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Hypolipidemic effects of curcumin, cinnamon, vitamin C and simvastatin in domestic rabbits

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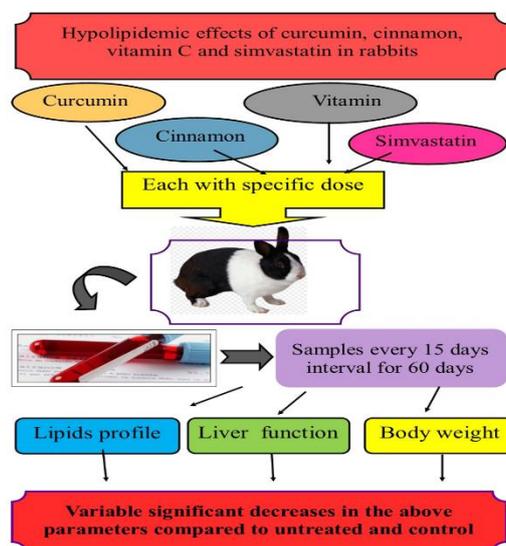
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Abstract

This study investigated the hypolipidemic effects of curcumin, cinnamon, vitamin C and simvastatin in male rabbits. The hypolipidemic effect of these materials were assessed by following the effects on body weight, the lipid profile and liver enzymes. The lipid profile includes total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL). The liver activities enzymes include aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) in serum. Highly significant increases in lipid profile parameters of rabbit group were found in rabbits fed with high lipid diet only over the respective values in the control group. Liver function profile showed a significant increase in this group as compared to those in the control group. The groups treated with curcumin, cinnamon, vitamin C and simvastatin showed a variable significant decrease in lipid profile in this order: cinnamon > vitamin C > simvastatin > curcumin and in liver functions profile in this order: curcumin > simvastatin > vitamin C > cinnamon. Groups treated with these materials showed significant body loss as compared to untreated rabbits in this order: cinnamon > curcumin > vitamin C > simvastatin.

Keywords: Curcumin; Cinnamon; Vitamin C; Simvastatin; Lipid profile; Rabbits

Graphical abstract



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1. Introduction

Hyperlipidemia is characterized by higher total serum cholesterol, low density lipoprotein cholesterol, very low density lipoprotein cholesterol and decreased high density lipoprotein cholesterol levels [1]. Several studies have proved a clear relationship between high cholesterol level in serum and cardiovascular disease [2]. Cardiovascular disease has been a major death implement accounting for 16.7 million mortalities per year [3]. Cardiovascular events and related deaths may be reduced by decreasing total cholesterol [4]. The use of plant extracts in treating different disorders is a common practice nowadays. A number of therapeutically and nutritional plants have shown promising effect in reducing serum lipids concentrations, for example: curcumin, cinnamon, vitamin C and simvastatin.

Curcumin (*diferuloylmethane*), a widely used yellow spice and a food coloring agent, is extracted from the rhizomes of *curcuma longa*, Linn (*Zingiberaceae*), is a herb distributed mainly throughout tropical and subtropical regions of the world [5]. Curcumin has many pharmacological effects including anti-inflammation, antioxidant, anti-tumor, eliminating free radicals, lipid reduction, anti-coagulation and antimicrobial [6]. It is also reported that administration of curcumin in coronary heart disease, the lipid level is significantly controlled and the occurrence of cardiovascular incidence is reduced. Some studies showed controversial results in animal and human studies on lipid profile improvement by curcumin [7]. Cinnamon (*Cinnamomum zeylanicum*), is an old spice that has been referred as sweet wood [8]. It has a history of uses as preservative, food flavoring, and a pharmacological agent [9]. In addition, Khan et al [10] showed in 2004 that patients with type 2 diabetes given cinnamon for 40 days showed significant decrease in fasting serum glucose and lipid profile. Cinnamate, a phenolic substance found in the internal bark of cinnamon, decrease cholesterol level in high lipid fed rats by inhibiting hepatic activity of HMG Co-A reductase [11]. Polyphenolic polymers existed in cinnamon have antioxidant effect and have been proven to decrease oxidative stress through inhibition of 5-lipoxygenase enzyme [12]. Vitamin C is an important antioxidant, effective in catching oxygen-derived free radicals [13]. In addition, vitamin C can catabolize cholesterol to bile acid in guinea pig and has been found to be a good factor in lipid regulation [14]. Ness et al [15] proved useful effects of vitamin C on lipids in human. Many studies showed decreased vitamin C level in diabetic patients and indicates that oxidative stress is increased in diabetes [16]. Most diabetes cases have lipid metabolism disorders; such as increased triglyceride decreased high density lipoprotein (HDL). High doses of ascorbic acid (2 g/day) improve blood glucose and decrease triglyceride and cholesterol in type 2 diabetes patients [17]. It was shown that vitamin C is important for transforming cholesterol to bile acids as a step of its biosynthesis [18]. Other research in humans found that the uptake of 500 mg/d can reduce total serum cholesterol in high lipid groups [19]. The hypocholesterolemic effect of ascorbic acid feeding in rats was studied in liver and plasma cholesterol. It was noted that, ascorbic acid concentrations decreased the plasma and the liver cholesterol levels significantly [20]. Simvastatin, one of the drug class known as statins, is used for lowering blood cholesterol [21]. It also prevents strokes and stabilizes plaque by anti-inflammatory and other mechanisms. Like all statins, simvastatin acts by inhibiting HMG-CoA reductase, which is accompanied with a decrease in total serum cholesterol and low-density lipoprotein (LDL) by as much as 28–42% and 20–31% through long term treatment [22]. Because of these properties, simvastatin is considered as one of the most used lipid-lowering drug in patients with high cholesterol levels. This study was made to evaluate the possible hypolipidemic effect of curcumin, cinnamon, vitamin C and simvastatin-drug on serum lipids profile.

2. Material and methods

2.1. Animals

Thirty-six healthy male rabbits weighing 1.5 to 2.0 kg were purchased from local market. Rabbits were kept under standard laboratory conditions (12 h light / dark and 24±3°C) in individual cages. They were kept for familiarization for one 7 days before the beginning of the experiment. The rabbits were fed with normal rabbit chow throughout the experiment and water ad libitum. Rabbits were indiscriminately divided into six equal groups (6 rabbits each): the first group was kept as untreated control, the second was fed with high lipids diet, the third was fed with curcumin, the fourth was fed with cinnamon, the fifth was fed with vitamin C while the sixth group was fed with simvastatin-drug. All the treated groups (third, fourth, fifth and sixth) were fed melted butter and powder cholesterol (mixed with ordinary diet) to produce experimental hyperlipidemia in rabbits at the rate of 500 mg/kg body weight in 5 mL coconut oil for 60 days [23].

2.2. Chemicals

Crude *curcuma longa* rhizomes were purchased from local market. The rhizomes were peeled, cut into small pieces and shade dried. Crude drug was powdered. The crude powder was then preserved in colored airtight glass and was placed in a refrigerator. Barks of cinnamon were procured from local market and dried in the shade and finely powdered with

an electric grinder. Vitamin C, and other chemical reagents were purchased from Sigma-Aldrich Chemical Company, St. Louis, USA. Simvastatin-drug (Tablet survive® 20 mg, Mepro pharmaceutical company) that was used as a synthetic lipid lowering agent, was purchased from local pharmacies. Cholesterol 1% powder was obtained from Merck, Darmstadt, Germany. The total cholesterol kit and total triglycerides (TG) kit were obtained from Biocon Diagnostik (Marienhagen, Germany). High density lipoprotein (HDL) and low density lipoprotein (LDL) kit was purchased from Stanbio (Boerne, Texas, USA). Aminotransferases (AST and ALT) and alkaline phosphatase (ALP) were obtained from a commercial kit (Quimica Clinica Aplicada SA, Amposta, Spain).

2.3. Methods

Four separate powdered doses of curcumin, cinnamon, vitamin C supplement and simvastatin- drug were mixed with distilled water to make suspensions which were given to animals by gavage twice daily for 8 weeks. The doses used in this study were selected on the basis of the previous studies [23,24,25,26,27]. Curcumin at the dose of 200 mg/kg body weight, cinnamon at the dose of 500 mg/kg body weight, vitamin C at the dose of 200 mg/kg body weight and simvastatin- drug at the dose of 5 mg/kg body weight. From individual animals of each group, blood samples were taken at 15 days interval (4 times during the 60 days study period). For the collection of blood samples jugular vein, located on either side of the neck, was used. The area of the neck was shaved, cleaned with antiseptic solution and then the blood samples were drawn. The samples were allowed to clot for 20 minutes at refrigeration temperature and then were centrifuged at 4000 rpm for five minutes. Serum was separated to small clean bottles. The bottles were stored at freezing temperature till analysis. Lipid profile parameters including triglycerides, total cholesterol, high density lipoprotein cholesterol (HDL-cholesterol) and low density lipoprotein cholesterol (LDL-cholesterol) were determined in serum of rabbits. Aminotransferases (AST and ALT) and alkaline phosphatase (ALP) were assayed using a commercial kit (Quimica Clinica Aplicada SA, Amposta, Spain) according to the method of Reitman and Frankel [28]. The collected data was expressed as mean lipid profile parameters \pm standard error of means (SEM). The significance of the differences between the treated and untreated values was tested using student's 't'-test with software Statistical Package for the Social Sciences (SPSS 17).

3. Results

Table 1, presents the effects of high lipid diet with or without curcumin on lipid profile, liver function profile and total body weight of rabbits. Feeding rabbits with high lipid diet only (untreated), resulted in hypercholesterolemia, evidenced by high serum total cholesterol which was more than that of the control animals. Feeding rabbits with high lipid diet and curcumin (200 mg/kg/b.wt.) (treated), resulted in lower serum total cholesterol compared to that of high lipid diet only (untreated), with high significant values for all time-intervals compared to control. Treated sample results of HDL and LDL cholesterol as well as triglycerides were also decreased in a high significant way with respect to untreated group during the four time-intervals. Supplementation of curcumin reduced the values of ALT, AST and ALP in a highly significant way. The same results were found for the change in total body weight with a very significant decrease in the presence of curcumin compared to high lipid diet only. Table 2, shows the influence of high lipid diet with or without cinnamon on lipid profile, liver function profile and total body weight of rabbits. Giving rabbits high lipid diet only (untreated), resulted in hypercholesterolemia, as shown by high serum total cholesterol which was more than that of the control animals. Feeding rabbits with high lipid diet and cinnamon (500mg/kg/b.wt.) (treated), resulted in lower serum total cholesterol compared to that of high lipid diet only (untreated), with high significant values for all time-intervals compared to control. Treated sample results of HDL and LDL cholesterol as well as triglycerides were also decreased in a high significant way compared to untreated group during the four time-intervals. Providing cinnamon reduced the values of ALT, AST and ALP in a highly significant way.

The same results were found for the change in total body weight with a very significant decrease in the presence of cinnamon compared to high lipid diet only.

Table 3, demonstrate the impact of high lipid diet with or without vitamin C on lipid profile, liver function profile and total body weight of rabbits. Feeding rabbits high lipid diet only (untreated), resulted in high cholesterol level, as shown by serum total cholesterol level higher than that of the control animals. Giving rabbits high lipid diet and vitamin C (200mg/kg/b.wt.) (treated), resulted in lower serum total cholesterol compared to that of high lipid diet only (untreated), with high significant values for all time-intervals compared to control sample. Treated sample results of HDL and LDL cholesterol as well as triglycerides were also decreased significantly compared to untreated group during the four time-intervals. Providing vitamin C reduced the values of ALT, AST and ALP significantly. The same trend was noticed with a significant decrease in total body weight in the presence of vitamin C compared to high lipid diet only.

Table 1 Effects of curcumin (200 mg/kg/b.wt.) on serum lipid profile and body weight of rabbits.

Parameter	Control (n=6)	High-Lipid diet (n=6)				High-Lipid diet + Vitamin C (n=6)			
		15 days	30 days	45 days	60 days	15 days	30 days	45 days	60 days
TC (mg/dL) P(sig.)	70.42±1.76	72.18±1.59 0.025	79.18±4.94 0.000	105.06±4.06 0.000	118.3±2.68 0.000	71.32±1.71 0.125	76.11±2.14 0.000	91.24±1.46 0.000	106.7±2.18 0.000
TG (mg/dL) P(sig.)	78.89±1.61	78.00±2.45 0.10	78.14±3.02 0.15	81.79±2.54 0.005	85.14±3.62 0.000	77.13±2.33 0.025	74.17±2.72 0.000	78.04±2.24 0.000	79.71±3.14 0.000
LDL (mg/dL) P(sig.)	27.48±1.79	29.17±1.73 0.025	29.88±1.12 0.01	30.67±2.03 0.0025	32.40±0.93 0.000	27.57±2.13 0.25	29.00±1.67 0.000	29.11±2.19 0.000	30.05±1.33 0.000
HDL(mg/dL) P(sig.)	21.91±1.56	25.91±2.23 0.0005	38.27±3.73 0.000	39.87±2.51 0.000	46.22±1.88 0.000	25.25±2.51 0.001	34.11±2.79 0.000	36.81±2.00 0.000	41.22±1.63 0.000
ALT(U/L) P(sig.)	33.41±1.13	34.52±1.19 0.0005	37.25±1.11 0.000	39.78±1.39 0.000	41.80±1.50 0.000	32.82±1.48 0.001	30.49±1.81 0.000	28.07±1.63 0.000	35.11±1.50 0.000
AST(U/L) P(sig.)	32.12±1.59	33.09±1.26 0.005	34.89±1.31 0.000	35.47±1.49 0.000	36.41±1.15 0.000	32.00±1.58 0.25	31.21±1.46 0.002	30.28±1.18 0.005	30.00±1.61 0.000
ALP(U/L) P(sig.)	44.75±1.09	47.12±1.36 0.001	48.72±1.86 0.000	50.60±1.31 0.000	51.11±1.43 0.000	43.89±1.69 0.05	42.11±1.57 0.000-	43.12±1.71 0.000	43.11±1.85 0.000
BW (gm) P(sig.)	1997±29.66	2096±31.58 0.000	2198±28.41 0.000	2275±34.18 0.000	2412±35.16 0.000	2000±30.24 0.0005	2101±29.89 0.000	2108±32.15 0.000	2103±34.88 0.000

TC- Serum Total cholesterol; TG- Serum triglycerides; LDL- low-density lipoproteins; HDL- high-density lipoproteins; ALT- Alanine transaminase; AST- Aspartate aminotransferase; ALP Alkaline phosphatase - ; BW- Total body weight

Table 2 Effects of cinnamon (0.5 g/kg/b.wt.) on serum lipid profile and body weight of rabbits.

Parameter	Control (n=6)	High-Lipid diet (n=6)				High-Lipid diet + Vitamin C (n=6)			
		15 days	30 days	45 days	60 days	15 days	30 days	45 days	60 days
TC(mg/dL) P(sig.)	70.42±1.76	72.18±1.590. 025	79.18±4.94 0.000	105.06±4.06 0.000	118.3±2.68 0.000	70.71±3.51 0.25	71.69±5.97 0.000	95.77±6.58 0.000	89.83±3.04 0.000
TG(mg/dL) P(sig.)	78.89±1.61	78.00±2.45 0.10	78.14±3.02 0.15	81.79±2.54 0.005	85.14±3.62 0.000	77.76±2.18 0.10	77.14±2.02 0.02	76.31±2.82 0.005	75.93±1.93 0.0015
LDL(mg/dL) P(sig.)	27.48±1.79	29.17±1.730. 025	29.88±1.12 0.01	30.67±2.03 0.0025	32.40±0.93 0.0005	29.10±2.09 0.0025	29.46±1.63 0.02	29.00±1.92 0.05	31.10±2.78 0.0025
HD(mg/dL) P(sig.)	21.91±1.56	25.91±2.230. 0005	38.27±3.73 0.000	39.87±2.51 0.000	46.22±1.88 0.000	25.12±2.49 0.0025	33.63±2.29 0.000	35.29±1.71 0.000	40.11±2.64 0.000
ALT(U/L) P(sig.)	33.41±1.13	34.52±1.19 0.0005	37.25±1.11 0.000	39.78±1.39 0.000	41.80±1.50 0.000	34.35±1.53 0.000	35.15±1.24 0.01	36.28±1.81 0.000	38.72±1.18 0.000
AST(U/L) P(sig.)	32.12±1.59	33.09±1.26 0.005	34.89±1.31 0.000	35.47±1.49 0.000	36.41±1.15 0.000	32.14±1.28 0.010	31.17±1.89 0.005	32.19±1.21 0.005	33.01±1.48 0.005
ALP(U/L) P(sig.)	44.75±1.09	47.12±1.36 0.001	48.72±1.86 0.000	50.60±1.31 0.000	51.11±1.43 0.000	46.00±1.21 0.000	45.41±1.80 0.000	49.23±1.10 0.000	49.01±1.43 0.000
BW(gm) P(sig.)	1997±29.66	2096±31.58 0.000	2198±28.41 0.000	2275±34.18 0.000	2412±35.16 0.000	2009±31.03 0.0005	2043±32.32 0.000	2060±29.67 0.000	2069±30.85 0.000

TC- Serum Total cholesterol; TG- Serum triglycerides; LDL- low-density lipoproteins; HDL- high-density lipoproteins; ALT- Alanine transaminase; AST- Aspartate aminotransferase; ALP Alkaline phosphatase - ; BW- Total body weight

Table 3 Effects of vitamin C (200 mg/kg/b.wt.) on serum lipid profile and body weight of rabbits.

Parameter	Control (n=6)	High-Lipid diet (n=6)				High-Lipid diet + Vitamin C (n=6)			
		15 days	30 days	45 days	60 days	15 days	30 days	45 days	60 days
TC(mg/dL) P(sig.)	70.42±1.76	72.18±1.59 0.025	79.18±4.94 0.000	105.06±4.06 0.000	118.3±2.68 0.000	71.00±1.22 0.25	70.13±2.53 0.25	95.27±3.16 0.000	92.11±2.77 0.000
TG(mg/dL) P(sig.)	78.89±1.61	78.00±2.45 0.10	78.14±3.02 0.15	81.79±2.54 0.005	85.14±3.62 0.000	78.65±2.37 0.0025	76.17±2.92 0.000	79.89±2.48 0.000	81.18±3.54 0.000
LDL(mg/dL) P(sig.)	27.48±1.79	29.17±1.73 0.025	29.88±1.12 0.01	30.67±2.03 0.0025	32.40±0.93 0.0005	28.19±1.23 0.20	27.00±2.02 0.25	25.36±2.82 0.02	28.63±1.73 0.10
HDL(mg/dL) P(sig.)	21.91±1.56	25.91±2.23 0.0005	38.27±3.73 0.000	39.87±2.51 0.000	46.22±1.88 0.000	21.87±2.27 0.25	30.16±2.79 0.000	30.12±2.81 0.000	39.21±1.55 0.000
ALT(U/L) P(sig.)	33.41±1.13	34.52±1.19 0.0005	37.25±1.11 0.000	39.78±1.39 0.000	41.80±1.50 0.000	34.56±1.43 0.0025	33.20±1.18 0.25	31.16±1.32 0.0025	36.82±1.48 0.0005
AST(U/L) P(sig.)	32.12±1.59	33.09±1.26 0.005	34.89±1.31 0.000	35.47±1.49 0.000	36.41±1.15 0.000	30.11±1.72 0.002	28.89±1.48 0.000	26.40±1.33 0.000	24.11±1.38 0.000
ALP(U/L) P(sig.)	44.75±1.09	47.12±1.36 0.001	48.72±1.86 0.000	50.60±1.31 0.000	51.11±1.43 0.000	46.42±1.52 0.005	47.49±1.38 0.000	48.12±1.75 0.000	48.67±1.83 0.000
BW(gm) P(sig.)	1997±29.66	2096±31.58 0.000	2198±28.41 0.000	2275±34.18 0.000	2412±35.16 0.000	2091±33.11 0.0005	2108±30.44 0.000	2112±33.72 0.000	2123±34.86 0.000

TC- Serum Total cholesterol; TG- Serum triglycerides; LDL- low-density lipoproteins; HDL- high-density lipoproteins; ALT- Alanine transaminase; AST- Aspartate aminotransferase; ALP Alkaline phosphatase - ; BW- Total body weight

Table 4 Effects of simvastatin (5 mg/kg/b.wt.) on serum lipid profile and body weight of rabbits.

Parameter	Control (n=6)	High-Lipid diet (n=6)				High-Lipid diet + Vitamin C (n=6)			
		15 days	30 days	45 days	60 days	15 days	30 days	45 days	60 days
TC (mg/dL) P(sig.)	70.42 ±1.76	72.18 ±1.59 0.025	79.18 ±4.94 0.000	105.06±4.06 0.000	118.3 ± 2.68 0.000	73.81 ±1.51 0.001	78.28 ±1.47 0.000	98.09 ±2.32 0.000	107.70±1.49 0.000
TG (mg/dL) P(sig.)	78.89 ± 1.61	78.00 ± 2.45 0.10	78.14 ± 3.02 0.15	81.79 ± 2.54 0.005	85.14 ± 3.62 0.000	77.13 ± 3.02 0.025	76.30 ±4.38 0.000	75.44 ±4.36 0.000	75.07±2.90 0.0005
LDL (mg/dL) P(sig.)	27.48 ± 1.79	29.17±1.73 0.025	29.88 ± 1.12 0.010	30.67 ± 2.03 0.0025	32.40 ± 0.93 0.0005	26.47 ± 1.73 0.100	25.61 ±1.15 0.000	30.27 ±1.60 0.000	27.11±1.17 0.010
HD(mg/dL) P(sig.)	21.91 ± 1.56	25.91 ± 2.23 0.0005	38.27 ± 3.73 0.000	39.87 ± 2.51 0.000	46.22 ± 1.88 0.000	22.73 ±3.83 0.15	27.4 1 ±4.11 0.000	28.49 ±3.77 0.000	38.91±1.88 0.000
ALT(U/L) P(sig.)	33.41±1.13	34.52±1.19 0.0005	37.25±1.11 0.000	39.78±1.39 0.000	41.80±1.50 0.000	27.10 ±1.29 0.000	34.39 ±1.34 0.05	31.60 ±1.25 0.005	39.15±1.61 0.000
AST(U/L) P(sig.)	32.12±1.59	33.09±1.26 0.005	34.89±1.31 0.000	35.47±1.49 0.000	36.41±1.15 0.000	30.81 ± 1.13 0.000	30.01 ±1.25 0.002	29.17 ±1.85 0.000	31.00±1.68 0.000
ALP(U/L) P(sig.)	44.75 ±1.09	47.12 ±1.36 0.001	48.72 ±1.86 0.000	50.60 ±1.31 0.000	51.11 ±1.43 0.000	46.90 ±1.75 0.0005	49.05 ±1.18 0.000	47.07 ±1.63 0.000	46.10±1.34 0.000
BW (gm) P(sig.)	1997± 29.66	2096±31.58 0.000	2198±28.41 0.000	2275±34.18 0.000	2412±35.16 0.000	2089±35.22 0.000	2115±32.70 0.000	2123±29.39 0.000	2136±31.24 0.000

TC- Serum Total cholesterol; TG- Serum triglycerides; LDL- low-density lipoproteins; HDL- high-density lipoproteins; ALT- Alanine transaminase; AST- Aspartate aminotransferase; ALP Alkaline phosphatase - ; BW- Total body weight

Table 5 % of changes of treated and un-treated rabbits compared to control, whereas: (A: Curcumin, B: Cinnamon, C: Vit C, D: Simvastatin).

Parameters	Treating With	% of Change for High Lipid Diet (Untreated)				% of Change for Treated				% of Change Between Treated & Untreated			
		15 days	30 days	45 days	60 days	15 days	30 days	45 days	60 days	15 days	30 days	45 days	60 days
TC	A	+ 2.5%	+12.4%	+49.1%	+67.5%	+1.3%	+8.1%	+29.6%	+51.5%	-1.2%	-3.9%	-13.2%	-9.8 %
	B	"	"	"	"	+0.41 %	+1.8%	+36%	+27.5%	-2.0%	-9.5%	-8.8%	-24.1%
	C	"	"	"	"	+0.82%	-0.41%	+35.3%	+30.8%	-1.6%	-11.4%	-9.3%	-22.1%
	D	"	"	"	"	+4.8%	+11.2%	+39.3%	+52.9%	-2.3%	-1%	-6.6%	-8.9%
TG	A	-1.0%	-.82%	+3.8%	+8.1%	-2.2%	-6.0%	-1.1%	+1.0%	-1.1%	-5.0%	-4.6%	-6.4%
	B	"	"	"	"	-1.4%	-2.2%	-3.27%	-3.7%	-0.31%	-1.3%	-6.7%	-10.8%
	C	"	"	"	"	-0.31%	-3.4%	+1.3%	+2.9%	+ 0.8%	-2.6%	-2.3%	-4.7%
	D	"	"	"	"	-2.2%	-3.3%	-4.3%	-4.9%	-1.1%	-2.4%	-7.8%	-11.8%
LDL	A	+6.25%	+8.7%	+11.6%	+17.9%	+0.32%	+5.5%	+5.9%	+9.3%	-5.5%	-2.9%	-5.4%	-7.3%
	B	"	"	"	"	+5.9%	+7.2%	+5.5%	+13.2%	-0.24%	-1.4%	-5.7%	-4.0%
	C	"	"	"	"	+2.6%	-1.7%	-7.7%	+4.1%	-3.4%	-9.6%	-17.5%	-11.6%
	D	"	"	"	"	-3.75	-6.8%	+10.2%	-1.3%	-9.3%	-14.3%	-1.6%	-16.3%
HDL	A	+18.2%	+74.6%	+81.5%	+99.3%	+15.2%	+55.6%	+68.0%	+88.1%	-2.5%	-34.1%	-7.7%	-10.8%
	B	"	"	"	"	+14.6%	+53.6%	+61.0%	+83.0%	-3.0%	-12.1%	-11.5%	-13.2%
	C	"	"	"	"	-0.2%	+37.6%	+37.4%	+78.9%	-15.6%	-21.2%	-24.5%	-15.2%
	D	"	"	"	"	+3.7%	+25.1%	+30.0%	+77.5%	-12.3%	-2.2%	-28.5%	-15.8%
ALT	A	+3.3%	+11.5%	+18.9%	+25.1%	-1.7%	-8.7%	-15.9%	+4.9%	-4.9 %	-18.1%	-29.4%	-16.0%
	B	"	"	"	"	+2.8%	+5.2%	+8.5%	+15.8	-0.5%	-5.6%	-8.8%	-7.4%
	C	"	"	"	"	+3.44%	-0.62%	-6.6%	+10.2%	-0.12%	-10.9%	-21.7%	-11.9%
	D	"	"	"	"	-18.8%	+2.9%	-5.4%	+17.2%	-21.5%	-7.7%	-20.6%	-6.3%
AST	A	+3.0%	+8.6%	+10.5%	+22.7%	-0.34%	-2.8%	-5.7%	-6.6%	-3.3%	-10.5%	-14.6%	-17.6%
	B	"	"	"	"	+0.12%	-2.9%	+0.20%	+2.77%	-2.9%	-10.7%	-9.2%	-9.3%

	C	"	"	"	"	-6.3%	-10.1%	-17.8%	-24.9%	-8.9%	-17.2%	-25.3%	-13.8%
	D	"	"	"	"	-4.0%	-6.5%	-9.2%	-3.5%	-6.9%	-14.0%	-17.7%	-14.8%
ALP	A	+5.3 %	+8.9 %	+13.1%	+14.2%	-1.9%	-5.9%	-3.6%	-3.6%	-6.9%	-13.5%	-14.8%	-15.7%
	B	"	"	"	"	+2.7%	+1.5%	+10.0%	+9.4%	-2.4%	-6.8%	-2.7%	-4.1%
	C	"	"	"	"	+3.7%	+6.1%	+7.5%	+8.7%	-1.5%	-2.6%	-4.9%	-4.6%
	D	"	"	"	"	+4.8%	+9.6%	+5.1%	+3.0%	- 0.57%	+0.7 %	-6.9%	-9.8%
T. B. weight	A	+5.0%	+10.1%	+13.9%	+20.8%	+0.15%	+5.2%	+5.6%	+5.3%	-4.6%	-4.4%	-7.3%	-12.8%
	B	"	"	"	"	+0.6%	+2.3%	+3.1%	+3.6%	-4.2%	-7.0%	-9.5%	-14.2%
	C	"	"	"	"	+4.7%	+5.5%	+5.7%	+6.3%	-0.23%	-4.2%	-7.2%	-12.0%
	D	"	"	"	"	+4.6%	+5.9%	+6.3%	+6.9%	- 0.57%	-3.8%	-6.7%	-11.4%

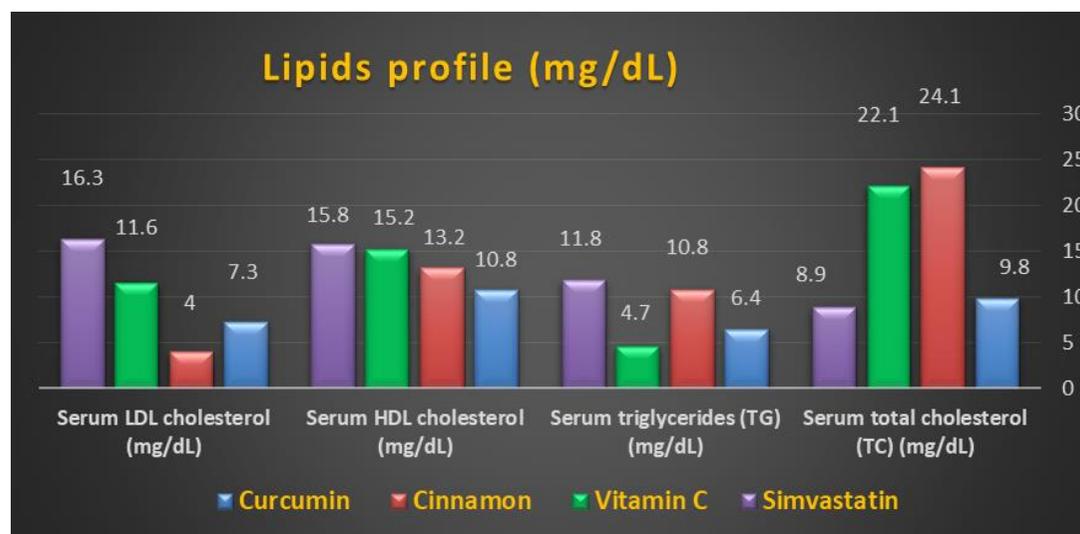


Figure 1 % of change between treated and untreated of serum lipid profile parameters (mg/dL) in rabbits fed with high-lipid diet and curcumin or cinnamon or vitamin C or simvastatin after 60 days.

Table 4, indicates the effect of high lipid diet with or without simvastatin on lipid profile, liver function profile and total body weight of rabbits. Providing rabbits high lipid diet only (untreated), resulted in high cholesterol level, as shown by serum total cholesterol level higher than that of the control animals. Giving rabbits high lipid diet and simvastatin (5mg/kg/b.wt.) (treated), resulted in lower serum total cholesterol compared to that of high lipid diet only (untreated), with high significant values for all time-intervals referred to control sample. Treated sample results of HDL and LDL cholesterol as well as triglycerides were also decreased significantly compared to untreated group during the four time-intervals. Administering rabbits with simvastatin reduced the values of ALT, AST and ALP significantly. The same trend was obtained with significant decrease in total body weight when administering simvastatin compared to high lipid diet only.

Table 5, shows the percentage of changes in untreated group, % of changes in treated group, and the % of changes between treated and untreated animals compared to control. The results show firstly a high increase in % of changes of untreated animals which then decreased very significantly when treated with curcumin, cinnamon, vitamin C and simvastatin. It was clear that the % of changes for treated animals were decreased more than untreated, while there was a high decrease on % of changes between treated & untreated in highly significant percent during the four time-intervals of all investigated parameters within the treating substances. There was variable change between the effects of each treatment substance throughout the experimental time-intervals.

The percentage of change between treated and untreated of serum lipid profile parameters (mg/dL) in rabbits fed with high-lipid diet and curcumin or cinnamon or vitamin C or simvastatin after 60 days were compared and illustrated in figure 1. It was shown that the results of serum total cholesterol for cinnamon and vitamin C have a higher % of change than curcumin and simvastatin. While the results of serum triglycerides for simvastatin and cinnamon are approximately equal but more than that of vitamin C and curcumin. Furthermore, % of change for serum HDL-cholesterol results for simvastatin and vitamin C are almost the same, while curcumin and cinnamon have less converging reading. Serum LDL-cholesterol % of change results for simvastatin and vitamin C are higher than cinnamon and curcumin.

The percentage of change for serum liver function profile parameters (U/L) in rabbits fed with high-lipid diet and curcumin or cinnamon or vitamin C or simvastatin after 60 days were compared and laid out in figure 2. It was noticed that the changes on ALT, AST and ALP for curcumin is the highest one followed by simvastatin and vitamin C, while cinnamon have a lower percentage of change readings.

The percentage of change for total body weight (gm) in rabbits fed with high-lipid diet and curcumin or cinnamon or vitamin C or simvastatin after 60 days was compared and shown in figure 3. It was found that cinnamon have the greater effect on total body weight followed by curcumin, vitamin C and finally simvastatin compared to control.

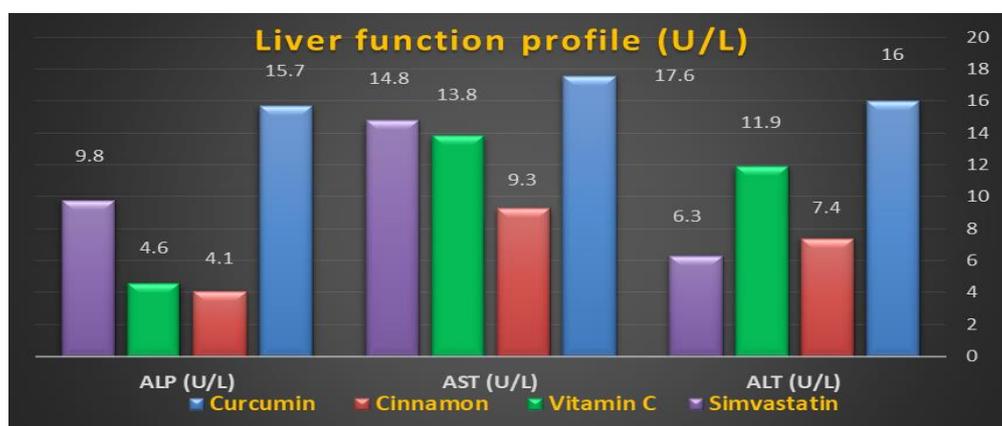


Figure 2 % of change between treated and untreated of serum liver function profile parameters (U/L) in rabbits fed with high-lipid diet and curcumin or cinnamon or vitamin C or simvastatin after 60 days.



Figure 3 % of change between treated and untreated of total body weight (gm) in rabbits fed with high-lipid diet and curcumin or cinnamon or vitamin C or simvastatin after 60 days.

4. Discussion

The induction of hyperlipidemia by feeding experimental animals a high-lipids diet, has been suggested by many scientists as a reliable model for detecting many diseases in humans. Therefore, our main objective in the current study was to induce hyperlipidemia in domestic rabbits after feeding the animals high-lipids diet, which was earlier described by Javed 2012 et al. [23]. After the model was established, we addressed the possible hypolipidemic effects of curcumin, cinnamon, vitamin C and simvastatin. In this context, the serum lipid profile, liver function enzymes and change in body weight were investigated. Feeding rabbits with high-lipids diet for 0-60 within four time-intervals consecutive days resulted in marked hypercholesterolemia, as the serum total cholesterol (TC) level, serum level of triglycerides (TG), Serum HDL-C and Serum LDL-C and total body weight were much greater than that of control animals during the investigated four time-intervals (15,30,45 and 60 days). This is in accordance with previous findings reported by Beynen et al.[29], who showed that feeding four different types of rats with high-lipids diet caused a notable hypercholesterolemia. A curcumin-enriched diet resulted in a hypolipidemic effect, as evidenced by its effects on the serum lipid profile of rabbits. Table (1) shows that curcumin lowered serum TC, but had no effect on serum TG. It elevated serum HDL-C, while reducing serum LDL-C. Also, the LDL-C/HDL-C ratio was decreased by more than half through the four experimental intervals. Contrary to these findings, Yasni et al.[30] reported that curcuminoids prepared from *Curcuma xanthorrhiza* had no significant effects on serum or liver lipids in rabbits fed a high cholesterol diet. Curcumin decreased the cholesterol levels when given to rabbits [31]. Diet-induced hyperlipemia is the most relevant stimulus for the induction of atherosclerotic lesions in humans. High cholesterol diet is useful for the assessment of agents that interfere with the uptake of cholesterol, with minimal effects on cholesterol biosynthesis. Cholesterol levels in the body result from two sources: absorption from the gastrointestinal tract and endo-genous synthesis. Thus, the hypolipidemic impact of curcumin noticed in the current study could possibly be referred to an effect on the absorption of cholesterol in the gut, especially curcumin was mixed with the high lipid diet. It may be explained that hypolipidemic effect of curcumin have the ability to increase the rate of cholesterol catabolism by increasing the activity of hepatic cholesterol 7- α -hydroxylase enzyme. This enzyme is the rate-limiting enzyme of bile acid biosynthesis [32]. The activities of serum ALT, AST and ALP were increased very significantly in rabbits maintained on high lipid diet compared to control animals. It was shown that curcumin lowered the activities of serum AST, ALT and ALP in rabbits fed with high lipid diet in very significant way. This finding is in line with Park et al. [33] and Akkrishnan & Menon [34] who found that curcumin could decrease the activities of serum AST and ALP in ethanol-induced liver damage in rats.

It was found that curcumin lowered total body weight for the rabbits fed by high lipid diet in a highly significant way through the four experimental intervals (Table 1). These results are in agreement with Földešiová et al., 2015,[35] who showed that addition of turmeric powder to rabbit diet positively affected body weight gain in rabbits, but in contrary with Ramirez-Tortosa et al. (1999)[31] and Basavaraj et al. (2010)[36] who found that turmeric addition did not affect the body weight gain of rabbits.

Cinnamon-enriched diet exhibited also a notable hypolipidemic effect, as evidenced by its modulating effects on the serum lipid profile of rabbits (Table 2). There was a highly significant reduction in TC, TG and LDL. This coincides with an elevation in HDL in diabetic animals treated with cinnamon, after 15,30,45 and 60 days of the treatment compared with the hyperlipidemic groups. The present results seem to be in concordance with the findings of other researchers

showed that giving cinnamon extract to hyperlipidemic animals decrease the lipid profile of TC, TG, LDL levels associated with an elevation in HDL levels [37]. The ability of the cinnamon to exhibit such changes may be explained by the effect of the cinnamon in preventing the synthesis of cholesterol or facilitating the excretion of cholesterol from the body [38]. On the other hand, it may improve the hepatic bile acid synthesis and increase degeneration of cholesterol to fecal bile acid and neutral sterol. When the bile is excreted, the body will try to break down cholesterol. This process might help lowering cholesterol levels [39,40]. The cinnamon has strong lipolytic action. Therefore, the cinnamon extract reduces triglycerides(TG) levels leading to inhibit of TG synthesis by the fat hydrolysis, which may maintain low value of TG [42]. Dugoua et al.,(2007) [40] reported that the effect can be due to cinnamaldehyde presence. As it is reported previously, the treatment with the cinnamon caused an increased in HDL levels. This effect may be due to the decreased conversion of HDL to VLDL in the liver and intestine, or it can be due to its ability to hydrolyze the fats that, in turn, leads to the increase in HDL level in blood [38]. Khan et al.,(2003) [38] showed that treatment with cinnamon might have a change in synthesis/ metabolism of LDL, through an increased LDL receptor, thus, stimulating the hepatic uptake of LDL and binding activity in a response to a decreased intracellular cholesterol concentration and a decrease in the serum TC and LDL concentration. The hepatoprotective effect of cinnamon reported in this study was evident from the significant decrease in serum levels of liver enzymes (AST, ALT and ALP) in rabbits. This effect was in agreement with the previous studies for cinnamon [48]. The possible mechanism explaining the hepatoprotective effect of cinnamon could be referred to the antioxidant activity of this substance which was found to increase serum levels of liver enzyme (AST, ALT and ALP) in diabetic rats [49]. It was found that cinnamon lowered total body weight for the rabbits fed by high lipid diet in a highly significant way through the four experimental intervals (Table 2). These results are in agreement with Alsoodeeri et al., 2020 [41] who reported that cinnamon extract powder at doses of 2 g/kg body weight per day for 30 days reduced body weight gain in Albino Rats.

Table (3) shows that vitamin C has significantly reduced the average TC, TG and LDL levels associated with an elevation in HDL level throughout the experimental periods (0-60 days). These results are consistent with [42] who found that the given vitamin C at dose 200 mg/kg to diabetic rats for four weeks resulted in lowering serum TC, TG, LDL and VLDL levels associated with an increase in the HDL level. The hypocholesterolemic effects of vitamin C could be due to its direct role as an antioxidant, in addition to its cholesterol lowering property due to the effect on cholesterol metabolism in the liver. In agreement with this theory, the serum cholesterol decreased and the activity of hydroxyl methyl-glutaryl-CoA reductase was inhibited by high dose of vitamin C [43]. Also may reduce the absorption of cholesterol and bile acid in the intestine and increase its excretion. This leads to a reduction in cholesterol by liver and help to decrease synthesis of TG by liver through inhibiting fatty acid formation [44]. The decreased serum LDL levels could be due to the performance of vitamin C catching free radicals which prevents lipid peroxidation [45]. The decreased conversion of HDL to VLDL may lead to an increased HDL level. So, vitamin C uptake lower VLDL level which may be due to the increased ability of conversion of VLDL to LDL by the lipoprotein lipase activity [46]. The activities of serum ALT, AST and ALP were increased very significantly in rabbits maintained on high lipid diet compared to control animals. It was shown that vitamin C lowered the activities of serum AST, ALT and ALP in rabbits fed with high lipid diet in a high significant way. This finding is confirmed by Sayed-Ahmed et al., (2018) [50] who reported that applying ascorbic acid will increase significantly serum ALT, AST, ALP, total protein and albumin of growing rabbits. Contrarily, Yousef et al. [51] found that rabbits treated with vitamin C did not show any changes in the activities of AST, ALT and ALP. It was found that supplementation of vitamin C to the rabbits fed by high lipid diet lowered total body weight in a highly significant way through the four experimental intervals (Table 3). These results are in agreement with Sallam et al., (2005) [47], who reported that treatment with vitamin C at 40 mg/kg body weight did not affect body weight gain.

The present study shows that administration of simvastatin improves lipid profile since they significantly decrease TC, TG, and LDL-C levels and a significant increase of serum HDL-C (Table 4). The resulting decrease in cholesterol concentration results in compensatory increase in the expression of hepatic LDL receptors, which remove LDL from circulation. Simvastatin effectively inhibit HMG-CoA reductase, the rate-limiting enzyme of the mevalonate pathway, therefore lowering intra-cellular cholesterol producing [52]. In this study rabbits treated with simvastatin showed a very significant reduction of cholesterol total (TC) and non-HDL-C levels compared to hypercholesterolemic rabbits. Al-Zuhair et al. (1997) [53] reported that simvastatin (1.86 mg/Kg, twice daily) give significant decrease in LDL, triglycerides and total cholesterol levels in cholesterol-fed rabbits. Simvastatin caused an increase of HDL compared to hypercholesterolemic rabbits [54]. Also, simvastatin prevented the rise of triglycerides during the experiment. Meanwhile, the HMG-CoA reductase inhibitors have been considered effective at lowering triglyceride or more specifically, VLDL triglyceride – levels [55]. Liver enzyme (ALT, AST & ALP) in the hypercholesterolemic rabbits at the four experimental intervals were significantly higher than control animals, while administration of simvastatin was found to significantly lower the activities of serum liver enzyme in rabbits (Table 4), which may be caused by hyperlipidemia resulted in damage of liver tissue so when cell membrane is damaged, these enzymes transferred into the blood streams, which usually indicate hepatocyte injury which lead to fatty liver[56]. Treating with simvastatin

caused a significant decrease in the activity of these enzymes, suggesting that simvastatin may play an important role in improving liver function, these results were supported by [56,57].

It was shown in this study that total body weight of hypercholesterolemic rabbits treated with simvastatin tended to be lower very significantly than those rabbits fed by high lipid diet only (Table 4). These findings are in agreement with Cavallini et al.; (2009) [58] and Baskaran et al.;(2015) [59].

5. Conclusion

Hyperlipidemia produced as a result of 0-60 days feeding butter ad libitum and cholesterol 500 mg/kg body weight along with the normal routine feed, and the anti-hyperlipidemic efficacy of curcumin at the dose of 200 mg/kg body weight, cinnamon at the dose of 500 mg/kg body weight, vitamin C at the dose of 200 mg/kg body weight and simvastatin- drug at the dose of 5 mg/kg body weight were given in tables 1,2,3,4 and figure 1. It was shown that there were significant decreases in lipid profile parameters of the treated rabbit group with the above substances than their respective untreated rabbit group. Liver function profile (ALT, AST and ALP) were also shown a significant decrease for the treated group compared to untreated one, figure 2. The same result trend was obtained when comparing total body weights of treated and untreated groups of rabbits in a high significant values, figure 3. The groups treated with curcumin, cinnamon, vitamin C and simvastatin showed a variable significant decrease in lipid profile in this order: cinnamon > vitamin C > simvastatin > curcumin and in liver functions profile in this order: curcumin > simvastatin > vitamin C > cinnamon. Groups treated with these materials showed significant body loss as compared to untreated rabbits in this order: cinnamon > curcumin > vitamin C > simvastatin.

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