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Original Article

Lipid Lowering and Antioxidant Effects of *C. Verum* on Liver in Cholesterol fed Rabbits

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ABSTRACT

Objective: Present investigation was undertaken to evaluate the hypolipidaemic and antioxidant activity of 70% methanolic crude extract of *Cinnamomum verum* bark in liver of high fat diet induced atherogenic rabbits.
Experimental approach: Lipid profile, lipid peroxidation level and histological changes in liver were investigated. The statistical analysis were carried out by student's 't'test.
Findings and discussion: High fat diet produced a significant increase in total cholesterol, Phospholipids, Triglycerides in liver. It also increases lipid peroxidation as well as shows severe fatty changes in liver. Treatment with *C. verum* extract 200 mg/kg and 300 mg/kg (p.o) concurrently for 120 days to cholesterol-fed rabbits corrected the disturbed lipid profile significantly and was effective in inhibiting lipid peroxidation. Normal histology of liver regained in animals given *C.verum* compared to the high cholesterol diet animals not given *C. verum* supplement. The phytochemical analysis of methanol extracts indicated strong presence of alkaloids, flavanoids, tannins, phenols, saponins and fatty acids that may be responsible for the significant hypolipidaemic as well as antioxidant activity.
Conclusion: Our study exhibited that the methanol extract of *C. verum* bark is a potent hypolipidaemic agent and contribute remarkably in managing lipid peroxidation levels in high cholesterol diet animals.

Keywords: Atherosclerosis, Hyperlipidaemic, Phytoconstituents, Cholesterol, *C. verum*

1. INTRODUCTION

Current studies have established that increased generation of free radicals/ reactive oxygen species (ROS) contributes considerably in the manifestation and development of cardiovascular disease (CVD).[1, 2] The formation of enormous number of reactive oxygen species can devastate the intracellular antioxidant defense, causing activation, DNA breakes and protein modification. ROS induced reduction of antioxidants is a crucial factor for the initiation of atherosclerosis and the progression of CVD.[1] The World

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Health Organization report emphasizes that CVD along with diabetes accounted for 32% of the total global deaths and contributed to 11% of the global burden of disability-adjusted life span in the year 2005.

Due to the growing concern of consumers regarding the better compatibility, improved patient tolerance of long-term pharmaceutical drug usage, the demand for nutraceutical compounds keeps on rising.[3] Among these phytoconstituents, plant secondary metabolites that function as dietary antioxidants , lipid-lowering compounds[4] and cholesterol-lowering compounds[5] have fascinated the interest of scientists the most.

Many spices and their active principles are excellent nutraceuticals.[6] One of the most popular spices used worldwide, cinnamon is known for its aromatic fragrance and sweet, warm taste. The spice is derived from the bark of an evergreen tree, which belongs to the family Lauraceae. The widespread investigation of literature exposed that a variety of bioactives have been found in Cinnamon which have immense medical potential. It mainly contains essential oils and important compounds like cinnamaldehyde, eugenol, cinnamic acid and cinnamate, coumarin, cinnamyl acetate, borneol etc.[7] Furthermore it is noted to have myriad pharmacological activities like anti-inflammatory,[8] antioxidant, [9,10,11] analgesic,[12] hypoglycemic,[13] anti-cancer,[14,15] antimicrobial.[16] The present study was undertaken to screen *C. verum* for its ability to decrease lipid levels as well as antioxidant activity in hypercholesterolemic rabbits.

2. MATERIALS AND METHODS

Collection and extraction of plant material

Authentic bark of *Cinnamomum verum* (Dalchini) were acquired from the National Institute of Ayurveda, Jaipur. The bark were powdered and extracted with 70% methanol for 72 hours by soxhlet extraction method. Then methanol was separated under reduced pressure and controlled temperature (55-60^{o}C) and dried to obtain a brown solid mass in a rotary evaporator and this was stored in a desiccator. This 70% methanolic crude extract of the *C. verum* was dissolved in distilled water and administered to the animals via oral gavage.

Animal model

New Zealand white male rabbits weighing 1.50-2.0 kg and age of 10-18 months were used for the present study. The animals were obtained from Sheep and Wool Research Institute (CSWRI), Avika Nagar, Rajasthan and were maintained in an air-conditioned experimental room at 12 hour light: dark cycles. The animals were grouped and housed in polypropylene cages at constant temperature and also maintained under a standard diet (Ashirwad Industrial Ltd., Punjab) and green leafy vegetables and water *ad libitum*. The animals were maintained in accordance with the "CPCSEA guidelines for laboratory Animal Facility" (Committee for the Purpose of Control and Supervision on Experiments on Animals), India.

Experimental design

The rabbits were divided into following groups of six animals in each:

Group I : Control –Placebo treated 120 days. (Vehicle treated)

Group II : Atherodiet + cholesterol feeding for 120 days

Group III : Atherodiet + cholesterol feeding +200 mg/kg b.wt. /day *C. verum* extract from day 1-120. (Concurrent treatment)

Group IV : Atherodiet + cholesterol feeding +300 mg/kg b.wt. /day *C. verum* extract from day 1-120. (Concurrent treatment)

Cholesterol feeding: 500 mg cholesterol/kg.b.wt./rabbit/day in 5ml coconut oil

Animal were sacrificed after completion of treatment, tissues were taken out for biological and histological examinations.

Induction of Hyperlipidaemia

Hyperlipidaemia was induced in New Zealand white male rabbits by daily oral administration of 500 mg cholesterol/kg.b.wt./rabbit/day in 5ml coconut oil .

Biochemical analysis

Total cholesterol,[17] triglycerides,[18] and phospholipids[19] were estimated in liver. Liver was also analysed for antioxidant parameters *i.e* lipid Peroxidation. [20]

Histological analysis

The liver was fixed in Bouin's solution for 24 hrs and then washed with water and stored in 70% alcohol. The tissue was dehydrated successively through upgrading alcohol series (50%, 70%, 90% and 100%), cleared in xylene and embedded in paraffin wax for the preparation of wax impregnated blocks. From these blocks, tissue was sectioned on a rotary microtome at 4-5 µm thickness and stained with haematoxylene and eosin (H & E) and observed under light microscope.

Statistical analysis

The results were expressed as mean±S.E.M. Statistical analysis was carried out by "t- test" by using SPSS software (16.0 version) and they considered statistically significant if the *p*-value was less than 0.05.

3. RESULTS AND DISCUSSIONS

Antihyperlipidemic parameters

As illustrated in table 1, the total cholesterol, triglyceride and phospholipid level of liver were elevated significantly by 171.05%, 140% and 67.40% respectively in the hypercholesterolemic rabbits of 120 days when compared with control group. In contrast, a significant ($P \leq 0.01$ and $P \leq 0.001$) dose dependent decline of -45.63% and -48.54% in total cholesterol -25.92% and -34.25% in triacylglycerides level, -23.89% and -25.66% in phospholipids level was

noticed at various doses *i.e* 200 mg and 300 mg/kg.b.wt/day in concurrently treated animals in comparison to hyperlipidemic group II.

In general, during conditions of increased free fatty acid flux to the liver (e.g., after the fatty meal or in the situation of increased lipolysis), hepatocyte initiate synthesis of triglycerides and cholesterol but due to anti-hyperlipidemic drug, hepatocytes may not be able to increase cholesterol synthesis and decrease hepatocyte cholesterol concentration by increasing the catabolic conversion of cholesterol to bile acids in liver.[21]

Liver plays an imperative role in regulation of cholesterol metabolism with the aid of two key enzymes HMG-CoA reductase and ACAT. *C. verum* administration significantly lowered the cholesterol level in liver might be due to inhibition of ACAT.[22] Cinnamate supplementation (Active compound of *C. verum*) significantly lowered hepatic HMG-CoA reductase activity and hence reduced hepatic cholesterol level.[22, 23]

Earlier studies have shown that a high-fat diet in rats increases the long-chain acyl-CoA content in liver and red muscle. Our study further confirmed that a diet high in carbohydrates and fat would increase the acyl-CoA pool, and lead to increased triglyceride storage.[24] After *C. verum* administration, the decrease in triglycerides has been ascribed to a stimulation of the degradation of triglycerides through increased expression and activity of lipoprotein lipases and to a decrease of hepatic synthesis and secretion of triglycerides.[25]

An increased storage of phospholipid in the liver was seen after 120 days of high cholesterol diet feeding. This may be due to mobilization of the lipid from the heart and aorta where the turnover is slow to the liver which has a higher turnover[26] and may be due to decreased phospolipase activity.[27] After supplementation with methanolic extract of *C.verum*, levels of phospholipid showed significant reduction as compared to hypercholesterolemic rabbits may also be due to the enhanced activity of phospholipases. [28]

Lipid Peroxidation (LPO) (n mol MDA/mg)

For analyzing lipid peroxidation, MDA levels were measured in liver homogenates. A significant rise ($P \leq 0.001$) in MDA was observed in the hyperlipidemic rabbits in comparison with the control. Moreover, lipid peroxidation was significantly reduced ($P \leq 0.01$ and $P \leq 0.001$) as depicted by the lower levels of MDA in liver after oral administration of *C. verum* in a dose-dependent manner when compared with hyperlipidaemc rabbits (Table 1). Lipid peroxidation value in liver tissue was raised by 385.7% in rabbits fed with cholesterol for 120 days as compared to control animals. Administration of *C. verum* concurrently with atherogenic diet prevented the rise in lipid peroxides by -58.8% and -64.7% according to the dose level.

Increased lipid peroxidation in hypercholesterolemic rabbits is thought to be a consequence of oxidative stress which occurs when the dynamic balance between prooxidant and antioxidant mechanism is impaired. [29] The dietary cinnamate administration suppressed lipid peroxidation via enhancement of hepatic antioxidant enzyme activities.[22] This indicates that *C. verum* extract react with peroxyl radicals including the inhibition of lipid peroxidation chain propagation.[30]The present results are in accordance with those reported by Priya Rani et al.,[31] Mazimba et al.,[32] they reported antioxidant properties of *C.verum* methanolic bark extract.

Histology of Liver

Control group animals showed normal histology of liver, having large polygonal hepatocytes with binucleated sinusoids. In the center of each lobule a central or intralobular vein is present. Sinusoids converge radially in to the central vein. (Fig. 1) In high cholesterol group, the hepatocytes and sinusoids became enlarged, congested and few seemed to be enucleated. Liver showed granular cytoplasm with foamy vacuolization of most of the cells. In some cells pyknotic and karyolitic changes were observed. (Fig. 2) After supplementation of various doses of *C. verum* extract concurrenly to animals, the histology resembled with control groups, however few foamy cytoplasm containing globi and fatty material was present. (Fig. 3 and Fig. 4).

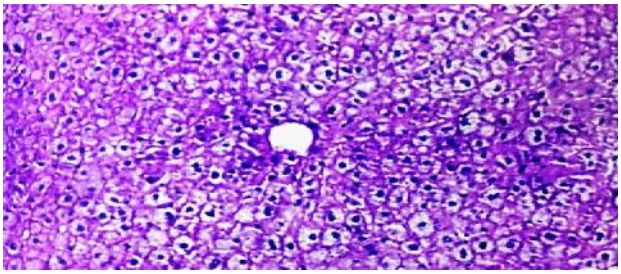

Fig 1: Liver of control rabbit

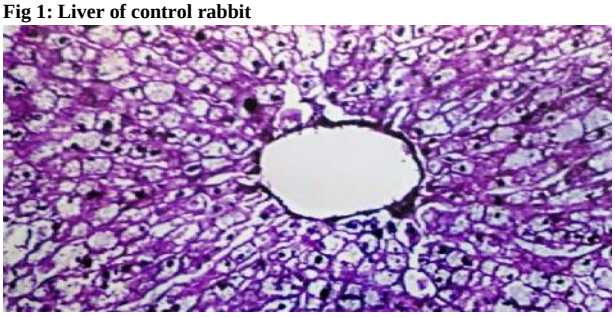

Fig 2: Liver of rabbit after cholesterol feeding for 120 days

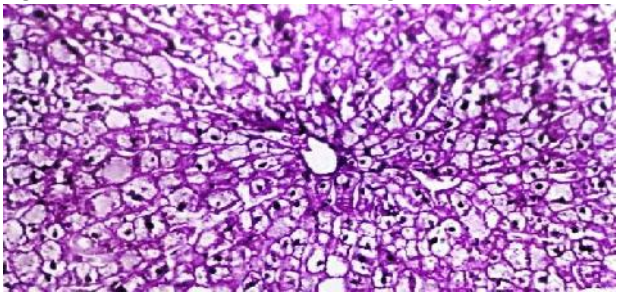

Fig 3: Liver of rabbit- Atherodiet + cholesterol feeding +200 mg/kg b.wt. /day *C. verum* extract from day 1-120 (Concurrently)

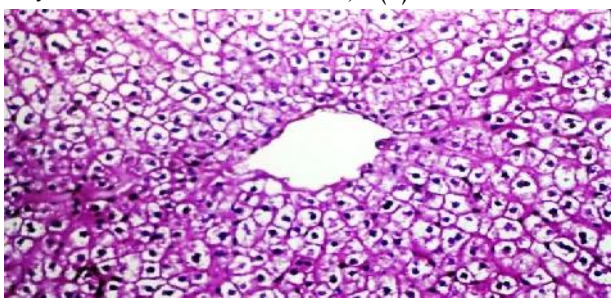

Fig 4: Liver of Rabbit- Atherodiet + cholesterol feeding +300 mg/kg b.wt. /day *C. verum* extract from day 1-120. (Concurrently)

In the histopathological study of high cholesterol diet fed rabbits showed progression of hepatic steatosis, inflammation, and fibrosis. [33, 34] Treatment with methanolic extract of *C.verum* resulted in less fatty cytoplasmic vacuolated cells in liver parenchyma as well as liver cell necrosis was prevented as compared to high cholesterol diet fed rabbits. Cinnamon possess three flavanols Procyanidin A2, procyanidin B2 and Procyanidin C1.[35] As a matter of fact, Chen and colleagues (2006)[36] revealed that there were multiple pathways regulating numerous genes and proteins involved in the cardioprotection of procyanidin B2 dimer against lipid-laden macrophages in cell culture studies.

Various phytochemical components, especially polyphenols (such as flavonoids, phyenyl propanoids, phenolic acids, tannins, etc) are known to be responsible for the free radical scavenging and antioxidant activities of plants.[37] Thakur et al., 2001[38] and Borradaile et al., 2002 [39]studies suggest that antihypercholesterolemic effect of flavonoids is related to decrease of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) and decrease in apo B secretion in hepatocytes.

Furthermore, anthocyanins prevents endothelial damages and act as an inhibitor of endothelial cell death.[39] Berberine (BBR), an alkaloid isolated from the Chinese herb huanglian, upregulates hepatic LDLR expression by extending the half-life of LDLR mRNA without affecting gene transcription.[40] It is possible that the presence of alkaloids in *C. verum* methanolic bark extract[32] may possess LDLR mRNA stabilization property and stimulating effect on hepatic LDLR expression.

The overall experimental results suggests that the possible mechanism could be the presence of biologically active phytoconstituents such as alkaloids, anthocynins, flavanoids, tannins, phenols, coumarins, saponins, sterols, terpenoids, quinines, fatty acids, carbohydrates, proteins and in the methanolic extract of *C. verum* bark that may demonstrates the multi target, multi component features for regulating lipid metabolism[41] Hence extensive research is required to find out the molecular mechanism and expression studies related to lipid metabolism in bioactive compounds of *C. verum.*

4. CONCLUSION

As a concluding remark, phytoconstituents in the *C. verum* methanolic bark extract are reported to posses the observed significant lipid lowering and antioxidant activity in hypercholesterolemic rabbits. These health promoting effects can range from providing dietary antioxidant effects to modifying signal transduction in the biological systems through alterations in gene expression. Attenuated level of this in extract treated animals is suggestive of the antioxidant nature of this spice. To elucidate the precise mechanism of action of specific biological moiety, further processing of methanolic fraction of *C. verum* is required to establish the efficacy of this plant extract as a hypolipidaemic drug.

Identification	Group	Cholesterol	Triglycerides	Phospholipids	Lipid peroxidation
			(mg/gm)		n mole MDA/ mg
Control(Placebo treated) from day 1-120	I	7.6 ±0.34	4.5 ±0.06	6.75 ±0.20	0.21 ±0.07
Atherodiet + Chol.feeding* from day 1-120	II	20.6[a] ±0.09	10.8[a] ±0.32	11.3[a] ±0.36	1.02[a] ±0.02
Atherodiet + Chol.feeding* + *C. verum* ext** from day 1-120 (Concurrent feeding)	III	11.2[c] ±0.54	8.0[c] ±0.10	8.6[c] ±0.10	0.42[c] ±0.02
Atherodiet + Chol. feeding* + *C. verum* ext** feeding from day 1-120 (Concurrent feeding)	IV	10.6[c] ±0.23	7.1[c] ±0.16	8.4[c] ±0.16	0.36[c] ±0.01

*Cholesterol feeding –500mg/ kg.b.wt in 5 ml coconut oil / day
** *C. verum* - 200 mg/ kg.b.wt. / day
*** *C. verum* 300mg/ kg.b.wt. / day
VALUES± 5 determination
a-P≤ 0.01 Significant Group II compared with Group I
b-P≤ 0.01 Significant Group III, IV compared with
c-P≤0.001 Highly Significant Group II
ns- non significant

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