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Full Length Research Paper

Lipid-lowering effects of *Coriolus versicolor* extract in poloxamer 407-induced hypercholesterolaemic rats and high cholesterol-fed rats

Sook Yee Hor[1*], Elham Farsi[1], Mun Fei Yam[1,3], Norazimah Mat Nuyah[2] and Mohd. Zaini Asmawi[1]

[1]School of Pharmaceutical Sciences, Universiti Sains Malaysia, Minden 11800, Pulau Pinang, Malaysia.
[2]School of Distance Education, Universiti Sains Malaysia, Minden 11800, Pulau Pinang, Malaysia.
[3]Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang 43400, Selangor, Malaysia.

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This study was initiated to evaluate the lipid-lowering effect of *Coriolus versicolor* (CV) extracts in poloxamer 407 (P-407)-induced hypercholesterolaemic and high cholesterol-fed rats. In the chemically induced hypercholesterolaemic rat model, hypercholesterolaemia was induced by intraperitoneal administration of P-407 (500mg/kg). Serum lipid levels, including total cholesterol (TC), triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C) levels, increased significantly ($p<0.001$) in the P-407-induced hypercholesterolaemic rats as compared to the normal control rats. Interestingly, CV extract administration caused a significant reduction in serum TC ($p<0.01$) and TG ($p<0.05$) levels in P-407-treated rats, as well as a reduction in the coronary risk index (CRI) in these rats. In the diet-induced hypercholesterolaemic rat model, the rats were fed a high cholesterol diet containing (by weight) 2% cholesterol, 0.5% cholic acid and 10% butter. The serum TC and LDL-C levels of rats that were fed a high cholesterol diet increased significantly ($p<0.001$) after 14 days as compared to the rats fed a normal diet. Serum TC and LDL-C levels were significantly reduced in a dose-dependent manner in rats given CV extract orally and fed a high cholesterol diet for 14 days. The administration of CV extract also significantly increased high-density lipoprotein cholesterol (HDL-C) levels in rats fed a high cholesterol diet; in addition, CV extract reduced the CRI ratio. Hence, the 14 days administration of CV extract resulted in significant reductions in the lipid profiles of these rats compared to the untreated hypercholesterolemic rats. Our results suggest that the consumption of CV extract has the potential to reduce or prevent hypercholesterolaemia.

Key words: Hypercholesterolaemia, poloxamer 407, high cholesterol diet, *Coriolus versicolor* extract.

INTRODUCTION

It is well known that hypercholesterolaemia is a risk factor for cardiovascular diseases (CVD) such as atheros clerosis (Wang, 1997). Several factors, including life style, a diet high in saturated fat and cholesterol, age and hypertension, have been reported to cause heart failure (Schaefer et al., 1995). High cholesterol levels, in particular low-density lipoprotein cholesterol (LDL-C) levels, are mainly responsible for hypercholesterolaemia (Krieger, 1998). The World Health Organization (WHO) has predicted that heart diseases and stroke are becoming more deadly, with a projected combined death toll of 24 million by 2030 (Reinhardt, 2005).Drugs that lower cholesterol, such as statins, have some adverse effects. In a previous study, certain statins were shown to be associated with liver function abnormalities and occasionally, rhabdomyolysis (Miller, 2001). Rhabdomyolysis is a rare, serious side effect that can cause acute renal failure, dialysis and death (Al Shohaib, 2000). Other adverse effects include cognitive loss, neuropathy, pancreatic and hepatic dysfunction and sexual dysfunction (Golomb and Evans, 2008). Certain patients on statin therapy also reported myalgias, muscle

*Corresponding author. E-mail: sookyee4321@yahoo.com.

cramps and an elevation of creatine kinase levels (Thompson et al., 2003). Hence, the search for new drugs capable of reducing and regulating serum total cholesterol (TC) and triglyceride (TG) levels has gained momentum over the years, resulting in numerous reports on the significant activities of natural agents.

Many classes of dietary components and natural compounds have been tested for the ability to regulate serum lipid concentrations with the aim of lowering the incidence of atherosclerosis and CVD (Martinez-Flores et al., 2004; Li et al., 2006; Ji and Gong, 2007; Hakimoglu et al., 2007). *C. versicolor* (CV), known as Yun Zhi in China, is a mushroom species that belongs to the Basidiomycetes class of fungi. Recently, its therapeutic potential has been gaining acceptance among patients worldwide. Many studies have found that the active ingredients in CV are polysaccharides, in particular polysaccharide krestin (PSK, a protein-bound polysaccharide) and polysaccharide-peptide (PSP).The PSK derived from CV was shown to significantly reduce the LDL-C levels in hyperlipidaemia patients (Tsukagoshi et al., 1984). Previous studies have reported that the polysaccharide extract of CV contains superoxide and hydroxyl radical scavenging activities (Liu et al., 1997). Also, regular consumption of CV might also be beneficial (without any adverse effects) for immunological function through the potential enhancement of cell-mediated immunity in healthy subjects (Wong et al., 2004).

A previous study also showed that the hot water extract of CV had hepatoprotective activity (Kim et al., 2000), and other studies have shown that PSP and PSK can inhibit the proliferation of leukaemia, human gastric cancer and lung tumour cell lines *in vitro* (Dong et al, 1997; Nakazato et al., 1994; Yang et al., 1992). However, there is little evidence regarding the hypercholesterolaemic effects of CV extract in high cholesterol-fed rats and in rats treated with poloxamer 407 (P-407). Thus, the aim of this study was to evaluate the effect of CV extract on the lipid profiles of rats treated with P-407 or fed a high cholesterol diet.

MATERIALS AND METHODS

Experimental samples

Lyophilized *C. versicolor* (CV) water extract was purchased from Herbasin Co., Ltd. (Shenyang). The CV extract was standardised by a spectrophotometric method and contained 33.8% of total polysaccharides. Analysis also showed that the extract contained <10ppm of heavy metal, <5ppm of lead, <2ppm of arsenic, <0.2ppm of cadmium and <0.1ppm of mercury.

Chemicals

Poloxamer 407 (P-407), cholic acid and cholesterol were purchased from Sigma-Aldrich (St. Louis, MO, USA). Atorvastatin and lovastatin were purchased from Ranbaxy Sdn. Bhd. (Malaysia).

Experimental animals

In our experiments, we followed The Guidelines for Care and Use of Laboratory Animals as approved by the Animals Health and Wellness Unit, Universiti Sains Malaysia. Male Sprague-Dawley (SD) rats weighing between 180 to 200g were used for the study. The animals were housed in a temperature controlled room (24°C±4°C) with a 12:12 h light:dark cycle and were allowed free access to water throughout the duration of the experiment. In addition, the animals were provided with a pelleted diet for 7 days to allow them to acclimatize.

Poloxamer 407-induced hypercholesterolaemic model

The animals were made hypercholesterolaemic by an intraperitoneal injection of 500 mg/kg of P-407, followed by 6 h of fasting. The P-407 solution was prepared for injection by combining the agent with saline, which was followed by refrigeration overnight to facilitate dissolution of the P-407 via the cold method (Schmolka, 1991). 2 h after administration of P-407, the rats were treated with CV extract or atorvastatin once daily for 3 days by oral gavage.

Group 1: Normal control (NC)
Group 2: P-407 control (PC)
Group 3: P-407 treated + 75 mg/kg of atorvastatin (PC +ATV)
Group 4: P-407 treated + 500 mg/kg of CV (PC + 500)
Group 5: P-407 treated + 1000 mg/kg of CV (PC +1000)

High cholesterol diet-induced hypercholesterolaemic model

Rats were randomly divided into 6 groups comprising of 6 rats each: a control group, a high cholesterol group, a lovastatin-treated group and three other treatment groups. The control group was fed a normal basal diet, and other groups were fed a high cholesterol diet. A high cholesterol diet was prepared by mixing the normal basal diet (48% carbohydrate, 23% crude protein, 3% crude fat, 8% crude ash, 5% crude fiber and 13% moisture) with cholic acid, cholesterol and butter in a ratio 87.5:0.5:2:10, followed by pelleting of the mixture.

Group 1: Normal basal diet (ND)
Group 2: High cholesterol diet (HC)
Group 3: High cholesterol diet + 60 mg/kg of lovastatin (HC + LV)
Group 4: High cholesterol diet + 250 mg/kg of CV (HC+ 250)
Group 5: High cholesterol diet + 500 mg/kg of CV (HC + 500)
Group 6: High cholesterol diet + 1000 mg/kg of CV (HC + 1000)

The CV extract was dissolved in distilled water prior to administration. Three treatment groups of animals were administered 250, 500 or 1000 mg/kg of CV water extract by oral gavage for 14 days. Lovastatin was prepared in distilled water. The animals in the lovastatin group were administered 60 mg/kg of lovastatin for 14 days in the same manner as the CV treatment groups. The other groups were orally administered with distilled water of equivalent volume, and they were administered concurrently with CV-treated groups and lovastatin-treated group. Animals were fed with the high cholesterol diet for the entirety 14 days treatment.

Collection of blood and biochemical analyses

At the end of the experimental period, the rats were fasted for 12 h and were anesthetized with ethyl ether. Blood samples were collected via cardiac puncture into tubes without anticoagulant. The

blood samples, which were kept at room temperature for 30 min, were centrifuged at a speed of 3500 rpm for 15 min. Serum, which was extracted from the centrifuged samples, was used for analysis of lipid content. The concentrations of total cholesterol (TC), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) in serum were determined using an automated analyser (Selectra Junior, Vital Scientific B. V., Netherlands), according to the manufacturer's instruction using reagents purchased from Fortress Diagnostics (United Kingdom). The concentration of low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula:

LDL-C = TC – HDL-C – TG/5

The coronary risk index (CRI) was calculated as follows:

CRI= TC/HDL-C

Statistical analysis

Results were expressed as the mean ± SEM. One-way analysis of variance (ANOVA) was used for the data analyses, using the SPSS 15.0 Statistical Package. Significant differences between groups were analysed using post-hoc Dunnett's comparison test. Values were considered significant at a level of $p < 0.05$.

RESULTS

Serum lipid profiles in P-407-treated hypercholesterolaemic rats

Figure 1 shows the effects of CV water extract on the serum lipid profiles of hypercholesterolaemic rats treated with P-407. These rats had remarkably high serum levels of TG, TC and LDL-C and significant increased CRI values when compared to normal control rats. Conversely, the administration of the CV water extract at a dose of 1000 mg/kg resulted in a significant reduction in the TC and TG levels by 24.6 and 27.0%, respectively. CV water extract administration also caused a reduction in CRI values when compared to the P-407-treated hypercholesterolaemic group.

The positive control treated with atorvastatin was also characterized by significantly reduced TC, TG and LDL-C levels, as well as the CRI. However, the administration of CV water extract did not significant increase the serum HDL-C levels and significant reduce serum LDL-C levels.

Serum lipid profiles in high cholesterol-fed rats

Figure 2 shows the effects of CV water extract treatment on the serum lipid profiles and CRI values of the rats fed the high cholesterol diet. These rats showed a remarkable increase in TG, TC and LDL-C serum levels and a significant increase in CRI values when compared to the rats fed a normal diet. However, the 1000 mg/kg CV dose in rats on a high cholesterol diet caused a significant reduction in serum TC ($p<0.01$) and LDL-C ($p<0.001$) levels (Figure 2 A and D) by 37.8 and 49.7% respectively, as compared to the HC group.

The lovastatin-treated group showed a significant decrease of 25.6 and 36.2% in serum TC and LDL-C ($p<0.05$) levels, respectively, as compared to the HC group (Figure 2 A and D). Administration of both the extract and lovastatin also significant decreased the CRI ratio as compared to the HC group (Figure 2E). However, the administration of CV water extract did not significantly decrease the serum TG levels (Figure 2 B). The serum HDL-C levels (Figure 2 C) in the rats which received 250 and 1000 mg/kg CV extract were significantly increased as compared to the HC group.

DISCUSSIONS

Hypercholesterolaemia is a major risk factor for the development and progression of atherosclerosis and coronary artery disease (Prasad and Kalra, 1993; Deepa and Varalakshmi, 2005). In hypercholesterolaemia, there is an increase in serum TC, TG and LDL-C levels, which results in an increased risk for the development of atherosclerosis. Thus, regulating serum cholesterols level is important for atherosclerosis prevention, as it has been shown that atherosclerosis can be suppressed by controlling the levels of serum cholesterol. The therapeutic benefits of plant extracts that are without side effects have been the focus of many recent extensive studies (Yokozawa et al., 2003, 2006).

In the present study, the effects of CV extract on serum lipid profiles were observed in the P-407-induced hypercholesterolaemia model and the high cholesterol diet-induced hypercholesterolaemia model. Most cholesterol in the body is present as an essential component of the cell membrane, while the remainder is in transit through the blood or functions as a starting material for the biosynthesis of bile acid, steroid hormones, and vitamin D (Libby et al., 2000). Elevated levels of serum TG and LDL-C that are accompanied by reduced HDL-C levels are often associated with an increased risk of coronary heart disease (Smith et al., 2004). According to many studies, LDL-C is considered the most dangerous among the serum lipids, and the oxidation of LDL-C leads to its increased penetration of arterial walls (Steinberg et al., 1989; Aviram, 1993).

Moreover, elevated LDL-C levels play a crucial role in the development of atherosclerotic lesions that progress from fatty streaks to ulcerated plaques (Schaefer et al., 1995; Ross, 1993). Thus, serum LDL-C levels are used as the basis for initiating and monitoring the treatment of patients with elevated blood cholesterol levels (Schaefer et al., 1995; Grundy, 1993). P-407 is a block copolymer composed of a hydrophobe that is flanked on each side by hydrophilic polyoxyethylene units (Johnston and

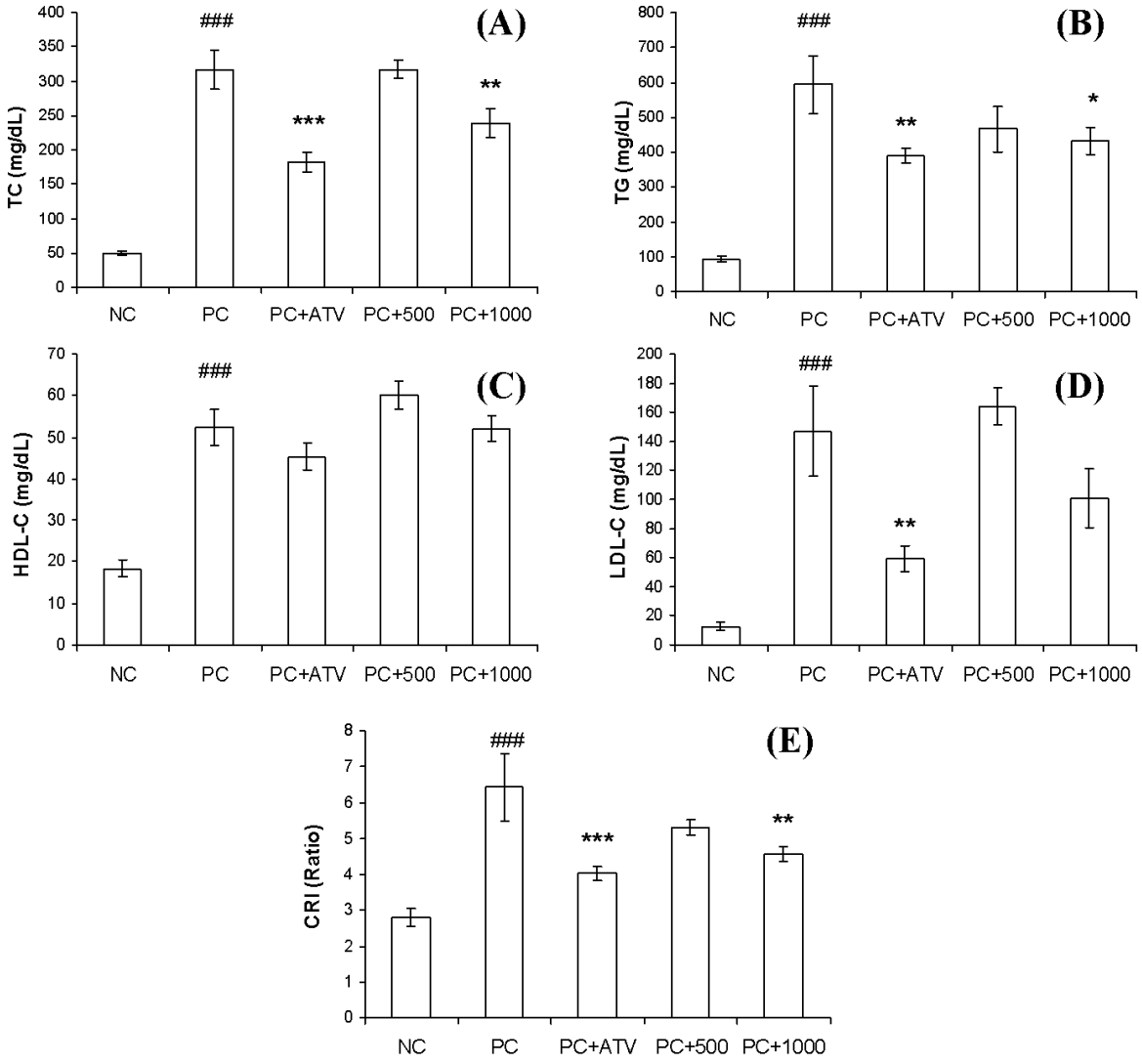

Figure 1. Effects of CV water extract the on serum levels of TC (A), TG (B), HDL-C (C), and LDL-C (D) and on the CRI values (E)of P-407-induced hypercholesterolaemic rats. Each bar represents the mean ± SEM from 6 animals. ###p<0.001 compared to the NC group, *p<0.05, **p<0.01, ***p<0.001 compared to PC the group.
Abbreviations: NC, Normal control; PC, P-407 control; PC+ATV, P-407 + 75 mg/kg of atorvastatin treatment; PC+500, P-407 + 500 mg/kg of CV treatment; PC +1000, P-407 + 1000 mg/kg of CV treatment.

Palmer, 1993). A rapid, convenient and low-cost hypercholesterolaemic animal model had been developed based on the administration of P-407 (Wout et al., 1992). P-407-induced hypercholesterolaemia is associated with alterations in activity of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, lipoprotein lipase (LPL), lecithin cholesterol acyltransferase (LCAT), cholesteryl ester transfer protein (CETP), hepatic lipase (HL) and lipoprotein lipase (LPL) (Johnston and Palmer, 1997). P-407 directly inhibits the heparin-releasable fraction of LPL and HL, and it indirectly increases thebiologic activity of CETP and LCAT (Johnston, 2004). A single injection of P-407 has been shown to cause elevations of serum cholesterol and triglyceride levels in rats (Wout et al., 1992).

In the present study, the rats treated with P-407 were characterized by high serum lipid profiles. The rats treated with 1000mg/kg of CV extract were characterized by a significant reduction in serum TC and TG levels. Hence, these results indicate that the CV extract causes a serum lipid-lowering effect in rats with hypercholesterolaemia induced by P-407. A high cholesterol diet is frequently used to increase serum cholesterol levels to evaluate the effectiveness of the

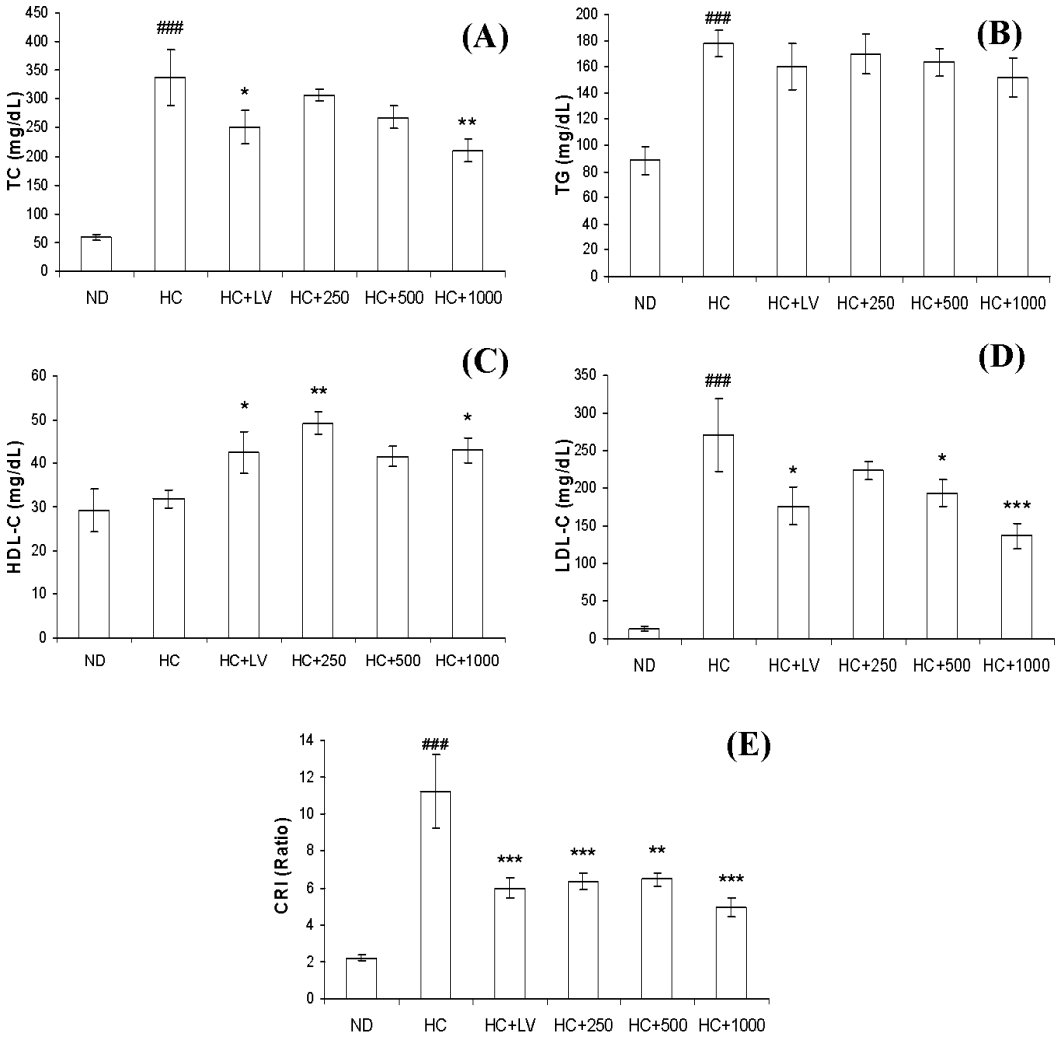

Figure 2. Effects of CV water extract on serum levels of TC (A), TG (B), HDL-C (C), and LDL-C (D) and on the CRI values (E) of rats fed a high cholesterol diet. Each bar represents the mean ± SEM from 6 animals. ###p<0.001 compared to the ND group, *p<0.05, **p<0.01, ***p<0.001 compared to the HC group.
Abbreviations: ND, Normal basal diet; HC, High cholesterol diet; HC + LV, High cholesterol diet + 60 mg/kg of lovastatin; HC+ 250, High cholesterol diet + 250 mg/kg of CV; HC + 500, High cholesterol diet + 500 mg/kg of CV; HC + 1000, High cholesterol diet + 1000 mg/kg of CV

extract on hypercholesterolaemia in different animal models (Du et al., 2009; Yoon et al., 2008). In rats, the high cholesterol diet results in marked alterations in the type and distribution of the plasma lipoproteins and their apoproteins (Mahley and Holcombe, 1977). The most distinctive change was in the prominence of the arginine-rich apoprotein (ARP), which is associated with cholesterol-induced β-migrating lipoprotein (B-VLDL), LDL-C, and HDL-C (Mahley et al., 1975). In this study, hypercholesterolaemia was induced in rats by adding cholesterol (2%), cholic acid (0.5%) and butter (10%) to their normal basal diet for 14 days.

The rats that were fed a high cholesterol diet had higher concentrations of serum TC and LDL-C levels than those fed a normal diet, which indicated that hyper-cholesterolaemia was successfully established in our rat model. In our current study, the administration of CV extract in rats fed a high cholesterol diet caused a reduction in the levels of TC and LDL-C as compared to the rats fed a high cholesterol diet without the addition of CV extract. Furthermore, the HDL-C levels in these rats were increased significantly as compared to the HC group. Hence, these results indicate that CV extract can prevent hypercholesterolaemia in high cholesterol-fed rats. The coronary risk index (CRI), which is the ratio of TC/HDL-C, is an indicator of coronary heart disease risk

(Stampfer et al., 1991). In the present study, the CRI values of rats treated with CV extract were sharply reduced in both hypercholesterolaemic models compared to the PC and HC groups. These results indicate that CV extract can function as a lipid-lowering agent that prevents hypercholesterolaemic atherosclerosis by lowering serum lipid levels.

In conclusion, we found in these models of experimental hypercholesterolaemia that CV extract contains anti-hypercholesterolaemic activity. Further investigations are needed to establish definitive evidence for the implication of CV extract on rat cholesterol metabolism.

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