En Evaluation of Anti-hyperlipidemic activity of *Rubusidaeus*on High Fat Induced Rat Model with Safety Profile Analysis

Abstract

One abundant source of medications is medicinal plants. Therefore, medicinal plants may be thought of as a broad class of medications against many illnesses. These days, hyperlipidemia is a prevalent condition that is causing a great deal of misery for its victims. There are a lot of synthetic medications available to treat this illness, but the most of them have a lot of adverse effects. Thus, a substitute in this case could be therapeutic plants. *Rubusidaeus* is one of the plant specimens that have been utilised as an alternative medication to treat hyperlipidemia. It can be used as a substitute source of hyperlipidemia treatment. In this study, rats with hyperlipidemia from a high-fat diet were treated with *Rubusidaeus* extract.Rats in the red *Rubusidaeus* extract administration groups demonstrated a significant ($p<0.05$) reduction in body weight and cholesterol levels after an 8-week intragastricRubusidaeus extract gavage compared to the group that did not receive *Rubusidaeus* extract treatment. The total cholesterol and triglyceride levels in the hyperlipidemia mice were significantly ($p<0.05$) reduced by the *Rubusidaeus* extract therapy. In you study we aimed to assess the therapeuteic consequences of our plant and as per our findings this plant possess compounds that may impart anti-hyperlipidemic activity evnethoug the concentration of therapeutic compound is not sufficient. More vigorous is needed to identify and isolate precise compound that can be a potential candidate of hyperlipidemia treatment.

Keywords: *Rubusidaeus*,hyperlipidemia, medicinal, high fat diet, cholesterol

Introduction

An excessive amount of lipids or fats in your blood is known as hyperlipidemia (high cholesterol). Due to the difficulty in blood flow via your arteries, this can raise your risk of heart attack and stroke. Increasing exercise and eating well-balanced meals helps reduce cholesterol. Certain people also require medicine.[1]

Globally, elevated LDL-C caused the deaths of 3.0 million individuals (95% confidence interval [UI], 2.35-3.76 million) in 1990[2] and 4.40 million (95% UI, 3.30-5.65 million) persons in 2019.[3]

Familial and acquired hyperlipidemia are the two primary subtypes. Your parents' genes are the source of the family type .This leads to the acquired type: underlying medical issues, prescription drugs, and lifestyle selections. Elevated LDL cholesterol has been repeatedly linked to an increased risk of atherosclerotic plaque development and eventual vascular disease, according to a wide range of trials and research. [4] On the other hand, high-density lipoprotein (HDL) cholesterol reduces the risk of atherosclerotic vascular disease by helping to maintain normal cholesterol levels. The ideal low-density lipoprotein (LDL) cholesterol level for each patient depends on their total cardiovascular risk, and each patient should receive individualized medical treatment.[5] "Primary prevention" refers to the control of risk factors, such as hyperlipidemia, to lower the risk of atherosclerotic cardiovascular disease. Widespread epidemiologic evidence showing a positive, continuous association between LDL cholesterol levels, cardiovascular events, and patient death provide the justification for decreasing LDL cholesterol. [6]

There are many different medications available on the market today to treat hyperlipidemia, such as statins (Atorvastatin, Simvastatin, Lovastatin), bile acid binding resins (Colestipol, Cholestyramine), fibric acid derivatives (Fenofibrate, Gemfibrozil, Bezafibrate), niacin, and ezetimibe, but long-term administration of these can be physically and financially taxing [4]. Statins, the most popular class of antihyperlipidemic medications, for instance, have been linked to SAMS (statin-associated muscular symptoms) and CNS complications[7]. Clinically relevant natural alternatives that are more long-lasting and have fewer adverse effects may be preferable for long-term use.

Many herbal remedies have already been shown to effectively and significantly lower cholesterol, including (but not limited to) Daming capsule (DMC), Glycyrrhizaglabra, chunghyul-dan, garlic powder (Allicor), green tea, black tea, licorice, Saturejakhuzestanica, Ningzhi capsule (NZC), Achilleawilhelmsii C. Koch, composition salviae dropping pill (CSDP. Numerous of these plants are used in a variety of ways in ethnomedicine and are also thought to have varied degrees of antidiabetic effects.[8]

The red-fruited *Rubusidaeus*, often known as the *Rubusidaeus* and occasionally as the red *Rubusidaeus* or European red *Rubusidaeus* to distinguish it from other *Rubusidaeus* species, is a native of Europe and northern Asia and is widely planted elsewhere in temperate climates.[9]The *Rubusidaeus* plant R. idaeus, whose leaves have historically been used as a uterine relaxant and stimulant during confinement, for the treatment of diarrhoea and similar enteric disorders, and as an astringent, is one of the most frequently documented species of the genus in the search for biologically active compounds. In the past 25 years, studies on different Rubus species have revealed potential applications for a variety of conditions, including as bacterial infections, anxiety, pain, and inflammation.[10]

The chemical makeup and biological characteristics of raspberries have drawn a lot of attention , but no comparable study has been done on *Rubusidaeus* shoots to far. The fruit of the *Rubusidaeus*is rich in phenolic compounds, with anthocyanins and ellagitannins being the most abundant. Flavonoids, phenolic acids, and flavan-3-ols are found in much less amounts .A class of hydrolyzable tannins unique to the Rosaceae family is called ellatannins. Singuiin H-6 is the primary ellagitannin found in Rubus species, while it is also present in tiny amounts along with lambertianin C and other ellagitannins . In *Rubusidaeus*leaves, ellagannins and some flavonoids have also been found.[11]

The effects of red *Rubusidaeus*extract consumption on hyperlipidemia-induced high-fat diet (HFD)-induced mice were examined. Mice in the plant extract administration groups lost significantly (p 0.05) less body weight and adipose tissue mass than mice in the control group after receiving RRE intragastrically for 8 weeks. RRE therapy decreased the triglyceride and total cholesterol levels in hyperlipidemic mice considerably (p 0.05). Transcriptome analysis and qRCR validation established Ppar, Hmgcr, Ldlr, Cyp7a1, Acsl3, Pnpla2, and Pin4 as the regulating genes.[12][15] KEGG pathway analysis revealed that the activation of PPAR caused by extract supplementation further regulated target genes including Cyp7a1 and Pin4 in the body. Hmgcr and other gene expressions, meanwhile, prevented the creation and conversion of liver cholesterol.Target genes including Cyp7a1 and Pin4 were further controlled by the activation of PPAR caused by RRE supplementation, according to KEGG pathway analysis.[13] The expression of the plant extract-regulated genes Hmgcr and Cyp7a1 also hindered liver cholesterol synthesis and conversion, while the Ldlr gene was down-regulated to reduce cholesterol transport. RRE therapy may also hasten the transition from triglyceride to fatty acid. In conclusion, RRE consumption would offer defense against hypertriglyceridemia brought on by diet.[14]

Overall, the plant is a strong candidate for testing its ability to improve hyperlipidemia.

Objective

The goal of this research is to develop a novel, effective treatment for hyperlipidemia because currently available, synthetic medications have a lot of side effects that could cause more issues. Therefore, the goal of this research is to reduce each of these adverse effects as much as possible and create new herbal medications that don't have any of them. Thus, if the plant can combat hyperlipidemia effectively, it will pave the road for the development of novel drugs with no side effects. In the end, this will provide a new angle for anti-hyperlipidemic medications with fewer side effects than those now on the market.

Materials and Methods

Drugs, Chemicals and Instruments:

Sigma-Aldrich, Germany is the source of ethanol, CCl 4, and alloxan.I was given a gift sample of rosuvastatin, a common antihyperlipidemic drug, by Healthcare Pharmaceutical Limited. Plasmatic Laboratory Product Ltd. in the UK provided the HDL, LDL, Triglycerides, Total Cholesterol, SGOT, SGPT, and Creatinine measurements. The glucometer Alere GI from Alere Inc., USA was provided by Shahbag in Dhaka, Bangladesh, and the biochemical parameters were measured using the Humalyzer 3000 (Semi-Automated Clinical Chemistry Analyzer).

The ingredients for the high fat diet were purchased froma supermarket.

Plant Collection and Extract Preparation:

We purchased the Rubusidaeus leaves from a nearby grocery. After that, taxonomic identification and authentication were completed. Plant specimens were maintained by Bangladesh's National Herbarium in accordance with regulations. For later use, the Herbarium was preserved.

After being crushed and steeped in 70% ethanol for 96 hours, the leaves were incredibly shaky. The extract was recovered when the liquid was filtered, after it had finished soaking. After that, the extracted solution was concentrated using a rotary evaporator. The dried extract was then meticulously collected and kept for further use.

Experimental criteria: All tests were conducted in accordance with the ethical criteria outlined in the 2013 Declaration of Helsinki [16].

Experimental Design: Each rat was weighed individually, and then the animals were divided into groups (Table 1) with an even distribution of rodents according to their body weight and five rats in each group.

Table 1: Antihyperlipidemic activity analysis

Group number	Group Status	Treatment specimen & Dose	Group Abbreviation
1	Negative Control	N/A	N
2	High Fat Diet	N/A	HFD
3	High Fat Diet +Rosuvastatin	Rosuvastatin and 10 mg/kg	HFD+ R_{10}
4	High Fat Diet + *Rubusidaeus*	*Rubusidaeus*and 500 mg/kg	HFD+I_{500}
5	High Fat Diet + *Rubusidaeus*	*Rubusidaeus* and 1000 mg/kg	HFD+I_{1000}

6	High Fat Diet + *Rubusidaeus*	*Rubusidaeus* and 1500 mg/kg	HFD+I1500
7	*Rubusidaeus*	*Rubusidaeus* 500 mg/kg	HFD+I500
8	*Rubusidaeus*	*Rubusidaeus*1000 mg/kg	HFD+I1000
9	*Rubusidaeus*	*Rubusidaeus*1500 mg/kg	HFD+I1500

The N/A denotes that no therapeutic treatment was given to the rats in this group.

High Fat Diet: The composition provided by Levin and Dunn-Meynell [17] was used to modify the high-fat diet. 50% fat, 40% carbs, and 10% protein make up the high-fat diet. Table 2 shows the nutritional breakdown of the diet. After the ingredients were thoroughly mixed, the rats were given a high-fat diet for 10 weeks in order to cause obesity [18].

Biological Sample Collection:
The heart was quickly perforated following the sacrifice in order to gain samples of blood, which were subsequently put into a microcentrifuge tube. To obtain supernatant fluid, five minutes of 5,000 rpm centrifugation were applied to the obtained samples. In order to execute this fluid was then transferred to another microcentrifuge tube for biochemical assays.

Estimation of Biochemical Parameters: Lipid profile, kidney, and liver function tests were carried out using Humalyzer 3000.

Statistical Analysis: To determine the statistical significance of each study parameter that belonged to each group and to assess intergroup heterogeneity in terms of several biological parameters, the "one-way ANOVA test" was employed. The "SPSS 16" software was used to do the analysis.
The result was considered statistically significant when the "p" value was less than 0.05 (p0.05).

Results and discussion:

Using wistar albino male rats in three different experimentally created hyperlipidemic scenarios, this study assessed the capacity of *Rubusidaeus*'s extract to prevent hyperlipidemia.

Lipid profile:

In this study, rats in groups 3, 4, and 5 (diseased + marketed drugs groups) had significantly higher levels of total cholesterol, triglycerides, and LDL cholesterol, but their serum HDL cholesterol levels were significantly lower. This finding contrasted sharply with the negative control group, whose serum lipid profile was found to bestandard [Table 3]. The hyperlipidemia, which is brought on by the excessive intake of fat, and the direct dietary absorption of high levels of fat combined to cause a significant abnormality in the serum lipid profile of rats treated with high fat diet (group 2) release of fat calories into the bloodstream from adipose tissue as a result of the inadequate glucose utilization [19,20]. Nevertheless, administering different dosages of *Rubusidaeus* to the ill rats led to a significant decrease in their serum levels of LDL, triglycerides, and cholesterol and an increase in HDL. In male mice given a high-fat diet, phenol-enriched *Rubusidaeus* fruit extract (*Rubusidaeus*) led to decreased weight gain, increased ambulatory activity, and enhanced production of heme oxygenase-1 and hepatic lipoprotein lipase.[21] However, the presence of sterol components (e.g., β-Sitosterol, β-Stigmasterol) may be the defensive mechanism underpinning the activity of *Rubusidaeus* against high fat diet-induced hyperlipidemia.Plant extract, which may assist in reducing blood triglyceride and cholesterol levels by cutting down on the amount of cholesterol absorbed by diet [22]. Plant sterols like these they are preferentially absorbed over cholesterol and compete with it for inclusion in mixed micelles cholesterol since they have a greater affinity for micelles and are more hydrophobic, hence decreasing the amount of cholesterol absorbed from food, which, in turn, causes a drop in the rats increased levels of blood HDL and triglycerides as well as LDL and HDL production [22–24] are some examples. It is noted that the disturbed pathological state is largely restored, as it is in the majority of cases. Therefore, additional genetic alteration or chemical isolation could add a new layer to the hyperlipidemia management system .Nonetheless; our results were rather similar to findings of a few earlier research projects that shown the encouraging effectiveness of in *Rubusidaeus*'s balancing rats with hyperlipidemia's serum lipid levels.

Table-3: Assessment of Lipid Profile test

Group number	Group Status	Total Cholesterol	HDL	LDL	Triglyceride
1	Negative Control	91.34±4.16	75.36±1.89	33.90±1.01	50.49±1.64
2	High Fat Diet	216.37±8.19	45.46±4.28	72.47±3.39	43.40±7.30
3	High Fat Diet +Rosuvastatin	111.32±12.42	63.60±5.57	46.26±4.6	67.83±6.38
4	High Fat Diet +	199.41±9.79	48.20±3.19	63.12±8.19	95.43±5.89

	Rubusidaeus				
5	High Fat Diet + *Rubusidaeus*	187.14±12.42	53.19±4.40	58.19±8.22	90.32±7.69
6	High Fat Diet + *Rubusidaeus*	178.33±7.52	59.37±5.81	52.73±6.44	86.22±6.49
7	*Rubusidaeus*	93.47±3.34	73.60±2.20	35.57±2.09	47.47±2.49
8	*Rubusidaeus*	97.10±2.12	76.18±2.12	32.37±1.42	48.24±3.31
9	*Rubusidaeus*	90.46±3.17	73.57±2.21	34.42±1.23	47.89±2.74

Liver function test:

Rubusidaeus potential to restore the liver functions of hyperlipidemic rats was examined by measuring the levels of two enzymes in their serum—SGPT and SGOT—that work as the most accurate indicators of liver damage [Table 4]. These values of serum enzymes were seen to be significantly greater in groups 5 and 6 (disease + plant extraction) —the three disease control groups—indicating the pathological manifestation of hepatotoxicity brought on by high-fat diets, raised serum enzyme levels by allowing those liver enzymes to seep into the bloodstream.

Nevertheless, the hepatotoxicity-mediated changes in the serum SGPT and SGOT levels were dramatically ($P<0.5$) reversed by the in-vivo administration of *Rubusidaeus* to the diseased rats in a dose-dependent manner, producing non-significant ($P>0.05$) statistical results with the usual prescription, Rosuvastatin.

This demonstrated the test extract's encouraging hepatic-level protective effect against biochemical changes brought on by hyperlipidemia. The extract's high phenolic content may be the cause of its protective properties has exceptional anti-inflammatory and antioxidant qualities [25].

Table-4: Assessment of Liver Functioning test

Group number	Group Status	SGPT	SGOT
1	Negative Control	32.67±2.14	43.67±1.52
2	High Fat Diet	81.37±6.45	87.47±9.51
3	High Fat Diet +Rosuvastatin	69.16±5.24	70.52±7.29
4	High Fat Diet + *Rubusidaeus*	78.40±6.15	84.98±5.16
5*	High Fat Diet + *Rubusidaeus**	74.52±5.32*	81.80±6.20*
6*	High Fat Diet + *Rubusidaeus**	70.37±3.16*	77.30±5.41*
7	*Rubusidaeus*	34.87±1.96	45.60±1.36
8	*Rubusidaeus*	34.24±1.26	42.17±1.70
9	*Rubusidaeus*	30.60±2.11	40.16±1.60

Kidney Function test:

By comparing the serum levels of creatinine and urea between the experimental groups, the impact of *Rubusidaeus* on the renal functions of hyperlipidemic rats was evaluated [Table 5]. Table 5's experimental results shows that there was a noticeable increase in the serum levels of creatinine and urea in rats from groups 4, 5, and 6 (disease control groups), suggesting that the rat's renal perfusion was compromised. However, giving different dosages of *Rubusidaeus* to these disease control groups considerably ($P<0.5$) decreased the hyperlipidemic rats' high levels of urea and creatinine in a dose-dependent manner, indicating the plant extract's nefroprotective efficacy against biochemically generated hyperlipidemia changes. Furthermore, several plants belonging to different genera, such as *Origanummajorana,Sidacordifolia, Capparisspinosa, Morus alba*, and *Lophiralanceolata* all showed similar results in earlier research [26- 29]

Table-5: Assessment of Kidney Functioning test

Group number	Group Status	Urea	Creatinine
1	Negative Control	25.25±2.01	6.6±0.02
2	High Fat Diet	93.37±9.37	2.2±0.09
3	High Fat Diet +Rosuvastatin	73.40±6.31	1.3±0.07
4*	High Fat Diet + *Rubusidaeus**	84.15±7.30*	1.9±0.09*
5*	High Fat Diet + *Rubusidaeus**	80.19±6.37*	1.5±0.08*
6*	High Fat Diet + *Rubusidaeus**	71.19±8.36*	1.2±0.07*
7	*Rubusidaeus*	26.41±2.18	0.8±0.04
8	*Rubusidaeus*	28.30±3.14	0.8±0.09
9	*Rubusidaeus*	25.50±2.26	0.9±0.03

Conclusion

Our research indicates the presence of anti-hyperlipidemic chemicals in *Rubusidaeus*. Furthermore, the extract dose-dependently restores the disturbed pathogenic state. Furthermore, the solvent that we utilize for extraction wouldnot the best for removing the leaf chemical that has anti-hyperlipidemic properties.Moreover, at the time of leaf harvest, these chemicals might not have been present in the plant in appreciable amounts. They might also exist in trace amounts in the plant naturally in the area where the plant was picked. Future research on *Rubusidaeus's* pharmacological activity will need to be conducted in-depth in order to ascertain the type and extent of the plant's ability to treat hyperlipidemia.

Ethical Approval:

As per international standard or university standards written ethical approval has been collected and preserved by the author(s).

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