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# PROTECTIVE EFFECT OF PERILLYL ALCOHOL (POH) A MONOTERPENE: ON HIGH FAT DIET INDUCED HYPERLIPIDEMIA IN ALBINO WISTAR RATS A PRELIMINARY STUDY

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**ABSTRACT:** To assess the effect of Perillyl alcohol (POH) on the lipid profile of high-fat-diet-induced hyperlipidemia in white male albino Wistar rats, the hyperlipidemia was induced by feeding cholesterol-rich high-fat diet for 45 days in male albino Wistar rats. The decline in the triglycerides, LDL and VLDL was significant at 100 & 200 mg/kg dose of POH compared to Atorvastatin group. The decrease in total cholesterol was significant at 100 and 200 mg/kg doses compared to hyperlipidemic control. The results demonstrate that POH at a dose of 100 and 200 mg/kg body weight lowers the serum triglyceride, LDL, VLDL, total cholesterol and increase HDL level significantly in high-fat-diet-induced hyperlipidemic rats. Though there was no significant effect on the lipid profile at 50 mg/kg dose. Thus, the results of the present study provide scientific validation for the use of Perillyl alcohol (POH) a terpene as an Antihyperlipidemic agent.

**INTRODUCTION:** Hyperlipidemia is a condition associated with increased level of lipids and cholesterol in plasma leading to various disorders including coronary artery disease. Hyperlipidemia is a highly predictive risk factor for atherosclerosis, coronary artery disease and cerebrovascular disease [1]. Statins form the mainstay of the treatment. However, they are associated with side effects like a headache, bowel upset, nausea, muscle tenderness, and sleep disturbances. Rise in creatinine phosphokinase and serum transaminase levels can occur, hence monitoring of these parameters is necessary with statin therapy. Fibrates, bile acid sequestrants, and nicotinic acid constitute other modalities of treatment, but control of lipid levels is far from satisfactory [2].

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Hence research is being conducted to pursue better drugs in this regard. Perillyl alcohol (POH) is a monoterpene found in essential oils of mints, cherries, citreous fruits, lavender, sage, peppermint, lemongrass and some other plants [3], reported having antioxidant and anti-inflammatory properties [4, 5]. Perillyl alcohol (IUPAC name: [4-(prop-1-en-2-yl) cyclohex-1-en-1-yl] methanol) is a naturally occurring monocyclic terpene derived from the mevalonate pathway in plants. It has some manufacturing, household, and medical applications. For example, Perillyl alcohol may be used as an ingredient in cleaning products and cosmetics [6] and as of 2015 it was in development as a potential treatment for people with brain cancer, Lung cancer, pancreas cancer [7]. Perillyl alcohol also acts as anti-stress agent [8]. Perillyl alcohol decreased lipid peroxidation, restored the endogenous antioxidant system. Perillyl alcohol also mitigated the inflammation by inhibiting IL-1β, IL-6 and TNF-α, NOS-2 COX-2 and NF-κβ expressions Perillyl alcohol may be considered as a good antioxidant and anti-inflammatory agent [9].

## MATERIALS AND METHODS:

**Animals:** Healthy male albino Wistar rats (150-180 g) were obtained from Biogen Laboratory, Bangalore India. The rats were kept in CENTRAL ANIMAL HOUSE, Rajah Muthiah Medical College, Faculty of Medicine, Annamalai University, Tamil Nadu, India. Rats were housed in clean polypropylene cages, three rats in each cage, in a controlled environment (24-26 °C) with a 12:12 h L:D cycle with standard chow containing fat 4.15%, protein 22.15%, carbohydrates 4% (supplied by Hindustan Lever Ltd, Mumbai, India) and water *ad libitum.* Before starting the experiment rats were allowed to acclimatize to laboratory conditions for one week. The rats were maintained as per the CPCSEA guidelines and regulations. The study was approved by the Institutional Animal Ethics Committee of Rajah Muthiah Medical College (Reg. no. 160/PO/ReBi/ S/1999/CPCSEA, Proposal no. 1192).

**Chemicals:** Perillyl alcohol- [IUPAC name 4R-4-prop-1en-2-ylcyclohexen-1-yl methanol], chemical formula $C_{10}H_{16}O$, the molecular weight of 152.237 g/mol] and Atorvastatin were purchased from Sigma-Aldrich (St. Louis, MO, USA). Atorvastatin was used as standard drug.

**Induction of Hyperlipidemia:** Hyperlipidemia was induced by feeding the rats with cholesterol-rich high fat diet for 45 days.

**Preparation of Cholesterol-Rich High Fat Diet:** Deoxycholic acid (5 g) was mixed thoroughly with 700 g of powdered rat chow diet. Simultaneously cholesterol (5 g) was dissolved in 300 g butter (Amul). This mixture of cholesterol and butter was added slowly into the powdered mixture of deoxycholic acid and rat chow to get a soft homogenous cake.

This cholesterol-rich high-fat diet (HFD) was molded into pellets of about 3 g each and was used to feed the animals with *ad libitum* [10, 11].

**Experimental Design:** Rats were randomly assigned to six groups of six rats each. For 45 days they were fed by a high-fat diet. The rats did not receive any treatment for the first 15 days to become hyperlipidemic before the beginning of treatment. During the last 30 days, the rats were treated with the drug. The feeding and treatment schedule for all the groups are shown in **Table 1**. Perillyl alcohol was administered in three different doses 50, 100, 200 mg/kg body weight.

**TABLE 1: FEEDING AND TREATMENT SCHEDULE**

| | |
|---|---|
| Group 1 | Normal diet (for 45 days) |
| Group 2 | High-fat diet (for 45 days) |
| Group 3 | High fat diet (for 45 days) + Atorvastatin 10 mg/kg/day (last 30 days) |
| Group 4 | High fat diet (for 45 days) + POH 50 mg/kg/day (last 30 days) |
| Group 5 | High fat diet (for 45 days) + POH 100 mg/kg/day (last 30 days) |
| Group 6 | High fat diet (for 45 days) + POH 200 mg/kg/day (last 30 days) |

On the 45$^{th}$ day, the blood samples were collected in simple glass tubes (for separation of serum). Serum was analyzed for total cholesterol, triglycerides, and HDL-C according to standard method [12] and LDL-C and VLDL-C were calculated using Friedewald formula [13].

**Statistical Analysis:** The data were presented as mean ± SE for six rats in each group and analyzed using One-way ANOVA followed by Tukey's multiple comparison tests, using the SPSS version 15 (SPSS, Chicago, IL). The limit of statistical significance was set at $p<0.05$.

**RESULTS:** The results are presented in **Table 2**. Feeding the animals with High-fat diet (HFD) significantly increased total cholesterol, serum triglyceride, serum VLDL-C, serum LDL-C and decreased the level of HDL-C compared to the normal group throughout 45 days. Atorvastatin (10 mg/kg) and Perillyl alcohol (100 and 200 mg/kg body weight) significantly show a reduction in total cholesterol levels compared to HFD control.

**TABLE 2: EFFECT OF PERILLYL ALCOHOL ON LIPID PROFILE IN NORMAL AND HIGH FAT DIET FED RATS**

| Groups / Parameters | TG (mg/dl) | TC (mg/dl) | HDL (mg/dl) | LDL (mg/dl) | VLDL (mg/dl) |
|---|---|---|---|---|---|
| Normal | 52.24 ± 3.98$^a$ | 80.14 ± 6.10$^a$ | 46.10 ± 3.51$^a$ | 23.60 ± 1.80$^a$ | 10.44 ± 0.80$^a$ |
| High fat diet (HDF) | 126.42 ± 9.68$^b$ | 162.24 ± 12.42$^b$ | 26.64 ± 2.04$^b$ | 110.38 ± 8.45$^b$ | 25.29 ± 1.94$^b$ |
| HFD + Ator. (10 mg/kg) | 66.05 ± 5.06$^d$ | 98.67 ± 7.55$^d$ | 42.84 ± 3.28$^a$ | 41.69 ± 3.19$^d$ | 13.22 ± 1.01$^d$ |
| HFD + POH (100 mg/kg) | 81.44 ± 7.03$^c$ | 116.40 ± 7.91$^c$ | 38.21 ± 2.92$^c$ | 61.53 ± 4.69$^c$ | 16.80 ± 2.30$^c$ |
| HFD + POH (200 mg/kg bw) | 79.57 ± 6.06$^c$ | 114.44 ± 8.71$^c$ | 36.23 ± 2.76$^c$ | 62.44 ± 4.75$^c$ | 15.80 ± 1.20$^c$ |

HDF-High fat diet; POH-Perillyl alcohol; Ator-Atorvastatin. All the data are expressed as the mean ± S.D. for 6 rats. The results with different superscripts (a,b,c) in each experimental group are significantly different at $p<0.05$.

Perillyl alcohol (100 and 200 mg/kg body weight) showed a significant decrease in serum triglyceride, serum LDL-C and serum VLDL-C levels compared to HFD control and atorvastatin group and significantly raised the level of HDL-C when compared to HFD control and atorvastatin. There were no significant changes in the total cholesterol, serum triglyceride, serum LDL-C, VLDL-C HDL-C levels with Perillyl alcohol (50 mg/kg b.w).

**DISCUSSION:** Hyperlipidemia indicates the onset of abnormalities in lipid metabolism secondary to the manifestation and progression of atherosclerosis. Hypertriglyceridemia is characterized by elevated triglyceride levels (>200 mg/dL) [14]. An increase of 89 mg/dL in the triglyceride level is associated with a 30% increase in coronary heart disease in men and a 70% increase in women [15]. As predictors of risk of cardiovascular disease, levels of triglycerides are independent of HDL-C and total cholesterol [17,] but the risk is highest when LDL-C levels are lower [15]. Monotherapy with statins has failed in controlling isolated hypertriglyceridemia. Niacin and statin combinations are recommended by National Cholesterol Education Program (NCEP) for patients with high triglycerides [18]. However, the use of niacin is associated with side effects, including flushing, dizziness, palpitation, tachycardia, hyperglycemia and gout [2].

Use of medicinal plants as a pharmacologic modality in preventing alteration in lipid metabolism has received wide attention from several workers [19]. Rats fed with a diet supplemented with 5 g cholesterol and 5 g deoxycholic acid in butter for 45 days served as the experimental model [10]. The mechanism of action of deoxycholic acid is two-fold: an increase in cholesterol absorption and concomitant suppression of cholesterol 7α-hydroxylase activity that results in decreased cholesterol excretion. Deoxycholic acid improves cholesterol absorption by its emulsifying property [20].

From the obtained result it was observed that feeding the animals on HFD significantly increased the total cholesterol, triglyceride, VLDL-C and LDL-C level in serum and decreased the level of HDL-C ($P<0.05$) as compared to rats on the normal diet. When Perillyl alcohol was co-administered with HFD at a dose of 100 and 200 mg/kg b.w during the last 30 days of study, there was a significant decrease in total cholesterol, triglyceride, serum LDL-C, and VLDL-C levels and increase in HDL-C when compared to HFD control and atorvastatin group. No significant changes were noted at 50 mg/kg b.w dose of Perillyl alcohol in any of the parameters. Free radical scavenging could be the possible mechanism for lowering of triglycerides & VLDL-C levels. This property of Perillyl alcohol can have potential benefits in familial hypertriglyceridemia [21]. Rats treated with atorvastatin also showed a marked reduction in all serum lipoproteins as compared with HFD group.

**CONCLUSION:** Results of the present study revealed that 100 and 200 mg/kg b.w of Perillyl alcohol improved the serum lipid profile in rats by decreasing total serum cholesterol, triglyceride, LDL-C, and VLDL-C and increase in HDL-C. This finding provides some biochemical basis for the use of Perillyl alcohol (POH) as an anti-hypertriglyceridemic agent having preventive and curative effect against hypertriglyceridemia. Further studies are required to gain more insight into the possible mechanism of action of Perillyl alcohol.

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**CONFLICT OF INTEREST:** The authors declare that there is no conflict of interest regarding this study.

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