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RESEARCH ARTICLE

THE THERAPEUTIC EFFECTS OF COSTUS (*SAUSSUREA LAPPA*) AGAINST HYPERCHOLESTEROLEMIA IN MALE ALBINO RATS

Azza M. Marei

Zoology Department, Faculty of Science, Benha University, Qalyubiyya, Egypt

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***Correspondence:**
Azza Marei
Zoology Department
Faculty of Science
Benha University
Qalyubiyya, Egypt
E-mail:
azza.marei@fsc.bu.edu.eg

ABSTRACT

Hypercholesterolemia represents the most essential dangerous factor for cardiovascular diseases, which continue to be a wide-spread problem worldwide. The current study aimed to evaluate the therapeutic effects of costus (*Saussurea lappa*) in hyper-cholesterolemic rats. Five groups (n=7) of male albino rats (*Rattus norvegicus*) were randomly allotted as follows: the control group, coconut oil group (coconut oil for 4 weeks + water for other 4 weeks), cholesterol group (450 mg cholesterol powder/kg body weight dissolved in coconut oil for 4 weeks + water for other 4 weeks), costus group (water for 4 weeks + 50 mg costus roots powder/kg body weight suspended in water for other 4 weeks), the cholesterol+costus group (cholesterol for 4 weeks + costus for other 4 weeks). All treatments were given in 0.5 mL by gavage. The hypercholesterolemic rats showed marked dyslipidemia and significant increases in the serum levels of the atherogenic index, malondialdehyde, nitric oxide, and vascular endothelium growth factor, as well as the activities of serum alanine aminotransferase, aspartate amino-transferase, and alkaline phosphatase, in comparison with the other groups. Additionally, hypercholesterolemic rats had significant decreases in the serum high-density lipoprotein cholesterol level and the activities of serum superoxide dismutase and catalase, and impairment in the kidney functions, in comparison with the other groups. Costus administration modulated significantly all the changes in the serum of the hypercholesterolemic rats. In conclusion, dietary supplementation of costus has a potential/effective role in alleviating the biochemical disturbances resulting from hyper-cholesterolemia.

INTRODUCTION

Hypercholesterolemia is defined as having high cholesterol levels in the blood and an elevation in the percentage of low and very low density lipoproteins, which is considered a major danger factor for cardio-vascular illness[1]. Using medicinal herbs may be an innovative method for treating different diseases and preventing the bad effects of pharmaceuticals. Many studies are focused on the herbal therapy to prevent the adverse effects of pharmaceuticals and to be utilized as an anti-hypercholesterolemia[2-4]. Costus (*Saussurea lappa*) is a plant in the

Asteraceae family that is extensively used as a natural herbal drug in traditional Indian medicine for treating different diseases. It is rich in antioxidants that defend against a variety of pathophysiological conditions as gastritis, liver diseases, inflammation, respiratory diseases, tumor, parasites, bacterial infections, and others[5,6]. Various chemical components are separated from the plant body, primarily the roots, and considered as bioactive components like flavonoids, polyphenols, dehydrocostus lactone, costunolide, and steroids that improve antioxidant defenses and are responsible for the beneficial effects of costus[6]. An extract of *Costus speciosus*, which is another species of costus was found to have antiatherogenic properties in hyperlipidemic rabbits[3]. In conduction with the previous literature, the present study was designed to evaluate the therapeutic impact of costus roots on the biochemical alterations in serum of a hypercholesterolemic rat model.

MATERIAL AND METHODS

Cholesterol

Cholesterol white powder ($C_{27}H_{46}O$; molecular weight: 386.65 g/mol; purity: >99%, easily dissolved in coconut oil) was obtained from the Middle East Company for Medical and Scientific Apparatus (Cairo, Egypt). Coconut oil (100% virgin coconut oil, 0% trans fatty acids) was purchased from a Pyramid Company for a New Industry (Cairo, Egypt) for dissolving cholesterol.

Plant material

Costus (*Saussurea lappa*) was purchased from Indian Herbal and Spices store (El-Azhar street, Cairo, Egypt). The plant root was identified at the Botany Department, Faculty of Science, Benha University by Dr. Heba S. Essawy. The roots were dried under shade, mechanically powdered, and stored in an air-tight container for further use. The dried root has a slightly bitter taste and a distinctive odor. It is grey to yellow in color, wrinkled, ridged, and rigid.

Induction of hypercholesterolemia

Hypercholesterolemia was induced in rat as described by Nwichi *et al*.[7] with some modifications. Briefly, 450 mg cholesterol/kg body weight was dissolved in 0.5 mL coconut oil and orally administered to rats daily for four weeks via oral gavage.

Animals and experimental design

Thirty-five healthy adult male albino rats (*Rattus norvegicus*), aged 6-8 weeks and weighing 100-120 g, were purchased from Helwan Farm of the Egyptian Organization for Vaccine and Biological Preparations (Cairo, Egypt), Experimental rats were given free access to the daily diet and water and they were acclimatized on the laboratory conditions for two weeks before the starting time of the experiment.

Rats were allotted into 5 groups (7 animals each) as follows:

- Group I: normal healthy rats received 0.5 mL water orally/daily (by gavage) for 8 weeks.
- Group II: received orally/daily 0.5 mL coconut oil for 4 weeks then received 0.5 mL water orally/daily for other 4 weeks.
- Group III: received orally/daily 450 mg cholesterol/kg body weight dissolved in 0.5 mL coconut oil for 4 weeks then received 0.5 mL water orally/daily for other 4 weeks.
- Group IV: received orally/daily 0.5 mL water for four weeks then received costus (50 mg/kg body weight)[5] suspended in 0.5 mL water orally/daily for other four weeks.
- Group V: received orally/daily 450 mg cholesterol/kg body weight dissolved in 0.5 mL coconut oil for 4 weeks then received costus (50 mg/kg body weight) suspended in 0.5 mL water orally/daily for other four weeks.

Sampling of blood

Rats were starved overnight after finishing the experiment and anesthetized by mild inhalation of diethyl ether. The blood samples were taken from vena cava, allowed

to coagulate, and centrifuged at 1500 ×*g* for 15 minutes, then sera were isolated and preserved at –20°C until used.

The biochemical analysis

Triacylglycerol (TG) was measured according to the method of Bucolo and David[8], total cholesterol (TC) was measured according to the method of Meiattini *et al*.[9], and high-density lipoprotein cholesterol (HDL-C) was determined according to the method of Friedewald *et al*.[10] by using Spinreact Company kits (Girona, Spain). The low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C) were calculated by Friedewald *et al*.[10] equations:

- LDL-C = Total C – [HDL-C + (Triacylglycerol/5)].
- VLDL-C = Triacylglycerol/5

Atherogenic index was calculated according to Hostmark *et al*. [11] as follow:

Atherogenic index = (TC – HDL-C)/HDL-C

The activity of serum superoxide dismutase (SOD) was evaluated according to Goldstein and Czapski[12], the catalase (CAT) activity was determined according to Aebi[13], and the level of malondi-aldehyde (MDA) was determined by using BioVision kits (Milpitas, CA, USA). Urea, uric acid, and creatinine were determined spectrophotometrically in serum according to Fawcett and Scott[14], Kageyama[15], and Mazzachi *et al*.[16] methods, respectively, by using Roche Diagnostics Egypt kits (Giza, Egypt). Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) activities are estimated according to Klauke *et al*.[17] by using Roche Diagnostics Egypt kits. Serum nitric oxide (NO) concentration was determined according to Ridnour *et al*.[18] using QuantiChrom™ nitric oxide assay kit (BioAssay Systems, Hayward, CA, USA). Vascular endothelium growth factor (VEGF) concentration was determined by rat ELISA kit purchased from the Cloud Clone Corporation (Katy, TX, USA) according to Zhu and Segura[19] method.

Statistical analysis

Data were analyzed by the one-way analysis of variance (ANOVA) followed by Duncan´s test[22] using the Statistical Package for Social Science SPSS (version 20) program produced by IBM Software, Inc. (Chicago, IL, USA) and expressed as the mean of 7 individual values ± the standard deviation "SD". Similar letters in the same raw indicate a non-significant difference at $P \geq 0.05$, while different letters indicate a significant difference at $P < 0.05$.

RESULTS

The impact of costus on serum lipid profile of hypercholesterolemic rats

The data presented in Table "1" revealed significant-increases ($P<0.05$) in levels of TG, TC, LDL-C, VLDL-C, and atherogenic index in the cholesterol-treated group when compared with all other groups. However, HDL-C level decreased significantly ($P<0.05$) in the same group compared with all other groups. On the other hand, administration of costus modulated significantly ($P<0.05$) the obtained dyslipidemia in the hyper-cholesterolemic rats (Table 1).

The impact of costus on oxidative stress markers of hypercholesterolemic rats

Table ''2'' revealed a significant decrease ($P<0.05$) in the activities of SOD and CAT and a significant increase ($P<0.05$) in lipid peroxidation marker (MDA) in the cholesterol-treated group when compared with all other groups. Treatment with costus increased significantly ($P<0.05$) the anti-oxidant enzyme activities and lowered significantly ($P<0.05$) the MDA level in the hypercholesterolemic rats (Table 2).

Costus normalized serum kidney functions in hypercholesterolemic rats

The data presented in Table "3" indicated that the levels of urea, uric acid, and creatinine were significantly increased ($P<0.05$) in the cholesterol-treated group in comparison with all other groups.

Table 1: Impact of costus (*Saussurea lappa*) on the serum lipid profile of the hypercholesterolemic rats.

	GROUP I	GROUP II	GROUP III	GROUP IV	GROUP V
TG (MG/DL)	104.8±0.6^{d}	105.3±0.6^{d}	131.3±0.4^{a}	90.1±0.9^{e}	115.4±0.5^{b}
TC (MG/DL)	70.6±0.6^{d}	70.8±0.3^{d}	100.6±0.8^{a}	68.5±0.8^{e}	77.9±0.1^{b}
HDL-C (MG/DL)	41.6±0.5^{b}	40.2±0.2^{b}	23.3±0.4^{e}	45.9±0.6^{a}	39.1±1.3^{c}
LDL-C (MG/DL)	30.0±0.7^{d}	30.9±0.4^{d}	51.2±1.1^{a}	28.3±0.5^{e}	40.2±1.4^{b}
VLDL-C (MG/DL)	21.2±0.1^{c}	21.5±0.1^{c}	27.1±0.1^{a}	19.3±0.5^{d}	22.9±0.1^{b}
ATHEROGENIC INDEX	1.76±0.29^{d}	1.72±0.18^{d}	3.32±0.83^{a}	1.20±0.28^{e}	1.98±0.01^{b}

Data are presented as means ± standard deviations (n = 7). Group I: control group, group II: coconut oil group, group III: cholesterol group, group IV: costus group, group V: cholesterol+costus group, TG: triacylglycerol, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, VLDL-C: very low-density lipoprotein cholesterol. In the same raw, values with similar letters mean a non-significant difference, and values with different letters mean a significant difference.

Table 2: Impact of costus (*Saussurea lappa*) treatments on the activities of antioxidant enzymes and malondialdehyde (MDA) level in serum of the hypercholesterolemic rats.

	Group I	*Group II*	*Group III*	*Group IV*	*Group V*
SOD (U/mg protein)	3.60±0.32^{b}	3.40±0.01^{b}	1.40±0.39^{e}	4.10±0.01^{a}	2.10±0.08^{d}
CAT (nmol/mg protein)	2.60±0.04^{b}	2.50±0.04^{b}	0.90±0.18^{e}	3.40±1.66^{a}	1.70±0.04^{d}
MDA (nmol/mg protein)	0.91±0.02^{c}	0.97±0.04^{c}	2.64±0.11^{a}	0.71±0.03^{d}	1.22±0.17^{b}

Data are presented as means ± standard deviations (n = 7). Group I: control group, group II: coconut oil group, group III: cholesterol group, group IV: costus group, group V: cholesterol+costus group, SOD: superoxide dismutase, CAT: catalase. In the same raw, values with similar letters mean a non-significant difference, and values with different letters mean a significant difference.

Table 3: Impact of costus (*Saussurea lappa*) treatments on kidney functions of the hypercholesterolemic rats.

	Group I	*Group II*	*Group III*	*Group IV*	*Group V*
Urea (mg/dL)	40.4±0.9^{b}	40.2±0.2^{b}	57.3±0.5^{a}	30.4±0.6^{c}	40.9±0.4^{b}
Uric acid (mg/dL)	1.3±0.2^{b}	1.3±0.1^{b}	2.3±0.4^{a}	0.8±0.1^{c}	1.4±0.3^{b}
Creatinine (mg/dL)	0.3±0.09^{b}	0.33±0.05^{b}	1.08±0.09^{a}	0.15±0.06^{c}	0.37±0.09^{b}

Data are presented as means ± standard deviations (n = 7). Group I: control group, group II: coconut oil group, group III: cholesterol group, group IV: costus group, group V: cholesterol+costus group. In the same raw, values with similar letters mean a non-significant difference, and values with different letters mean were significantly different.

On the other hand, there were no significant differences ($P \geq 0.05$) in the kidney functions between the control group and the cholesterol+costus group.

The impact of costus on tissue-injury markers in hypercholesterolemic rats

Serum ALT, AST, and ALP activities were significantly elevated ($P<0.05$) in the cholesterol-treated group in comparison with all other groups (Table 4). Treatment of costus resulted in significant decreases in the activities of these enzymes in the hypercholesterolemic rats (Table 4).

The impact of costus on serum NO and VEGF of hypercholesterolemic rats

Figures "1 and 2" showed that the NO and VEGF levels increased significantly ($P<0.05$) in the cholesterol-treated group in comparison with all other groups. On the other hand, the hypercholesterolemic rats treated with costus showed a significant decrease ($P<0.05$) in NO and VEGF levels in comparison with the cholesterol-treated group.

Table 4: Impact of costus (*Saussurea lappa*) treatments on tissue injury markers in serum of the hypercholesterolemic rats.

	Group I	Group II	Group III	Group IV	Group V
ALT (U/L)	24.6 ± 3.7^{c}	25.1 ± 5.8^{c}	42.0 ± 2.5^{a}	20.6 ± 0.8^{d}	26.6 ± 1.4^{b}
AST (U/L)	74.3 ± 6.2^{c}	74.4 ± 7.7^{c}	103.0 ± 10.9^{a}	62.6 ± 2.7^{d}	77.95 ± 5.0^{b}
ALP (U/L)	13.0 ± 1.4^{c}	13.3 ± 2.8^{c}	16.0 ± 1.4^{a}	11.0 ± 0.8^{d}	14.90 ± 1.8^{b}

Data are presented as means ± standard deviations (n = 7). Group I: control group, group II: coconut oil group, group III: cholesterol group, group IV: costus group, group V: cholesterol+costus group, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase**.** In the same raw, values with similar letters mean a non-significant difference, and values with different letters were significantly different.

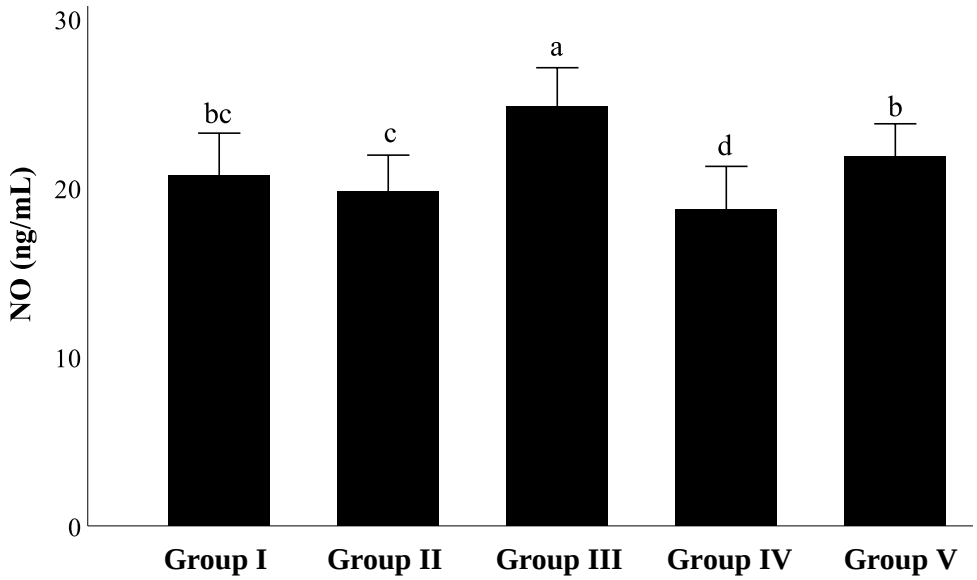

Figure 1: Impact of costus (*Saussurea lappa*) treatments on serum nitric oxide level in the hypercholesterolemic rats. Data are presented as means ± standard deviations (n = 7). Group I: control group, group II: coconut oil group, group III: cholesterol group, group IV: costus group, group V: cholesterol+costus group. Values with different letters on the columns were significantly different.

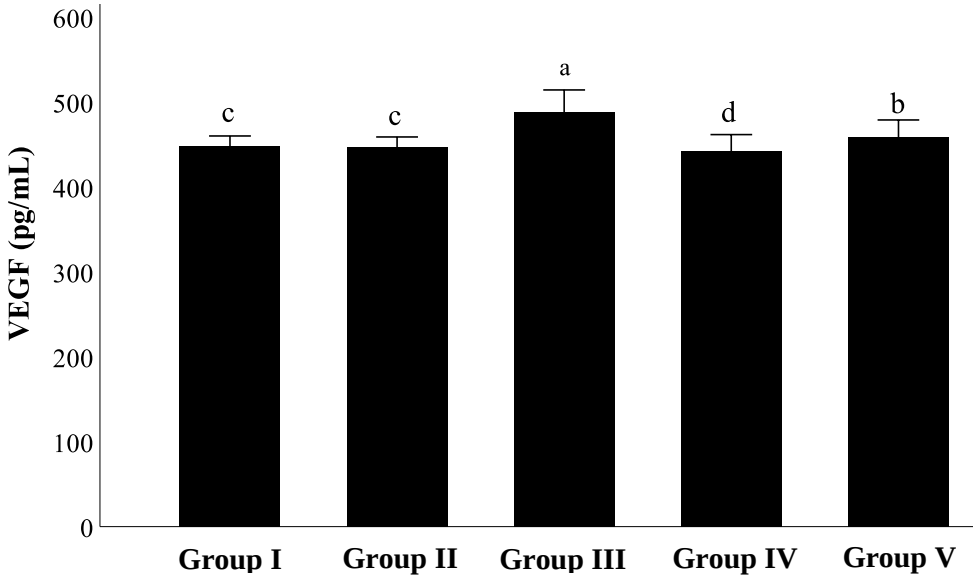

Figure 2: Impact of costus (*Saussurea lappa*) treatments on serum vascular endothelium growth factor (VEGF) of the hypercholesterolemic rats. Data are presented as means ± standard deviations (n = 7). Group I: control group, group II: coconut oil group, group III: cholesterol group, group IV: costus group, group V: cholesterol+costus group. Values with different letters on the columns were significantly different.

DISCUSSION

Hypercholesterolemia is considered a risk factor for cardiovascular ailments such as atherosclerosis and its complications, acute infarction of the myocardium, hypertension, cerebral infarctions, and stroke[21-23]. Costus (*Saussurea lappa*) is a well-known medicinal plant that is utilized in a variety of medications around the world. The present study was designed to explore additional therapeutic effects of costus in a hypercholesterolemic rat model. The results of the current study revealed that hypercholesterolemic rats showed abnormal elevation in serum lipid levels with a significant increase in the TGs, TC, LDL-C, and VLDL-C levels, as well as atherogenic index, and induced a significant decrease in HDL-C level compared with those in the control and all other groups. Interestingly, treatment with costus modulated significantly all changes in the serum lipid profile of the hypercholesterolemic rats, which probably due to the antidyslipidemic activity of their phytochemicals especially costunolide[6].

The hypercholesterolemic diet caused a significant reduction in the activities of enzymic antioxidant (SOD and CAT) with a marked increase in the level of MDA, which is a marker lipid peroxidation since the degree of lipid peroxidation can be reflected by detecting the amount of MDA. The recorded biochemical alterations in the hypercholesterolemic rats, especially those related to the kidney dysfunctions, were significantly changed by treatment with costus and may be attributed to the tannins, triterpenes, alkaloids, inulin, and essential oil present in the costus roots[5]. The above-mentioned chemical components of the costus played important roles in the alleviation of lipid peroxidation and oxidative stress, which caused due to an imbalance between ROS (reactive oxygen species) production and the free-radical scavenging ability of the antioxidant enzymes; the excessive ROS production causes antioxidant imbalance and anti-oxidant depletion[5,6].

The results of the present study revealed that serum urea, uric acid, and creatinine levels were significantly elevated in

hypercholesterolemic rats when compared with all other groups indicating kidney dysfunctions, which probably due to: (a) cellular leakage and a rupture in the integrity of the cell membrane of the kidneys resulting from oxidative stress caused by hypercholesterolemia, (b) an increase the production in free radical's that caused severe congestion in the cortical blood vessel with swelling and degeneration in the epithelial cells lining the tubules of kidney[24]. Successfully, the kidney functions were improved in a significant manner in the cholesterol+costus group, where there were no significant differences between this group and the control group. Thus, the nephroprotective activity of costus may be attributed to their antioxidant bioactive compounds[5]. The activities of AST, ALT, and ALP (tissue injury markers) increased significantly in the cholesterol-treated group compared with the control group and all other groups. On the other hand, costus caused a significant decrease in all tissue injury markers of the hypercholesterolemic rats, which may be attributed to its free radical scavenging activity that can keep the integrity of the cell membrane[25].

In the current study, cholesterol-treated rats showed a significant increase in serum NO level compared with the control and other treated groups causing enhancement of the oxidative stress and imbalance in oxidant/antioxidant status evidenced by increased MDA and decreased the activities of enzymatic antioxidants. Successfully, costus treatment after cholesterol induction caused a significant decrease in NO in comparison with the cholesterol-treated group, which may be due to dehydrocostus lactone that can be separated from costus and inhibited the generation of NO *via* suppressing the expression of NO synthase enzyme[6]. In addition, treatment with cholesterol induced a significant increase in serum VEGF level compared with the control and other treated groups, which could consider as a protective response against hypoxia and endothelial injury in an early atherosclerosis caused by hypercholesterolemia. Costunolide of costus inhibits the proliferation of endothelial cells-induced by VEGF by blocking the angiogenic factor signaling pathway[6] leading to a significant decrease in VEGF in comparison with cholesterol-treated group.

In conclusion, our results revealed the safely potential benefits of costus (*Saussurea lappa*) as an adjuvant in the treatment of hypercholesterolemia through potentiating the antioxidant defense system.

ETHICAL APPROVAL

The study was conducted according to approval No. 000089 from the Scientific Research Ethics Committee of the Faculty of Medicine, Benha University (REC-FOMBU) that operates according to the international guidelines, including the Declaration of Helsinki, Islamic Organization for Medical Sciences (IOMS), World Health Organization (WHO), and International Council on Harmonization and Good Clinical Practice (ICH-GCP).

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This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

CONFLICT OF INTEREST

The author declares that there is no conflict of interests.

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التأثيرات العلاجية للقسط الهندي "*Saussurea lappa*" ضد فرط الكوليسترول في ذكور الجِرذان المَهقاء

عزة محمد عبد الرحمن مرعي

قسم علم الحيوان، كلية العلوم، جامعة بنها، القليوبية، جمهورية مصر العربية

يُعتبر فرط كوليسترول الدم العامل الأكثر خطورة لأمراض القلب والأوعية الدموية والتى لا تزال مشكلة منتشرة فى جميع أنحاء العالم. هدفت الدراسة الحالية إلى تقييم التأثيرات العلاجية للقسط الهندي "*Saussurea lappa*" في الجِرذان المصابة بفرط كوليسترول الدم. تم توزيع خمس مجموعات (ن=7) من ذكور الجِرذان المهقاء (*Rattus norvegicus*) بشكل عشوائي على النحو التالي: مجموعة ضابطة، مجموعة زيت جوز الهند (زيت جوز الهند لمدة 4 أسابيع + ماء لمدة 4 أسابيع أخرى)، مجموعة الكوليسترول (450 مجم من مسحوق الكوليسترول/كجم من وزن الجسم "مذاب في زيت جوز الهند" لمدة 4 أسابيع + الماء لمدة 4 أسابيع أخرى)، مجموعة القسط الهندي (الماء لمدة 4 أسابيع + 50 مجم من مسحوق القسط الهندي/كجم من وزن الجسم "معلق في الماء" لمدة 4 أسابيع أخرى)، مجموعة الكوليسترول+القسط الهندي (كوليسترول لمدة 4 أسابيع + القسط الهندي لمدة 4 أسابيع أخرى). أعطيت جميع المعاملات في 0.5 مل بالتزقيم. وقد أظهرت الجِرذان المصابة بفرط كوليسترول الدم عسرًا كبيرًا في شحميات الدم، وزيادات ملحوظة إحصائيًا في مستويات المصل لمؤشر تصلب الشرايين والمالونداي‌ألديهيد وأكسيد النيتريك وعامل نمو البطانة الوعائية، وكذلك أنشطة الإنزيمات الناقلة لمجموعة الأمين والفوسفاتاز القلوي، مقارنة مع المجموعات الأخرى. وكان أيضا لدى الجِرذان المصابة بفرط كوليسترول الدم انخفاض ملحوظ إحصائيًا في مستوى البروتين الدهني عالي الكثافة المرتبط بالكوليستيرول وأنشطة فوق أكسيد الديسميوتاز والكاتلاز في مصل الدم، وخلل في وظائف الكُلى، مقارنة بالمجموعات الأخرى. وقد أدت المعاملة بالقسط الهندي إلى تعديل جميع التغيرات في مصل الجِرذان المصابة بفرط كوليسترول الدم. والخلاصة أن المكملات الغذائية من القسط الهندي لها دور محتمل/فعال في تخفيف الاضطرابات البيوكيميائية الناتجة عن فرط كوليسترول الدم.