Asian Journal of Advanced Research and Reports

Volume 18, Issue 9, Page 63-70, 2024; Article no.AJARR.121952
ISSN: 2582-3248

Determination of the Anti-hyperlipidemic Effects of *Cissus quadrangularis* Ethanolic Extract on High Fat Induced Hyperlipidemic Rat Model

Zulqarnain Haider [a*], Sadiya Binte Rashid [a], Shariful Islam [b], Md Shakil [a], Bushratul Jannat [a] and Md. Mustafiz Chowdhury [c]

[a] Department of Pharmacy, University of Asia Pacific, 74/A Green Road,Dhaka, Bangladesh.
[b] Depatrment of Botany, Faculty of biological Sciences, University of Chittagong. Bangladesh.
[c] Department of Pharmacy, Southern University Bangladesh.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/ajarr/2024/v18i9735

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/121952

Original Research Article

Received: 20/06/2024
Accepted: 22/08/2024
Published: 29/08/2024

ABSTRACT

The practice of utilizing herbs and herbal remedies to prevent, treat, or cure diseases, as well as to maintain and promote maximum health, is known as herbalism. In certain areas, people may confuse herbal medicine with treatments. Among the leading causes of mortality globally,

**Corresponding author: Email: zulqarnainuap91@gmail.com;*

Cite as: *Haider, Zulqarnain, Sadiya Binte Rashid, Shariful Islam, Md Shakil, Bushratul Jannat, and Md. Mustafiz Chowdhury. 2024. "Determination of the Anti-Hyperlipidemic Effects of Cissus Quadrangularis Ethanolic Extract on High Fat Induced Hyperlipidemic Rat Model". Asian Journal of Advanced Research and Reports 18 (9):63-70. https://doi.org/10.9734/ajarr/2024/v18i9735.*

atherosclerotic cardiovascular disease (ASCVD) and its long-term effects are particularly notable. Adolescents who have atherosclerosis are at progressively higher risk of cardiac events, including heart disease, myocardial infarction (MI), and stroke, throughout later life. This research examined the effects of a *Cissus quadrangularis* extract on lipid profiles in rats with high-fat-induced hyperlipidemia. When the high fat dosage was 800 and 1200 mg/kg, respectively, the SGPT and SGOT levels in groups 5 and 6 showed statistically significant results ($p<0.05$). The SGPT clearly demonstrated this. Still, none of the 400, 800, or 1200 mg/kg doses produced statistically significant results, according to the SGOT. However, the SGPT and SGOT levels decreased in a dose-dependent manner. Statistical analysis during the renal function test showed that the doses of urea in groups 5 and 6, which received 800 and 1200 mg/kg, respectively, were substantially different ($p<0.05$). However, the creatinine analysis did not provide any statistically significant results. Taking into account high-density lipoprotein (HDL) and low-density lipoprotein (LDL), groups 5 and 6 had statistically significant results ($p<0.05$) in HDL levels. More specifically, groups 5 and 6, given doses of 800 and 1200 mg/kg, respectively, showed statistically significant results. Triglyceride levels in Group 5 differed statistically significantly ($p < 0.05$). When it came to total cholesterol levels, Group 5, which received a dosage of 800 mg/kg, showed statistically significant results ($p<0.05$).

Keywords: Herbal medicine; Cissus quadrangularis; HDL; LDL; phytochemicals.

1. INTRODUCTION

The liver, the largest glandular organ, regulates the majority of physiological activities in the human body. The liver is the organ that receives an individual's entire blood volume many times throughout the day. It is crucial to the metabolic activities of humans [1, 2]. Excessive alcohol consumption, drug addiction, exposure to some hazardous compounds, or infection with viruses or parasites may lead to an elevation in the levels of reactive oxygen species (ROS), such as OH, H_2O_2, and O_2 [3]. This may lead to hepatocellular injury. The Centers for Disease Control and Prevention conducted research involving 1492 clinicians who offer ambulatory treatment in non-government facilities. The survey revealed that hyperlipidemia is the second most prevalent chronic disease seen by these doctors, with hypertension being the only condition more often encountered [4]. The study's results suggest that the primary factor leading to hyperlipidemia is the overconsumption of high-fat meals [5]. The liver plays a crucial role in metabolizing commonly used anti-hyperlipidemic drugs, such as atorvastatin, pravastatin, fluvastatin, simvastatin, lovastatin, and rosuvastatin. Consequently, the bioavailability of these drugs is quite poor [6]. Statins have the ability to transiently inhibit the enzyme 3-hydroxy-3-methylglutaryl-co- A reductase (HMG-CoAR). This enzyme reduces cholesterol levels. This allows them to reduce cholesterol synthesis inside the cells. This is because statins have the ability to enter hepatocytes and inhibit HMG-CoAR, which is responsible for their pharmacological effects [7]. Statin-associated muscle symptoms (SAMS), commonly known as muscular problems, are the primary side effects that limit the use of statins. Two other potentially detrimental consequences include the onset of diabetes mellitus (DM) and complications affecting the central nervous system [8]. These synthetic medicines not only have substantial adverse effects, but they are also expensive, potentially causing financial hardships for patients who need to continue taking them during the whole therapy [9]. In the United States, there are almost 28 million people with a cholesterol level of 240 mg/dl or more. These individuals have a risk of developing atherosclerotic cardiovascular disease (ASCVD) that is nearly twice as high as those with normal lipid levels. Hyperlipidemia poses a significant risk to human health. Therefore, it is crucial to develop highly effective antihyperlipidemic medications with minimal unwanted effects such as constipation, pancreatitis, liver dysfunction and muscle pain. Plants are essential in the process of discovering and synthesizing novel therapies [10]. They serve as a useful and abundant reservoir of naturally occurring chemicals for therapeutic applications. Specialists on the subject propose that certain chemical constituents extracted from medicinal plants have therapeutic properties. As a result, researchers are always searching for novel herbal remedies and other medicines derived from plants to effectively treat various ailments [4]. Traditional medicines have long been used in several nations worldwide as remedies derived from plants, dietary supplements, and alternative medical methods. In recent years, there has been a significant increase in the use of

traditional medicine, with many across the country depending on it as a major form of care [11]. Plants used for medical reasons include a diverse range of chemical constituents, enabling them to exert a broad spectrum of pharmacological and therapeutic effects. These substances include many constituents, including tanning agents, glycosides, alkaloids, saponins, polysaccharides, essential oils, terpenoids, resins, and plant lipids [12–14]. Genetically engineered plants provide the ability to finely regulate chemical levels, eventually resulting in the desired therapeutic outcome. Reverse genetics has several potential uses, one of which is the augmentation of secondary metabolite synthesis, including the generation of alkaloids [15]. The global advancements in scientific research have led to an increase in the investigation of plant species' therapeutic attributes [16]. Plants are becoming more popular because of their inherent safety, potent pharmacological properties, and cost-effectiveness compared to synthetic drugs.

Cissus quadrangularis L. is a shrub belonging to the Vitaceae family, often found in the hot areas of India and Sri Lanka. People commonly refer to this plant as the Devil's Backbone or Hadjora. It is cited by Ayurveda as a tonic for promoting bone health in fracture patients and accelerating tissue recovery. In addition, it has shown efficacy in treating rheumatoid arthritis, osteoarthritis, osteoporosis, scurvy, menstrual problems, otorrhoea, epistaxis, and weight management [17]. The plant's root and stem extracts exhibit antioxidant and antimicrobial properties [18]. The stem juice is abundant in minerals such as calcium and phosphorus [19], and it contains a significant amount of vitamin A, vitamin C, anabolic steroids, β-sitosterol, δ-amyrin, δ-amyrone, and flavonoids (quercetin) [20]. This plant has several pharmacological activities, including bone healing, anti-obesity, anti-ulcerative, anti-diabetic, antioxidant and free radical scavenging, gastroprotective, central nervous system, analgesic, anti-inflammatory, and stimulatory activities [21].

Our current investigation aims to evaluate the hepatoprotective properties of *Cissus quadrangularis*.

2. MATERIALS AND METHODS

2.1 Plant Collection and Extract Preparation

Cissus quadrangularis specimens were obtained from a local market in Dhaka. The National Herbarium of Bangladesh verified the authenticity of the sample. The first step was thoroughly rinsing *Cissus quadrangularis* with water, followed by allowing it to dry naturally. Finally, we pulverized the withered leaves into a fine powder. We immersed the powder in 70% ethanol for a duration of 15 days. The solution was stored for a duration of 15 days. Intermittent, vigorous shaking was also conducted. Subsequently, the solution underwent filtration. The filtrate that was collected was subjected to drying using a rotary evaporator under conditions of reduced temperature and pressure. Ultimately, the unrefined remains were submitted to the necessary pharmacological examination.

2.2 Drugs and Chemicals

Sigma-Aldrich in Germany provided the ethanol. Healthcare Pharmaceutical Limited sent a complimentary sample of Atorvastatin, a commonly used drug for reducing high levels of lipids in the blood. The Humalyzer 3000, a semi-automated clinical chemistry analyzer, was used to evaluate the biochemical parameters. The ingredients for the high-fat diet were purchased from a supermarket.

2.3 Experimental Animal Procurement, Nursing, and Grouping

Obtained from Jahangirnagar University in Savar, Dhaka, a total of 90 male rats weighing between 120 and 150 grams were acquired. Each specimen was kept in a controlled environment with a temperature range of 25±3°C, relative humidity between 55±5%, and a 12-hour cycle of light and darkness. This environment was provided at the Institute of Nutrition and Food Science (INFS) at the University of Dhaka. They were provided with standard meals and allowed to consume purified water. All the animals were housed in this environment for a minimum of one week before the study to observe their adaptation.

2.4 Experimental Design

Rats were individually weighed and then divided into nine independent groups for research on anti-hyperlipidemic action. The distribution of rodents among the groups was based on their body weight, with each group consisting of five rats. The atorvastatin control group in Table 1

shows rats that were given atorvastatin with a high-fat diet since using simply atorvastatin would result in the animals dying. N/A indicates that rats in this group did not receive any therapeutic treatment.

High Fat Diet: The high-fat diet was modified based on the composition supplied by Levin and Dunn-Meynell. The high fat diet is composed of 50% lipid, 40% carbohydrate, and 10% protein. The diet's composition is shown in Table 2.

Table 1. Antihyperlipidemic activity analysis

Group number	Group Status	Treatment specimen & Dose	Group Abbreviation
1	Negative Control	Physiological Saline	N
2	Positive Control	High Fat Diet	P
3	High Fat Diet +RV_{10}	High Fat Diet + Atrovastatin	HFD + ATV
4	High Fat Diet + *C. quadrangularis*	High Fat Diet+ CQ_{400}	HFD + CQ_{400}
5	High Fat Diet + *C. quadrangularis*	High Fat Diet + CQ_{800}	HFD + CQ_{800}
6	High Fat Diet + *C. quadrangularis*	High Fat Diet + CQ_{1200}	HFD + CQ_{1200}
7	*C. quadrangularis*	CQ_{400}	CQ_{400}
8	*C. quadrangularis*	CQ_{800}	CQ_{800}
9	*C. quadrangularis*	CQ_{1200}	CQ_{1200}

Table 2. Composition of high fat diet

Food Ingredients	Composition
Lipid (50%)	Milk powder (10%) Ghee (30%) Mutton fat (40%) Coconut oil (10%) Butter (10%)
Carbohydrate (40%)	Boiled rice (40%) Smashed potato (40%) Boiled corn (20%)
Protein (10%)	Dry powdered prone (40%) Dry boiled mutton (20%) Cheese (20%) Egg (20%)

After mixing the ingredients thoroughly, the high fat diet was given to the rats to induce obesity for 10 weeks [22].

2.5 Evaluation of anti-hyperlipidemic Activity

Table 3. Application of treatment efficacy

Group Number	Group Specification	Treatment species	Dose treatment species (mg/kg)	Abbreviation of Groups
1	Negative control	Physiological saline	10 ml/kg	N
2	High Fat	N/A	N/A	HF
3	HF+RV_{10}	Rovast 10mg/kg	10	At_{10}
4	HF +CQ_{400}	*Cissus quadrangularis*	400	CQ_{400}
5	HF+CQ_{800}	*Cissus quadrangularis*	800	CQ_{800}
6	HF+CQ_{1200}	*Cissus quadrangularis*	1200	CQ_{1200}
7	CQ_{400}	*Cissus quadrangularis*	400	CQ_{400}
8	CQ_{800}	*Cissus quadrangularis*	800	CQ_{800}
9	CQ_{1200}	*Cissus quadrangularis*	1200	CQ_{1200}

For this experiment, 100 rats were randomly picked and equally divided into fourteen groups.

Table 4. Lipid profil of *Cissus quadrangularis* on rat model

Groups	SGPT	SGOT	Creati-nine	Urea	TC	HDL	LDL	TG
NC	38.46±4.29	38.93±4.23	0.63±0.012	34.29±2.43	120.24±6.21	90.22±5.32	38.46±3.21	53.21±4.81
HF	92.46±5.39	93.21±8.24	3.14±0.86	103.47±8.91	209.59±12.21	48.21±6.20	147.22±14.23	114.21±12.32
HF+At_{10}	61.29±6.20	54.59±6.14	1.49±0.62	52.29±6.18	152.29±9.36	69.25±7.30	68.41±10.22	68.50±8.26
HF +CQ_{400}	88.80±5.59	90.28±5.16	2.64±0.82	100.26±6.22	204.93±8.63	50.50±6.29	142.25±11.63	110.29±11.39
HF+CQ_{800}	84.21±7.61*	86.29±7.28	2.29±0.73	95.24±7.32*	198.46±7.97*	55.53±7.29*	134.23±11.67*	106.21±6.21*
HF+CQ_{1200}	81.29±5.56*	80.17±6.29	1.87±0.63	91.50±6.32*	192.91±6.20	59.93±8.93*	127.57±10.29*	100.29±5.21*
CQ_{400}	36.17±5.53	37.21±3.28	0.71±0.31	37.21±3.21	122.20±7.39	93.20±6.39	36.27±4.52	55.55±2.37
CQ_{800}	40.20±6.17	35.50±5.21	0.84±0.26	34.20±3.19	117.70±6.29	89.18±4.20	35.20±5.29	52.21±3.39
CQ_{1200}	43.19±5.53	39.20±6.20	0.57±0.23	30.21±3.90	119.32±6.82	90.91±4.21	39.16±5.39	56.19±4.02

Note: *The results were expressed in Mean±SEM (standard mean error) *p< 0.05, **p< 0.01, and ***p< 0.001 were considered as statistically significant. The statistical analysis followed by one-way analysis of variance (Dunnett's test) compared to the control.*

2.6 Statistical Analysis

All of our findings (raw data) in terms of numerical parameters were recorded and analyzed on a broadsheet using the MS Excel application. The gathered data were subjected to descriptive statistics, with the findings reported as mean SD. To evaluate statistical significance, we used the SPSS 16 software's "One-way Anova test" to interpret inter-group heterogenicity in terms of several biological factors. The occurrences are considered statistically significant since the 'p' value was less than 0.05 ($p<0.5$).

3. RESULTS AND DISCUSSION

Traditional medicine and ethnomedicine, which study traditional medical practices among various ethnic groups, have been present since the beginning of human civilization. In the past, traditional medicine relied on natural resources for therapeutic purposes. Historically, herbs, which are botanical substances derived from plants, together with plant extracts, were the primary constituents of the first remedies used in the traditional medical practices of several cultures and civilizations. Plants and herbs have historically served as a prominent reservoir of medications, either in the form of traditional extracts or as isolated active constituents.

This research examined the effects of a *Cissus quadrangularis* extract on lipid profiles in a rat model of high-fat-induced hyperlipidemia. Both the SGPT and SGOT levels showed statistically significant ($p< 0.05$) results in groups 5 and 6, where the high fat dosage was 800 and 1200 mg/kg, specifically in the case of the SGPT. However, the SGOT did not provide any statistically significant results in any of the dose 400, 800 and 1200mg/kg. Two further studies reached the same outcomes [23, 24]. Saponins, alkaloids, flavonoids, and triterpenoids are some of the phytochemical components found in this plant. They have antioxidant capabilities, meaning they may scavenge free radicals and decrease lipid peroxidation activity [25].

During the renal function test, it was shown that the levels of urea were statistically significant ($p< 0.05$) in groups 5 and 6, which received doses of 800 and 1200 mg/kg, respectively. However, the analysis of the creatinine did not provide any statistically significant results in any of dose 400, 800 and 1200mg/kg though it reduced creatinine level in a dose dependent manner. Two independent inquiries [26, 27] arrived at identical findings about the topic. One possible explanation for *C. quadrangularis*'s protective impact on the renal tubular cell membrane is its antioxidant characteristics [28].

Regarding high-density lipoprotein (HDL) and low-density lipoprotein (LDL), groups 5 and 6 exhibited statistically significant results ($p< 0.05$) in HDL levels. Specifically, groups 5 and 6, who received doses of 800 and 1200 mg/kg, demonstrated statistically significant outcomes ($p< 0.05$). The triglyceride levels in group 5 exhibited a statistically significant difference ($p< 0.05$) in which group the dose was 800mg/kg. But the other groups didn't show any statistically significant outcomes. Group 5, which received a dosage of 800 mg/kg, had statistically significant results ($p< 0.05$) in terms of total cholesterol levels. The other groups didn't show any statistically outcome in reducing cholesterol levels. Two further studies reached the same outcomes [29, 30]. Potentially lowering LDL, cholesterol, and triglyceride levels include indoles, flavonoids, lignans, and phytosterols [31].

4. CONCLUSION

This work focused on examining the hepatoprotective characteristics of an ethanolic extract derived from *Cissus quadrangularis.* According to the results of this study, it seems that an ethanol extract obtained from the *Cissus quadrangularis* plant has the potential to provide defense against high cholesterol, liver damage, and impaired kidney function. Further investigation is required to identify the specific active constituents within the complete extract that possess the capacity to mitigate hyperlipidemia and diabetes. Once the active compounds have been identified, it becomes feasible to carry out a thorough examination.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

ETHICAL APPROVAL

The experimental techniques adhered to the guidelines set out by the Institutional Animal Ethics Committee (IEAC). A total of 90 rats were randomly allocated into 9 groups, with each group consisting of 10 rats. Ethical approval

committee of Chandupr Central Hospital have authorized research project under the ethical approval number CCH-PR-24-0018.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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