ORIGINAL RESEARCH ARTICLE EXPERIMENTAL

The hypolipidemic activity of Ayurvedic medicine, *Arogyavardhini vati* in Triton WR-1339-induced hyperlipidemic rats: A comparison with fenofibrate

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ABSTRACT

Background: Hyperlipidemia is a major risk factor of coronary heart disease. Currently available hypolipidemic drugs have been associated with number of side effects. *Arogyavardhini vati*, an Ayurvedic polyherbal formulation has been used for liver disorders. Therefore, present study was designed to evaluate the effect of *Arogyavardhini vati* in Triton WR-1339-induced hyperlipidemia in rats. **Objectives:** Anti-hyperlipidemic activity evaluation of *Arogyavardhini vati* against Triton WR-1339-induced hyperlipidemia in rats. **Materials and Methods:** Overnight fasted male Wistar rats (150-200 g) were randomly divided into normal control group [4% Dimethyl Sulfoxide (DMSO), i.p.], positive control group (Triton WR-1339 in 4% DMSO, 400 mg/kg, i.p.), standard drug treated (fenofibrate 65 mg/kg, p.o. for 7 days after inducing hyperlipidemia) and *Arogyavardhini vati* treated (50, 100, 200 mg/kg, p.o. for 7 days after inducing hyperlipidemia). Rat doses were calculated by extrapolating the equivalent human dose (therapeutic dose, sub-maximum, and maximum dose). Serum total cholesterol, triglyceride, low-density lipoprotein (LDL), high-density lipoprotein HDL, liver malondialdehyde (MDA), and glutathione (GSH) levels were estimated at end of experiments. **Results:** *Arogyavardhini vati* significantly decreased serum cholesterol, triglyceride, LDL, and C-reactive protein (CRP) and significantly increased serum HDL in a dose-dependent manner. Decreased MDA and increased GSH levels in liver were observed at all doses of *Arogyavardhini vati* (50, 100, 200 mg/kg) and fenofibrate-treated groups when compared with Triton-treated group. Atherogenic Index (AI) level was significantly decreased in fenofibrate and *Arogyavardhini vati* (200 mg/kg) treated rats when compared with normal control. **Conclusion:** *Arogyavardhini vati*, a traditionally used Ayurvedic medicine may be a useful therapy for hypercholesterolemia through reducing oxidative stress (decreasing MDA and increasing GSH) and lipid levels.

Key words: *Arogyavardhini vati*, atherogenic index, hypolipidemia, oxidative stress, Triton WR-1339

INTRODUCTION

The scourge of cardiovascular diseases (CVDs) is the most prevalent cause of death.[1] According to National Commission on Macroeconomics and Health (NCMH), a Government of India undertaking, there would be around 62 million patients with coronary artery disease (CAD) by 2015 in India and of these, 23 million would be patients younger than 40 years of age.[2] CAD is due to atherosclerosis of large- and medium-sized arteries, and dyslipidemia has been found to be one of the most important contributing factors [National Cholesterol Education Program, The Adult Treatment Panel III (NCEP, ATP III)]. During the past three decades, dyslipidemia as a risk factor for CVD has increased markedly in India.[3]

Currently available hypolipidemic drugs (statins) have been associated with a number of side effects.[4] Patients on treatment with crystalline niacin or extended-release niacin showed significant elevation in ALT and risk of hepatotoxicity is much greater with slow-release niacin.[5] Increases in plasma creatinine from 15% to 20% are common in fibrate-treated patients and more significant increases can occur in patients with underlying renal disease.[6,7] Hence, there has been pursuit for new

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safe and effective drug for dyslipidemia. Herbs have been used as a food and for medicinal purpose for centuries. Research interest has focused on various herbs that possess hypolipidemic effect that may be helpful adjunct in reducing the risks of CVD. *Arogyavardhini vati* is a polyherbal formulation mentioned in Ayurvedic formulary of India.[8] It has been used for centuries with claimed efficacy and safety in treatment of jaundice, liver disorders and various skin disorders. It consists *Picrorrhiza kurroa* (Kutki), *Terminalia chebula* (Haritaki), *Terminalia bellerica* (Bibhitaka), *Emblica officinalis* (Amalaki), *Asphaltum* (Silajatu), *Commiphora wightii* (Guggulu), *Ricinus communis* (Eranda), *Azadirachta indica* (Neem leaves) and metal including *suddh rasa* (detoxified mercury), *Gandhaka suddha* (detoxified sulfur), *Lauha-bhasma* (iron), *abhraka bhasma* (mica), *tamra bhasma* (copper). Safety of *Arogyavrdhini vati* has been evaluated by Kumar *et al*. The findings of the study showed that *Arogyavardhini vati* in the doses equivalent to 10 times of the human dose, administered to rats for 28 days, do not have appreciable toxicological effects on brain, liver, and kidney.[9]

Endothelial dysfunction plays a vital role in triggering ischemic events in the development of CVD. Lipid peroxidation represents an early step of endothelial dysfunction. C-reactive protein (CRP), an acute phase protein, has been clinically used as a sensitive marker for systemic inflammation.[10] Therapies have been developed to lower hs-CRP concentrations and reduce the potential risk factor for CVDs.[11-13] There are plethora of clinical and experimental studies showing that antioxidants such as vitamin E have been shown to reduce the oxidative susceptibility of lipoproteins and may have anti-atherosclerotic effects.[14-16] In hypercholesterolemic animal models, vitamin E increased resistance to lipoprotein oxidation and preserved normal endothelial function.[17] Epidemiologic studies also indicate an inverse association between the intake of vitamin E and coronary heart disease.[18,19]

Hence, considering the antioxidant, anti-inflammatory and hypolipidemic property, the present study was designed to study the effect of *Arogyavardhini vati* in Triton WR-1339-induced hyperlipidemia in rats.

MATERIALS AND METHODS

Experimental animal

Male Wistar rats (150-200 g) were used in the present study. The animals were obtained from the Central Animal Facility, All India Institute of Medical Sciences, New Delhi and stock bred in the departmental animal house. The rats were group-housed in polyacrylic cages (38 × 23 × 10 cm) with not more than four animals per cage and maintained under standard laboratory conditions with natural dark and light cycle. They were allowed free access to standard dry diet (Ashirwad, Punjab, India) and tap water *ad-libitum*. All experimental procedures described were reviewed and approved by the Institutional Animal Ethics Committee, All India Institute of Medical Sciences, New Delhi India (497/IAEC/09).

Drugs preparation and duration of treatment

Arogyavardhini vati was purchased from the GMP certified company (Maharshi Ayurveda Pharmaceutical Limited, New Delhi, India). Single batch of the drug was used in entire study duration (Batch No. AVV 013, Date of manufacturing: November 2009). Drug was prepared according the Ayurvedic literature and Ayurvedic pharmacopeia standards were followed. Drug was crushed, powdered, and dissolved in distilled water. Triton WR-1339 was purchased from Sigma-Aldrcih (St. Louis, MO, USA) and dissolved in DMSO. Fenofibrate tablet was purchased from market (Intra Lab India Pvt. Ltd, Bangalore, India).

Experimental design

Overnight fasted rats were randomly divided into six groups of six animals each. The first group was given standard pellet diet, water and administered intraperitoneal injection of 4% DMSO. The second hyperlipidemic group received Triton WR-1339 dissolved in 4% DMSO (400 mg/kg body weight). After 72 h of Triton injection, this group received a daily dose of 4% DMSO (p.o.) for 7 days. Third group was administered with the standard fenofibrate (65 mg/kg, p.o.) for 7 days. The fourth, fifth, and sixth group was administered daily doses of *Arogyavrdhini vati* (50, 100, 200 mg/kg, p.o.) for 7 days, after inducing hyperlipidemia. Human dose of *Arogyavardini vati* is 500-2000 mg per day. Human equivalent rat dose of 500, 1000, and 2000 mg will be 50, 100, and 200 mg/kg (human to rat dose conversion factor is 6 and average human body weight is 60 kg). The doses of *Arogyavardhini vati* (50, 100, 200 mg/kg) in rat was calculated by extrapolating the equivalent human dose (therapeutic dose, sub-maximum, and maximum dose) and was administered orally between 10 and 11 a.m. daily for 7 days, in a volume not exceeding 1 ml/100 g rat weight. After 12 h of treatment, animals were anesthetized with diethyl ether and blood was withdrawn from retro-orbital sinus. The blood samples were immediately centrifuged (3000 rpm for 10 min) and serum was used to estimate the levels of total cholesterol, triglyceride, LDL, and HDL using semi-auto analyzer (Mini Techno, Newark, DE 19711, USA) according to the instruction of manufacturer of assay kits (Logitech India Pvt. Ltd., Delhi, India). The level of serum CRP was estimated by ELISA, according to the instruction of manufacturer of assay kits (Life Diagnostics Inc., Mill Valley, CA 94941, USA;

Catalog number: 2210-21-HR). Cardiac risk was determined by estimating its atherogenic index (AI = TC/HDL-C) as stated by Malaspina.[20] Animals were euthanized and liver was removed to determine the levels of MDA and GSH.

Measurements of MDA and GSH levels in liver

Malondialdehyde, an indicator of lipid peroxidation was determined by the method of Ohkawa *et al*.[21] The concentration was expressed in nmol/g-wet tissue. Glutathione was measured according to the method of Ellman and concentration was expressed as mg/g-wet tissue.[22]

Statistical analysis

Data are expressed as mean ± standard error of the mean (SEM). A one-way analysis of variance (ANOVA), followed by Tukey's test was used for statistical analysis. SPSS (version 16) statistical software was used for the analysis of data and $P < 0.05$ was taken as the level of significance.

RESULTS

Effect of *Arogyavardhini vati* in Triton WR-1339-induced dyslipidemia on rat's serum lipid levels

The serum total cholesterol, triglycerides, LDL, and HDL levels were measured in normal and Triton WR-1339-induced rats [Table 1]. There was significant increase in serum total cholesterol, triglycerides, and LDL levels and decreased HDL levels in Triton-induced hyperlipidemic rats. Administration of Arogyavardhini vati at doses of 50, 100, 200 mg/kg and standard drug fenofibrate (65 mg/kg) significantly decreased serum total cholesterol, triglycerides, and LDL, and increased HDL when compared with Triton-induced hyperlipidemic rats ($P < 0.001$). There were no statistically significant differences in the level of serum total cholesterol, triglycerides, LDL, and HDL in fenofibrate-treated rats as well as normal control rats.

Effect of *Arogyavardhini vati* in Triton WR-1339-induced dyslipidemia on rat's serum C-reactive protein levels

CRP level was increased in Triton-treated rats. Fenofibrate (65 mg/kg) treated rats showed significant decrease in CRP levels when compared with Triton-treated rats; however levels were raised when compared with normal control. There was no significant change in the level of CRP at low dose of *Arogyavardhini vati* (50 mg/kg) when compared with Triton- treated rats. However, significant decrease in the level of CRP was observed at higher doses (100 and 200 mg/kg) of *Arogyavardhini vati* ($P < 0.001$). There was no statistical significant difference in the level of CRP at maximum dose of *Arogyavardhini vati* (200 mg/kg) when compared with fenofibrate-treated rats [Table 1].

Effect of *Arogyavardhini vati* in Triton WR-1339-induced dyslipidemia on rat's liver MDA and GSH levels

There was significant decrease in liver MDA and increased GSH level observed at all doses of *Arogyavardhini vati* (50, 100, 200 mg/kg) and fenofibrate (65 mg/kg) treated rats when compared with Triton-treated rats ($P < 0.001$). A significant increased MDA and decreased GSH levels in liver of Triton-treated rats ($P < 0.001$) was observed when compared with normal control. There was significant decrease in MDA and increased GSH was observed in a dose-dependent manner [Table 2].

Effect of *Arogyavardhini vati* in Triton WR-1339-induced dyslipidemia on atherogenic index level in rats

Treatment with *Arogyavardhini vati* (50, 100, 200 mg/kg) in Triton WR-1339-induced dyslipidemic rats significantly decreased AI level in a dose-dependent manner when compared with Triton-treated rats ($P < 0.001$). There was no statistically significant change in the level of AI in fenofibrate (65 mg/kg) treated rats and maximum dose of *Arogyavardhini vati* (200 mg/kg) treated rats when compared with normal control [Figure 1].

DISCUSSION

Hyperlipidemia is a well known risk factor for CVDs. Atherosclerotic CAD is one of the major causes of premature death globally and it is expected to be the most important cause of mortality in India.[23] There are several lines of evidence with respect to the fact that HDL

Table 1: Effect of *Arogyavardhini vati* on serum lipid profiles and C-reactive protein in the rats

Groups	Parameters				
	Total cholesterol (mg/dL)	Triglyceride (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	C-reactive protein (µg/mL)
Group I-Normal control	66.2±1.5	76.1±1.9	24.4±1.1	20.5±0.9	26.8±1.5
Group II-Triton treated	205.1±2.1[a]	123.1±1.7[a]	158.4±1.4[a]	11.7±1.1[a]	59.1±5.1[a]
Group III-Triton+fenofibrate (65 mg/kg)	70.8±4.3[b]	81.6±2.4[b]	28.7±1.5[a,b]	18.2±0.9[b]	35.2±3.4[a,b]
Group IV-Triton+*Arogyavardhini vati* (50 mg/kg)	157.2±1.9[a,b,c]	109.2±3.2[a,b,c]	122.3±3.3[a,b,c]	13.9±1.3[a]	52.3±1.6[a,c]
Group V-Triton+*Arogyavardhini vati* (100 mg/kg)	110.1±2.9[a,b,c]	90.9±1.8[a,b,c]	102.8±4.3[a,b,c]	15.1±1.2[a]	45.3±2.2[a,b,c]
Group VI-Triton+*Arogyavardhini vati* (200 mg/kg)	81.9±2.5[a,b]	76.2±2.1[b,c]	43.6±2.2[a,b,c]	16.8±1.0	39.1±2.1[a,b]

Values are expressed as mean±SEM, $n=6$, $P<0.001$. [a]As compared to normal control, [b]as compared to triton treated, [c]as compared to fenofibrate treated, LDL=Low-density lipoprotein, HDL=High-density lipoprotein

Table 2: Effect of *Arogyavardhini vati* on liver oxidative stress marker (MDA and reduced glutathione levels) in the rats

Treatment groups	Liver	
	MDA (nmol/g wet-tissue)	GSH (mg/g wet-tissue)
Group I-Normal control	64.65+1.43	3.11±0.28
Group II-Triton treated	175.12+3.49[a]	1.71±0.17[a]
Group III-Triton+fenofibrate (65 mg/kg)	83.12±2.11[a,b]	2.65±0.18[a,b]
Group IV-Triton+*Arogyavardhini vati* (50 mg/kg)	132.56±3.24[a,b,c]	1.93±0.9[a,b,c]
Group V-Triton+*Arogyavardhini vati* (100 mg/kg)	112.89±4.56[a,b,c]	2.11±0.13[a,b,c]
Group VI-Triton+*Arogyavardhini vati* (200 mg/kg)	98.23±2.44[a,b,c]	2.36±0.7[a,b,c]

Values are expressed as mean±SEM, *n*=6, *P*<0.001. [a]As compared to normal control, [b]as compared to triton treated, [c]as compared to fenofibrate treated, MDA=Malondialdehyde, GSH=Glutathione

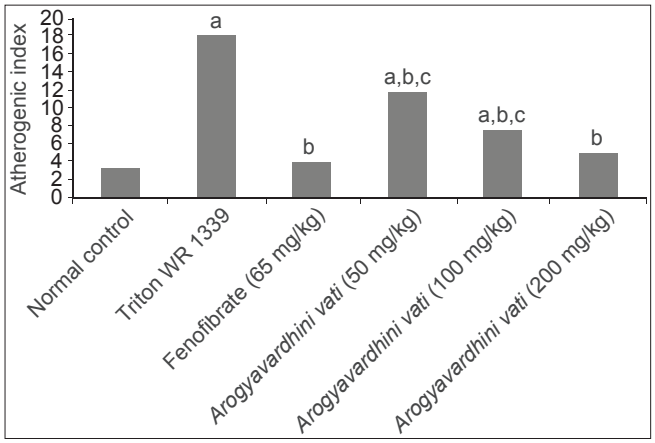

Figure 1: Effect of *Arogyavardhini vati* on atherogenic index level in rats. Values are expressed as mean ± SEM, *n* = 6, *P* < 0.001, a when compared with normal control; b when compared with Triton-treated group, c when compared with fenofibrate-treated group

cholesterol is inversely related to total body cholesterol and a reduction of plasma HDL cholesterol concentration may accelerate the development of atherosclerosis leading to ischemic heart diseases, by impairing the clearing of cholesterol from the arterial wall.[24]

Triton WR-1339 has commonly been used for screening of hypolipidemic drugs.[25] There is plethora of studies which has investigated the plants for their acute hypolipidemic activity in Triton WR-1339-induced hyperlipidemic animals.[26-28] Triton WR-1339 injection results increase in plasma cholesterol and triglycerides due to increase in VLDL secretion by the liver accompanied by a strong reduction of VLDL-C and LDL-C catabolism.[29] Fenofibrate (65 mg/kg) treated group was taken as positive control because it is effective in hypertriglyceridemia and hypercholesterolemia.

It has been well established that nutritional supplements such as herbal medicinal products, vitamin E, etc., plays an important role in the etiology of hyperlipidemias and atherosclerosis. Our present study clearly shows that *Arogyavardhini vati* significantly lowered serum total cholesterol, triglycerides, and LDL levels, and increased HDL in a dose-dependent manner (50, 100, 200 mg/kg) [Table 1].

The treatment with *Arogyavardhini vati* also reduced the AI which is an important and sensitive indicator to determine the cardiac risk [Figure 1]. The results of present study are in accordance with several studies.[26-28] There are several components of *Arogyavardhini vati* which are known to have hypolipidemic effects, i.e., *Picrorrhiza kurroa, Terminalia chebula*, *Terminalia bellerica*, *Emblica officinalis*, and Guggulu.[30-35]

The mechanisms by which *Arogyavardhini vati* exerted the beneficial effects is presently not clear. *Picrorhiza kurroa*, a major component *Arogyavardhini vati* has choleretic effect.[36] Amla which is another component has HMG CoA reductase inhibitory activity.[37] Ellagitannins and the ellagic acid obtained on hydrolysis of these tannins (by lipases and/or esterases) are inhibitors of squalene epoxidase, a rate-limiting enzyme of cholesterol biosynthesis.[38] These inhibitory activities may explain the beneficial effects of *Arogyavardhini vati* on lipid parameters. Inflammation is known to reduce HDL[39] and the enhancement of HDL observed in the present study may arise from the control of inflammation by *Arogyavardhini vati*. The serum CRP level which is a marker of systemic infection was significantly reduced at the end of the treatment in our study which are also reported in literature.[10] Therefore, it is likely that a reduction in serum lipid levels observed in the present study by *Arogyvardhini vati* may be mediated through above mechanisms.

Lipid peroxidation is the most commonly used parameters for assessing oxidative damage in the human body.[40] In this process LDL-C and other lipid containing molecules may be oxidized in the blood stream, exerting adverse effects on a variety of processes like inhibiting antithrombin III activity, producing procoagulant activity, enhancing platelet aggregation, modulating vascular responses, and acting as mitogen.[41]

The formation and activation of atherosclerotic lesion is a multi-faceted process involving many determinants, including oxidative modification of LDL. Oxidized LDL causes foam cell formation, leukocyte adhesion to the endothelium, cytotoxicity, and vascular endothelial dysfunction leading to impaired EDNO synthesis and biological activity.[42] In

the present study, *Arogyavardhini vati* administration caused a significant reduction of liver MDA and increased GSH level [Table 2]. Lowering of oxidative stress with concomitant lowering of cholesterol indicated that there was reduced oxidative stress after administration of *Arogyavardhini vati* in a dose-dependent manner. The results of present study indicate antiatherosclerotic roles of *Arogyavardhini vati* which can indirect effect due to enhanced lipid metabolism by liver. This study showed that the liver antioxidants induced by *Arogyavardhini vati* may have protective effect against LDL oxidation, thereby preventing or slowing the events leading to the initiation of atherosclerosis. The observation made from this study showed that *Arogyavardhini vati* possesses a stronger antioxidant potential.

CONCLUSION

Arogyavardhini vati may be a useful therapy for hypercholesterolemia through reducing oxidative stress (decreasing MDA and increasing GSH) and lipid levels (decreasing serum total cholesterol, triglyceride, LDL levels and increasing serum HDL level). The results of the present animal study pave the path to conduct clinical study and *Arogyavarhdini vati* was found to be safe and efficacious in dyslipidemia patients.

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