flavonoids (Sharaf, 1997). P. harmala alkaloids have a wide spectrum of pharmacological action including platelet aggregation inhibition (Saeed, 1993), mono amine oxidase inhibition, anxiolytic and behavioral effects, and immune modulator influences (Wang, 1996). There were some reports concerning the cardio vascular actions of harmala alkaloids such as harmine, harmaline and harmalol that reduced systemic arterial blood pressure and total peripheral vascular resistance (Wang, 1997). Previously, we reported the vasorelaxant effect of a methanolic extract of P. harmala seeds, harmine and harmaline (Berrougui, 2005; Tse, 1991), which alkaloids contained in P. harmala showed an antioxidant activity when using harman in hepatic microsomal preparations. However, the antioxidant effect of the major compounds of this plant (harmine and harmaline) and related extracts have not been investigated thoroughly.

MATERIALS AND METHODS

Animals and experimental design

The experiment was conducted on 48 male Wistar rats each weighing approximately 180 g which were obtained from ACECR, Qom, Iran. Animals were divided into six groups in a controlled environment with 12 h light and dark cycles, they were fed with feeds of high lipid, oil content and water ad libitum for 4 weeks. The Control normal was fed a standard diet, and Control hyper-cholesteremia was fed high oil and extract of P. harmala with concentration of 8 and 11 mg/ml on water ad libitum for 4 weeks. The water and extract was replaced every day.

Methanolic extraction of P. harmala

P. harmala were collected in the month of May 2011 from desert of Qom city (Figure 1). To obtain methanolic extract, 1 kg ground was immersed in 3 L 80% (v/v) aqueous methanol at room temperature for five days and filtered through Whatman Filter Paper (No.42). Extraction was performed Barij Esans (Golkaran co.), kashan City. The extract was then transferred to a glass bottle and stored in refrigerator before use.

Animal toxicity

All parts of plant are thought to be toxic (Budavari and O’Neil, 1996). All domesticated animals are susceptible to poisoning from P. harmala, camels especially young animals are the most affected in dry seasons (El-Bahri and Chemli, 1991). There are reports of sever intoxication in cattle donkeys (Bailey, 1979), sheep and horses (Bailey, 1981). Digestive and nervous syndromes have been reported in animals that consume a sub-lethal amount of the plant (Bellil, 1983). The animal initially becomes prostrate and then anorexia, hyper-salivation, vomiting and diarrhea occur. Usually, the nervous syndromes are predominant: the first signs are excitability followed by muscular trembling and stiffness, an uneasy staggering gait, and goes recumbency quickly. The animal appears in a narcotic state interrupted by occasional short periods of excitement. After a few hours, dyspnea and mydriasis are noted. Frequent urination and subnormal temperature has also been reported in cattle (Bellil, 1983). Abortion frequently occurs. The course of the nervous syndrome is usually short and death follows within 30-36 h after the onset of signs of CNS.
intoxication. The chronic intoxication of cattle is characterized by anorexia, restlessness, weakness of the hind limbs and knocking of the fetlock joint. In postmortem examination of the animal, no distinctive lesion is observed. Rapid rigor mortis has been noted. The heart, pulmonary, renal and gastrointestinal systems are reported to be congested and sub-capsular hemorrhage in the liver has been observed (Bailey, 1979).

**Human toxicity**

While this plant has traditionally been used in Bedouin medicine as an emmenagogue and as abortifacient agent (Casey, 1960; Boulus, 1983) there are few reports on its human toxic effects and syndrome (Salah et al, 1986). A case of overdose with *P. harmala* was reported in a young lady (aged 27 years) who has taken 50 g of seeds of this plant for the treatment of amenorrhea. Few minutes after ingestion of seeds in a cup of coffee, signs of intoxication were obtained with *P. harmala* over dose comprised of hallucinations and neurosensorial syndromes, bradycardia and GI disturbances such as nausea and vomiting. But we used the flowering season of the plant and because its toxicity effects and of their seeds is at minimum.

**Assay kits and biochemical determinations**

The assay kits for cholesterol, HDL-C, LDL-C, triglycerides were obtained from ACECR Laboratories Ltd. Infertility Center, Qom city, Iran. They were measured with enzymatic Trinder kits (Pars Azmoon, IRAN). The VLDL- and LDL-cholesterol concentrations were calculated from the Friede Wald equation:

\[
\text{LDL-Cholesterol} = \text{Total cholesterol} - (\text{HDL-cholesterol} + \text{VLDL-cholesterol}),
\]

and VLDL cholesterol= Triglycerides/5, according to the manufacturer’s instructions (Figure 2).

**Statistical analysis**

Data were expressed as mean ± standard deviation. In order to compare the groups, analysis of variance (ANOVA) was used. *P*< 0.05 values were considered to be statistically significant.

**RESULTS**

**High density lipoprotein (HDL) cholesterol**

Significant differences (*P*<0.05) were recorded between the control group and treated groups as well as among the treated groups at all recorded stages. The effect of different levels of *P. Harmala* methanolic extract on serum HDL in rat is presented in Table 1. There was gradual increase in the HDL level with increasing level of *P. harmala* at all recorded stages in all groups. However, other medicinal plant shave been explored for their HDL increasing potential.

**Low density lipoprotein (LDL) cholesterol**

*P. harmala* methanolic extract had a significant influence on
altering low density lipoprotein (LDL) cholesterol level of rat as examined in present study; this is shown in Table 1. To our knowledge, no such data has been reported regarding effects of *P. harmala* on LDL cholesterol, however, effect of other medicinal plants has been reported for LDL decreasing potentials (Manan, 2012).

**DISCUSSION**

The effects of different levels of *P. harmala* methanolic extract on total cholesterol were presented in Table 1. Decrease in total cholesterol by *P. harmala* might be due to the inhibition of 3-hydroxy-3-methyl-glutaryl-CoA (HMGCoA) reductase by different alkaloids harmine, harmaline, and harmol present in *P. harmala*. These alkaloids have also been reported to have hypoglycemic properties (Singh et al., 2008). *P. harmala* has antioxidant properties (Jinous and Fereshteh, 2012) which reduces LDL oxidation, thereby reducing total cholesterol content (Abaza, 2001) as reported in 26-31% reduction of serum cholesterol when supplemented with *Trigonella foenumgraecum* on mice (Anuja et al., 2012). When fed with an aqueous extract of *Stevia rebaudiana*, *Momordica charantia*, *Tamarindus indica* and *Gymnema sylvestre*, *Allium sativum* and *Murraya koenigii* rats and observed decreased serum cholesterol level. The mechanism and efficacy of diverse medicinal herbs to reduce serum cholesterol level might be due to the presence of different levels and types of alkaloid.

It was concluded from the results of the study that total cholesterol, triglycerides and LDL cholesterol showed gradual significant decrease with the increasing dosage level of *P. harmala* up to 250 mg/L in drinking water, while HDL cholesterol showed significant increase with increasing level of *P. harmala*. Symptoms of *P. harmala* toxicity experienced by our patient were similar to what had been reported for animals (El-Bahri and Chemli, 1991) and in French case (Salah et al., 1986). These mainly consist of neurosensorial symptoms, hallucination, slight elevation of body temperature (Abdel-Fattah et al., 1996) and cardiovascular disorder such as bradycardia and low blood pressure (Aarons et al., 1977). However, despite animal intoxication both in French (Salah, 1986) and our cases, signs and symptoms of intoxication relieved in few hours and patients left the hospital in good health. This difference was probably due to the amount, which has been consumed by humans compared to hungry animals. However, since this material traditionally has been used as an abortifacient agent in the Middle East (Shapira et al., 1989; Gupta et al., 1978), therefore the physicians working in this region must be familiar with the signs and symptoms of its toxicity to be able to deal with the emergencies, which may arise from its illegal consumption.

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Cite this article as:  
parameters in hypercholesterolemia-induced male Wistar Rat. 2(5): 074-078.

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