ORIGINAL ARTICLE

Antihyperlipidemic potential of a polyherbal preparation on Triton WR 1339 (Tyloxapol) induced hyperlipidemia: A comparison with Lovastatin

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We investigated the antihyperlipidemic activity of an aqueous extract of a herbal preparation from a combination of six Indian medicinal plants. The current study was undertaken to assess the hypolipidemic, hypocholesterolemic and hypotriglyceridemic potential of the polyherbal extract using Triton WR 1339 (Tyloxapol) induced hyperlipidemia. The animals were divided into four groups'normal control, hyperlipidemic control, hyperlipidemic plus polyherbal extract and hyperlipidemic plus Lovastatin. Hyperlipidemia was induced by single intravenous injection of Triton WR 1339. Intragastric administration of polyherbal extract (500mg/kg of body weight) significantly decreased plasma cholesterol, triglyceride, non-HDL-C and phospholipids levels and increased HDL-C levels. Atherogenic index and triglyceride secretion rate were lowered in the polyherbal extract fed animals when compared to hyperlipidemic animals. Polyherbal extract exhibited quite competitive potential when compared with the reference drug Lovastatin affording a possible alternative therapeutic agent in the treatment of hyperlipidemia.

Key words: Hypercholesterolemia, polyherbal, triton WR 1339

INTRODUCTION

Both diabetes and obesity are emerging as leading health problems in India.[1] Hyperlipidemia and Hyper-cholesterolemia are not only secondary metabolic dysregulations associated with diabetes but also represent increased risk factors for development of diabetes.[2-4] Besides the cause effect relationship with diabetes, elevated serum levels of triglycerides, cholesterol and low density lipoproteins are major risk factors in the premature development of cardiovascular diseases like atherosclerosis, hypertension, coronary heart disease etc.[5,6] Plants are important sources of medicinal compounds and more than 80% of population of developing countries is dependent on traditional folk medicine therapies for treating their ailments. This fact has been recognized by WHO and its recommendations include evaluation of traditional medicines in primary health care of these countries. [7] In the traditional system of Indian medicine, plant formulation and combined extracts of plants are used as drug of choice rather than individual. We are in the progress of evaluating the antidiabetogenic properties of a polyherbal extract consisting of *Cassia fistula L.*, Caesalpiniaceae (pod), *Ocimum sanctum L.*, Lamiaceae (leaves), *Annona squamosa L.*, Annonaceae (seeds), *Terminalia arjuna Roxb.*, Combretaceae (bark), *Azadirecta indica.A.*, Meliaceae (leaves), *Aegle marmelose* (L) Correa ex Roxb., Rutaceae (leaves). These plants were selected on the basis of their purported actions at different loci of diabetic lesions[8-16] as well as on a cost effective basis as these plants are available commonly and reported to possess antidiabetic, antilipidemic and antioxidant properties. During the course of the study we thought it pertinent to evaluate the antihyperlipidemic and antihypercholesterolemic effects of our polyherbal extract as these manifestations can be cause or consequence of diabetes. Since these clinical manifestations can also occur independently causing greater risk towards development of cardiovascular disorders, in the present study we have tried to evaluate the antihyperlipidemic and antihypercholesterolemic properties of our aqueous extract in Triton WR 1339 induced hyperlipidemic rats.

MATERIALS AND METHODS

Chemicals

Tyloxapol (Triton WR 1339 Sigma Aldrich, USA), Lovastatin (Lostatin, Dr. Reddy's lab). Enzymatic kits were purchased from Merck Diagnostics India Ltd. All other chemicals were of Analytical grade.

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Preparation of Aqueous Extract

All plants were purchased from local market (M/s G.Y Hakim and Sons, Vadodara) and authenticated [Table 1]. All plants were shade dried, powdered and equal proportions (100 gms each) were mixed thoroughly. The mixture (600 gms) was further boiled in distilled water (3 litres) at 100°C for 60 minutes and filtered. The filtrate was evaporated to dryness and lyophilized.The extractive value in terms of yield was 38% (w/w).It was suspended in 0.5% Sodium Carboxymethyl cellulose (as vehicle) and used for subsequent experiments.

Animals and Drugs

Adult Female *Charles Foster* rats weighing (230-250 gms) were fed pellet diet (Pranav Agro, Baroda) and given water *ad libitum*. The experiment was carried out according to the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals, India and approved by the Animal Ethical Committee of Department of Zoology, The M.S University of Baroda, Vadodara (Approval No. 827/ac/04/ CPCSEA).

The animals were divided into four groups of five rats each a) Normal Control (NC): Received 1% CMC b) Hyperlipidemic Control (HL): Received 1% CMC and Triton WR 1339 c) Hyperlipidemic +Polyherbal extract (HL + PH): Received 500 mg extract/kg bodyweight in 1% CMC and Triton WR 1339. d) Hyperlipidemic + Lovastatin (HL + LVS): Received 50mg/kg bodyweight in 1% CMC. The animals were administered extract and drug (Lovastatin) for seven consecutive days via intragastric tube once daily.On 8th day, the animals were fasted for 18 hrs (had only access to water) and Triton WR 1339 dissolved in 0.9% Saline (200 mg/kg of bodyweight) was injected intravenously.

Biochemical Estimations

Blood was collected at 6 and 24 hr by retro-orbital sinus puncture method in EDTA coated vials. After 24 hr, the animals were sacrificed by cervical dislocation and liver were quickly excised, blotted free of blood and washed in Phosphate buffered Saline (pH 7.4) and stored in –80 refrigerators until analysis of hepatic cholesterol. Blood samples were centrifuged immediately at 2500 rpm for 10 min and plasma separated. Plasma total cholesterol, HDL-cholesterol, triglyceride and phospholipids were quantified using enzymatic kits and triglyceride secretion rate (TGSR) was calculated.[17] Since the Friedwald's Equation[18] does not holds true for calculation of LDL-C at higher triglyceride levels, sum of LDL-C+VLDL was taken to calculate non-HDL-C component.

Statistical Analysis

Statistical evaluation of the data was done by student's *t*- test and results are expressed as mean ± S. E using Graph Pad Prism version 3.0 for Windows, Graph Pad Software, San Diego California USA.

Table 1: Polyherbal drug: Compostion and concentration

Botanical name	Family	Common name	Weight	Parts used
Cassia fistula.L.	Leguminosae	Golden shower tree	100 gms	Pod
Ocimum sanctum.L	Lamiaceae	Holy basil	100 gms	Leaves
Annona squamosa.L	Annonaceae	Sugar apple	100 gms	Seeds
Terminalia arjuna Roxb	Combretaceae	Arjuna	100 gms	Bark
Azadirachta indica A. Juss.	Meliaceae	Neem	100 gms	Leaves
Aegle marmelose (L) Correa ex Roxb	Rutaceae	Holy fruit tree	100 gms	Leaves

RESULTS

Induction of hyperlipidemia with Triton WR 1339: The levels of plasma total cholesterol, triglyceride, phospholipids, HDL-C, non-HDL, and AI in NC, HL, HL + PH and HL+ LVS assayed after respective treatments are shown in [Figures 1-6]. Significant elevation is seen in the levels of plasma total cholesterol after 6 and 24 hour tritonization (36.70% and 58.10% respectively). Simultaneously the triglyceride levels also significantly amplified during both 6 and 24 hour treatment (89.54% and 83.41%). Also the phospholipids levels showed significant upsurge after the treatment at 6 and 24 hour (74.07% and 70.97%). At the same time, plasma total non- HDL levels also augmented in both 6 and 24 hour treatment (80.37% and 83.57% for non- HDL respectively). While in case of total plasma HDL, after tritonization significant decrease was observed in both 6 and 24 treatment (52.99% and 48.16% respectively).

Effect of PH and LVS: In HL + PH treated group of animals, moderate decrease was seen in the levels of plasma total cholesterol (15.41% and 27.32%) at 6 and 24 hour, also the levels of triglyceride show significant decline in HL + PH treatment (38.25% and 20.70% respectively). Moderately significant reduction is seen in plasma phospholipids after PH treatment at both 6th and 24th hour (20.34% and 16.40% respectively). At the same time, the non- HDL levels in plasma also showed significant decrement after PH treatment at both 6th and 24th hour (44.46% and 37.95% for non- HDL respectively). The HL + LVS group of animals also showed similar set of changes with respect to all parameters with the percentage changes being slightly more than the PH treated animals. However, significant decrease is observed in triglyceride and VLDL levels in LVS treated animals as compared with the PH treated group. While a reverse trend is observed in LVS treated animals when compared with PH treated group for plasma LDL levels. In PH treated animals significant decrease is seen in LDL values while in

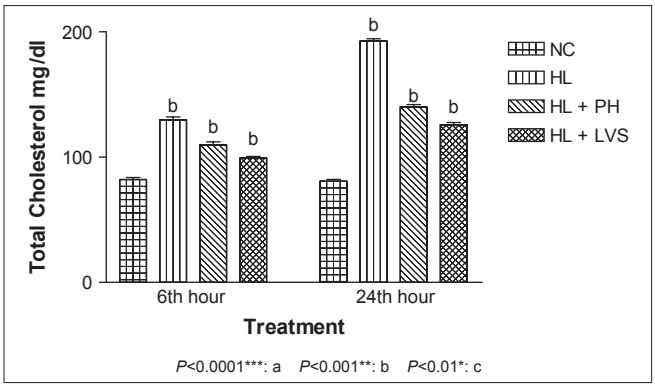

Figure 1: Effect of polyherbal extract and Lovastatin on plasma total cholesterol levels after 6 and 24 hrs of hyperlipidemia induced by triton in rat. Values are ±SD from six animals. NC: Normal control; HL: Hyperlipidemic; HL+ PH: Hyperlipidemic + polyherbal treated group; HL + LVS: Hyperlipidemic + Lovastatin treated group

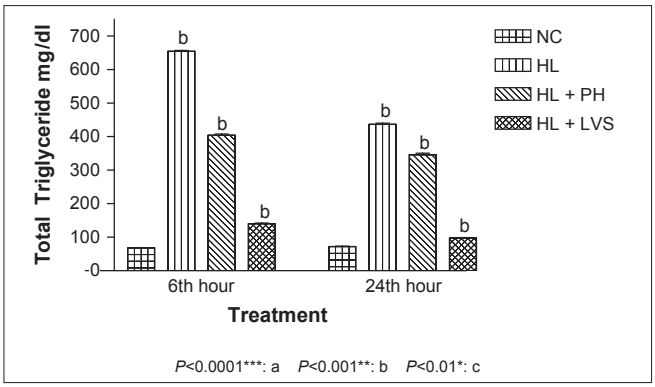

Figure 2: Effect of polyherbal extract and Lovastatin on plasma total triglyceride levels after 6 and 24 hrs of hyperlipidemia induced by triton in rat. Values are ± SD from six animals. NC: Normal control; HL: Hyperlipidemic; HL+ PH: Hyperlipidemic + polyherbal treated group HL + LVS: Hyperlipidemic + Lovastatin treated group

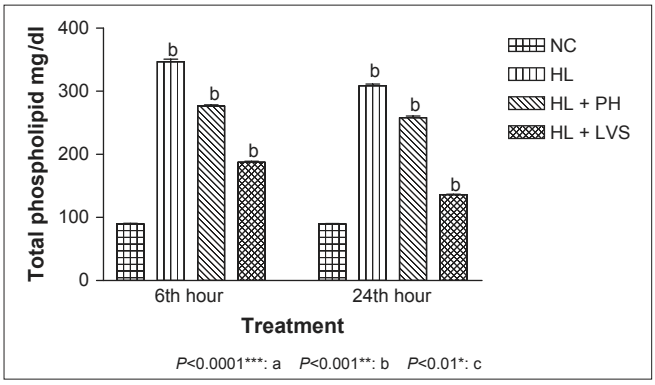

Figure 3: Effect of polyherbal extract and Lovastatin on plasma total phospholipid levels after 6 and 24 hrs of hyperlipidemia induced by triton in rat. Values are ± SD from six animals. NC: Normal control; HL: Hyperlipidemic; HL+ PH: Hyperlipidemic + polyherbal treated group; HL + LVS: Hyperlipidemic + Lovastatin treated group

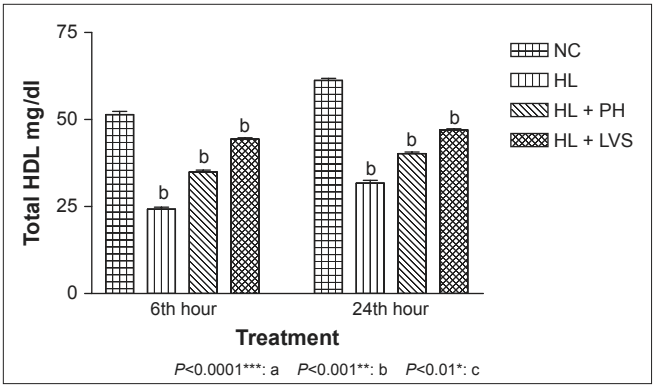

Figure 4: Effect of polyherbal extract and Lovastatin on plasma total HDL levels after 6 and 24 hrs of hyperlipidemia induced by triton in rat. Values are ± SD from six animals. NC: Normal control; HL: Hyperlipidemic; HL+ PH: Hyperlipidemic + polyherbal treated group; HL + LVS: Hyperlipidemic + Lovastatin treated group

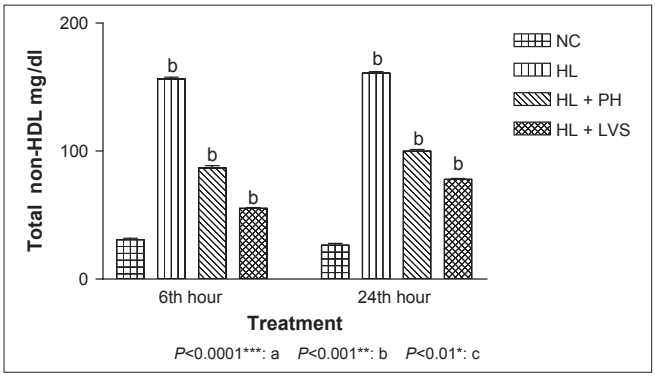

Figure 5: Effect of polyherbal extract and Lovastatin on plasma total non- HDL levels after 6 and 24 hrs of hyperlipidemia induced by triton in rat. Values are ± SD from six animals. NC: Normal control; HL: Hyperlipidemic; HL+ PH: Hyperlipidemic + polyherbal treated group; HL + LVS: Hyperlipidemic + Lovastatin treated group

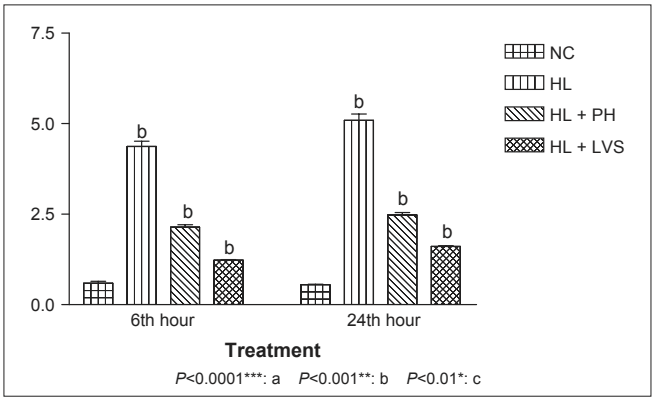

Figure 6: Effect of polyherbal extract and Lovastatin on AI after 6 and 24 hrs of hyperlipidemia induced by triton in rat. Values are ± SD from six animals. NC: Normal control; HL: Hyperlipidemic; HL+ PH: Hyperlipidemic + polyherbal treated group; HL + LVS: Hyperlipidemic + Lovastatin treated group

LVS group moderate decline is observed for the same. The amount of total plasma HDL increased in both HL+ PH and HL + LVS treated groups, the increment being more in HL + LVS treated animals in both 6 and 24 hour treatments (30.70% and 21.07% for HL+ PH, 45.50% and 32.52% for HL + LVS). No significant difference was observed between HL+ PH and HL + LVS treated groups for plasma total cholesterol, triglyceride, HDL, phospholipids, VLDL, non-HDL in both 6th and 24th hour, while the amount of plasma total LDL shows significant difference between HL+ PH and HL + LVS treated groups (77.90% and 47.54% for 6th and 24th hour respectively).

Effect on Atherogenic Index (AI) and triglyceride secretion rate*:* Atherogenic index showed significant progressive increase at 6 and 24 hrs in HL animals. AI was significantly lowered in HL + PH and HL + LVS animals; relatively the HL + LVS animals showed more prominent decrement. [Figure 6]. TGSR was calculated to evaluate efficacy of polyherbal and lovastatin to lower triton induced triglyceride secretion during 6th hour post injection. Results clearly demonstrated control of triglyceridemia via decreased TGSR in both HL + PH ($P < 0.01$) and HL + LVS ($P < 0.001$) animals [Figure 7].

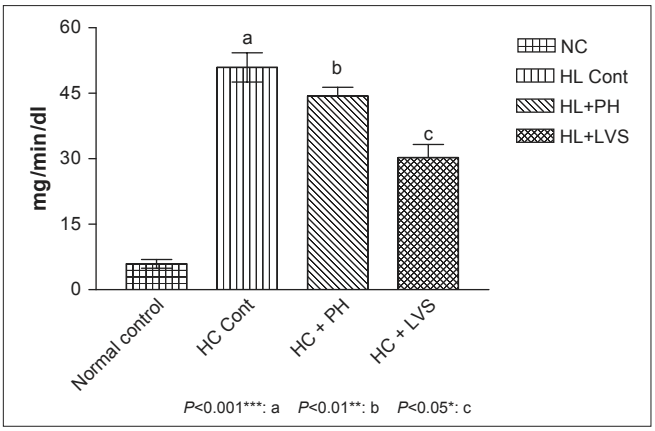

Figure 7: Effect of polyherbal extract and Lovastatin on TGSR after 6 hr of hyperlipidemia induced by triton in rat. Values are ± SD from six animals. NC: Normal control; HL: Hyperlipidemic; HL+ PH: Hhyperlipidemic + polyherbal treated group HL + LVS: Hyperlipidemic + Lovastatin treated group

DISCUSSION

Diseases associated with high TG levels (Diabetes mellitus, obesity, chronic renal disease, primary hyperlipoproteinamia) carry high risk of cardiovascular disorder (CVD).[19] Hypertriglyceridemia in combination with abnormally low concentrations of HDL cholesterol (High Density Lipoprotein Cholesterol) is one of the most common and atherogenic profile of lipid metabolism of high prevalence seen in Indian population.[20] Hyperlipidemia and hypercholesterolemia are reportedly the major risk factors in life style related diseases such as atherosclerosis and related cardiovascular complications including cerebral paralysis and myocardial infarction.[21] Prevention or treatment of such disorders can be achieved by targeting the causative hyperlipidemia and hypercholesterolemia through diet and/or drug administration.[5,22] Research on herbal medicines is gaining ground and the demand to use natural products in the treatment of various disorders is increasing worldwide. Investigations on herbal products might lead to the development of alternative drugs and strategies. Such alternative strategies are required for the effective management of dyslipidemic disorders as; cost and poor availability of modern therapies make the rural populations particularly in developing countries vulnerable to such ailments.

In the current study, tritonised animals have been used to test the antitriglyceridemic and anticholesterolemic efficacy of polyherbal extract as, such a model has been used for the induction of acute hyperlipidemia[23] as well as for testing the potential of natural/chemical hypolipidemic drugs.[24-30] Our data show that the polyherbal extract exerts significant antihyperlipidemic effect marked by significantly lower plasma cholesterol and triglyceride levels in HL+ PH rats compared to HL rats. Our polyherbal extract seems to have potent antitriglyceridemic effect as it could protect against Triton induced hypertriglyceridemia by 38.25% and 20.70% at 6 and 24 hrs respectively. It is shown that Triton elevates plasma triglyceride level essentially by preventing its uptake and clearance by inhibiting catabolising enzymes like lipoprotein lipase (LPL) and lecithin cholesterol acetyl transferase (LCAT)[31-34] Apparently our polyherbal extract is able to reduce the inhibition on LPL and LCAT activity making triglycerides available for uptake and metabolism by tissues. The antilipidemic drug Lovastatin seems more potent in preventing the elevation in triglyceride levels. This is clear from the recorded minimal elevation of triglyceride by 78.59% and 77.63% at 6 and 24 hrs respectively as against 89.54% and 83.41% elevation in the HL animals. Since the polyherbal extract could prevent the elevation in plasma cholesterol level almost to a similar extent as that of Lovastatin (15.41% PH v/s 23.45% LVS at 6 hrs and 27.32% PH v/s 34.73% LVS at 24 hrs). It is clear that our polyherbal extract is relatively more anti-hypercholesterolemic than antitriglyceridemic. Triton WR 1339 induced hyper-cholesterolemia has been related to its ability to alter the physico-chemical properties of lipoproteins and thereby prevent their uptake by liver for clearance.[35] An extract of *Phyllanthus niruri* has been shown to facilitate catabolism of LDL through its hepatic receptors in triton treated rats.[36] In our present study it is seen that the polyherbal extract is effective in minimizing triton induced decrease in HDL-C as well as increase in non-HDL-C (LDL+VLDL) suggesting promotion of increased catabolism of non-HDL-C by the hepatic tissue. Similar conclusion has also been drawn by Hicham *et al*.,[37] in their study on hypolipidemic activity of aqueous extract of *Erica multiflora* flower on triton induced hyperlipidemia.

The hypolipidemic efficacy of the polyherbal extract is also substantiated by the calculated cardiovascular risk factor and Atherogenic Index and despite being a crude extract it seems to be quite competitive to the hypolipidemic drug Lovastatin. A generalized plasma lipid lowering effect is also indicated by the resistance to hyperlipidemia including phospholipids.

CONCLUSIONS

Overall, the results indicate that the active principles

possessing single or diverse range of biological activities hold promise in developing polyherbal drug as a preventive measure in treatment of hyperlipedemia. The results are encouraging enough for further studies aimed at understanding the mechanism of action and identify the bioactive compounds. Since ayurvedic/herbal medicines are needed to be used in higher doses and for relatively longer periods for permanent effects, studies are on currently to ascertain the efficacy of our polyherbal extract in chronic diet induced hyperlipidemia.

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